PSYCH 3: PHYSIOLOGICAL PSYCHOLOGY



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Psych 3: Physiological Psychology

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1: FOUNDATIONS AND HISTORY OF PHYSIOLOGICAL PSYCHOLOGY

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1.2: The Scientific Approach to Understand Brain and Behavior

1.3: History of Biopsychology

1.4: Applications of Biological Psychology

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1.1: The Field of Biological Psychology

What is Biological Psychology? Biological psychology is the scientific study that links brain and behavior. Biological psychology, or biopsychology or biopsych for short, is related to neighboring disciplines including psycho-biology and behavioral neuroscience (Pinel & Barnes, 2017). The distinction is subtle, but we use the term biological psychology here because it emphasizes the centrality of psychology (i.e., the science of mental processes and behavior). Our goal is to understand the biological bases of psychology, rather than psychological aspects of biology or neuroscience. Thus, biological psychology investigates how biological factors like the brain, nervous system, hormones, and genes influence our cognition, emotions, motivations, memories, and actions. Biological psychology is not only a scientific discipline, but also a viewpoint that emphasizes that brain mechanisms underlie all of our thoughts and actions and that these brain mechanisms have evolved over eons from our ancient ancestors who survived and reproduced (Kalat, 2019).

The History of Biological Psychology. Thinkers have long mused about the nature of human behavior and experience, but the scientific discipline of biological psychology has roots in physiology, philosophy, and the early psychologists who adopted **empiricism** in the 19th century (Garrett, 2015). Wilhelm Wundt, considered the founder of experimental psychology, started the first psychology laboratory in the 1870s in Leipzig, Germany, where his research emphasized systematic observation to understand consciousness and mental processes. In *The Principles of Psychology* (1890), William James argued that the scientific study of psychology should be grounded in an understanding of biology (Walinga, 2019). Although we can't pin down the exact start of the field of biological psychology, the publication of Donald Hebb's groundbreaking book *The Organization of Behavior* in 1949 marked a defining moment. Hebb proposed the first brain-based account of how psychological phenomena like perception, thought, and memory could emerge from brain activity, and thereby challenged the prevailing view that psychological phenomena were too complex to originate from brain processes (Pinel & Barnes, 2017).

Divisions of Biological Psychology. Nowadays, biological psychology is a broad and diverse field that consists of many different approaches to studying links between the brain and behavior. Here are some major branches of biological psychology:

- **Psychopharmacology** examines how drugs and other substances affect the brain and behavior, as well as how they can be used to treat psychological disorders.
- **Neuropsychology** investigates the relationship between brain function and behavior, focusing on how brain damage or dysfunction can impact cognitive and psychological functioning especially in human patients.
- **Psychophysiology** studies of the relation between physical functions of organisms (physiology) and psychological processes. Common physiological measures include electroencephalogram (EEG), heart rate, and pupil dilation.
- **Psychoneuroimmunology** examines the relationships between the nervous system, immune system and hormones, and behavior. Psychoneuroimmunologists often study the impact of stress and stress hormones on illness susceptibility and recovery.
- **Evolutionary psychology** explores how evolutionary processes, like natural selection, have adaptively shaped human traits and behaviors.
- **Behavioral genetics** analyzes how genetic factors contribute to individual differences in behavior, cognition, personality, etc. and how genetic factors interact with environmental influences.
- **Cognitive neuroscience** studies the neural basis of human cognitive processes, including perception, attention, memory, language, and decision-making. It often uses tools like functional brain imaging.
- **Comparative psychology** examines the behavior and mental processes of nonhuman animals to gain insights into the evolutionary and environmental factors that shape animal and human behavior and mental processes.

Biological psychology can be parsed into even more subfields, the subfields overlap, and researchers often work in more than one area. But this list shows the breadth of approaches used to study links between the brain and behavior.

Biological psychology is highly interdisciplinary and researchers may have trained in psychology, neuroscience, biology, computer science, medicine, philosophy, or engineering. Each discipline contributes a different approach to understanding the brain and its functions, but also poses new questions and problems that require collaboration and integration. Understanding and integrating knowledge from various subfields can be challenging for both students and researchers, but that integration provides a richer understanding of the brain and leads to breakthroughs that propel scientific progress.

Figure 2. Pyramidal neurons in the mouse cerebral cortex expressing green fluorescent protein. The red staining indicates GABAergic interneurons.

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definition

A method for acquiring knowledge is one based on observation, including experimentation, rather than a method based only on forms of logical argument or previous authorities.

×Close definition

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1.2: The Scientific Approach to Understand Brain and Behavior

Biological psychology uses many techniques to observe, measure, and manipulate the brain, but researchers across all fields use the same underlying approach—science and the scientific method. The scientific method is a systematic way of gathering and testing evidence based on observation and experimentation.

The scientific process usually starts with an observation or question that one wants to understand. A researcher proposes a tentative explanation, called a **hypothesis**, to explain the phenomenon. A valid hypothesis must be testable. It should also be **falsifiable**, meaning that experimental results can disprove it. Importantly, science does not claim to "prove" anything because scientific understandings are always subject to modification with further information. This step—openness to disproving ideas—distinguishes science from non-science. The presence of the supernatural, for instance, is neither testable nor falsifiable. A hypothesis should also fit into the context of a scientific **theory**, a broad explanation for some aspect of the natural world that is consistently supported by evidence over time. A theory is the best understanding we have of that part of the natural world.

The researcher then tests the validity of the hypothesis by making observations or carrying out an experiment. An experiment will have one or more variables and one or more controls. A variable is any part of the experiment that can vary or change during the experiment; an **independent variable** is manipulated by the researcher, and a **dependent variable** is the outcome variable that is measured. The control group contains every feature of the experimental group except the manipulation from the researcher's hypothesis. Therefore, if results from the experimental group differ from the control group, that difference must be due to the hypothesized manipulation, rather than some outside factor.

For example, if a researcher hypothesizes that a certain drug decreases appetite, they could perform an experiment with the independent (manipulated) variable "drug or no-drug," and the dependent (measured) variable "amount of food eaten." The researcher would randomly assign some participants to the experimental group who gets the drug, and other participants to the control group who gets a placebo pill that looks like the drug. Through **random assignment** and a proper control condition, only the drug would differ between the experimental and control groups. If the experimental (drug) group eats less than the control (placebo) group, then one could conclude that the hypothesis is supported. Conversely, the research could lead to rejecting the hypothesis if not supported by the experimental data.

After analyzing their data, researchers communicate their results and conclusions in publications or presentations so that others can critique, replicate, or build on the results. In addition to publishing a report, researchers now regularly publish their datasets, so that others can re-analyze the data to ensure quality and maybe find something new without having to collect new data. Study results inform future studies and help refine hypotheses (see Figure 3). Experimental outcomes can prompt shifts in approach or spark new research questions. Many times, science does not operate in a linear fashion. Instead, scientists continually draw inferences and make generalizations, finding patterns as their research proceeds.

Science and the scientific method are the best way to understand and study the brain because they provide us with rigorous, objective, and verifiable knowledge that can help us improve our health, education, and well-being.

Figure 3. The scientific method consists of a series of well-defined steps. If a hypothesis is not supported by experimental data, one can propose a new hypothesis. The scientific method is an ongoing, iterative process, wherein the results from one study will inform and guide the process for a future hypothesis or study.

Basic and Applied Research. Across the various subfields of biological psychology, research can be categorized as basic or applied. **Basic research**, also known as pure research, is driven by scientific curiosity or an interest in understanding the mechanisms of brain function and brain-behavior relationships. It seeks to answer fundamental questions about how the brain works and explores the biological basis of behavior, emotions, and cognitive processes, by examining genetics, neurotransmission, brain circuitry, and other physiological processes. On the other hand, **applied research** in biological psychology takes findings from basic research and uses them to solve real-world issues. Examples of applied research include developing therapeutic interventions for mental disorders, devising strategies to optimize learning and memory, or creating neurofeedback methods for stress reduction. While the two types of research may seem distinct, they are interdependent. Basic research lays the groundwork for the applications that emerge from applied research, and applied research often raises new questions that drive basic research. In public and political debates, people sometimes argue for cutting funding of basic science because they contend it has no practical value. However basic science works in synergy with applied science—together they are

both essential to the development of biological psychology and science more broadly.

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definition

a tentative explanation of some phenomenon that is used as a starting point for further investigation.

×Close definition

A theory or hypothesis is falsifiable (or refutable) if it can be logically contradicted by an empirical test.

×Close definition

A broad explanation or group of explanations for some aspect of the natural world that is consistently supported by evidence over time

×Close definition

A variable that is manipulated by the researcher. The independent variable is “independent” of other variables and is typically considered the cause.

×Close definition

The outcome variable that is measured by the researcher. The dependent variable depends on changes of the independent variable.

×Close definition

A way of placing participants into different groups with randomization. Every member of the sample has an equal chance of being placed in a control group or an experimental group.

×Close definition

Also known as pure or fundamental research, seeks to expand scientific knowledge and understand the mechanisms of brain function

×Close definition

Research that can be directly applied to an existing problem

×Close definition

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1.3: History of Biopsychology

Learning Objectives

1. Discuss the history of biopsychology.
2. Discuss the important contributors to biopsychology and the contributions each made.
3. Explain the current direction of biopsychology.

Overview

Biopsychology as a scientific discipline is relatively new. However, early philosophers such as Hippocrates wrote about the importance of biological factors in human behavior. In this section, we will examine the emergence of biopsychology as a scientific field. We will further outline important events and contributions to biopsychology, beginning with early philosophers and their understanding of the biological aspects of behavior and mental processes. We then examine a number of more recent historical figures who made major contributions to the development of biological psychology and discuss their contributions to the discipline. Lastly, we will look at current directions in the field.

Biopsychology as a Discipline

Biopsychology as a scientific discipline emerged from a variety of scientific and philosophical traditions in the 18th and 19th centuries. Although the exact date of inception of biological psychology is unknown, there have been a number of milestones in its emergence. William James in his book, *The Principles of Psychology* (1890), argued that the scientific study of psychology should be grounded in an understanding of biology (Walinga, 2014). Like many early psychologists, James had extensive training in physiology.

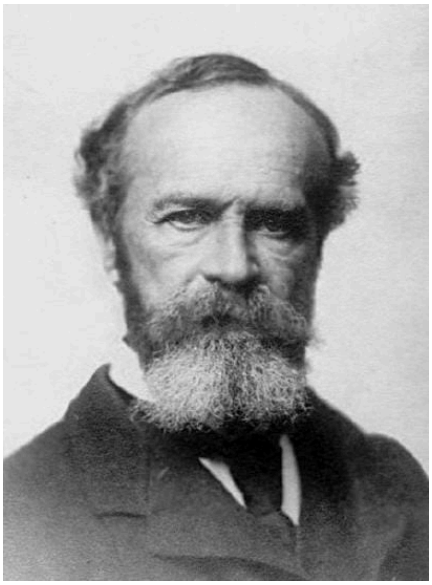


Figure 1.3.1: William James. (Public Domain; via Wikimedia Commons)

In *An Outline of Psychobiology,* Knight Dunlap used the term "psychobiology" to explain the role of biology in behavior. In 1949, Donald Hebb wrote his influential book, *The Organization of Behavior*, where he introduced the first comprehensive theory on how the brain might create and control complex psychological functioning, such as thought, memories, emotions and perceptions. In other words, even before biopsychology was formally recognized as a branch of psychology or as a discipline, the connection between psychology and biology was recognized. With case studies such as Phineas Gage and invention of methods such as the electroencephalogram (EEG) and computed tomography (CT or CAT) scans, scientists began to link the brain to specific behavior and cognition as biopsychology as a discipline began to emerge.

The Origins of Biopsychology

It is important to examine the historical path of our understanding of the brain and its role in our behavior and mental processes. Examining the history of biopsychology allows us to understand its development over time, highlighting instances where researchers were wrong about the nature of brain-behavior relationships and revealing what we have yet to explain (Saucier and Elias, 2006). Studying the history of a scientific discipline gives us a roadmap of where we have traveled from and in what direction we need to go.

Early Views of Brain and Behavior

Early philosophers, such as Aristotle (384-322 B.C.E.), believed that one's mind resided in the heart. He believed that since our blood started from the heart, the soul also originated there. Plato (428-347 B.C.E.) argued that the executor of reason was the heart and our animalistic desires and emotions were controlled by the liver (Gross, 1987). Many ancient cultures, including the Chinese, Indian, and Egyptian also shared the same belief (Carlson, 2014). When the Egyptians embalmed a person, the heart was saved and buried with the individual but the brain was discarded (Klein and Thorne, 2006). However, there were early Greeks, such as Hippocrates (460-377 B.C.E.) , who believed that it was the brain and not the heart where the locus of the mind resided. He wrote: "It ought to be generally known that the source of our pleasure, merriment, laughter, and amusement, as of our grief, pain, anxiety, and tears is none other than the brain. It is specially the organ which enables us to think, see, and hear.....It is the brain too which is the seat of madness and delirium, of the fears and frights which assail us" (Gross, 1987, p. 843-844).

During the 3rd Century B.C., in Alexandria, a science museum was established. Since human dissection was practiced in that city for centuries, the anatomical study of the human body flourished (Gross, 1987). Two neuroanatomists, Herophilos and Erasistratos, contributed to our knowledge of the human brain. Herophilos distinguished the cerebellum (at the very base of the back of the brain) and the cerebrum (the two cerebral hemispheres). He hypothesized that since the cerebellum was denser than the other parts of the brain, it must control the muscles (a guess of impressive accuracy). And he provided the first clear description of the cavities within the brain known as ventricles (Figure 1.2.1). Erasistratos continued the work of Herphilos and proposed that human intelligence was related to the number of convolutions (ridges) in the brain; the more convolutions an individual's brain had, the more intelligent that person would be.

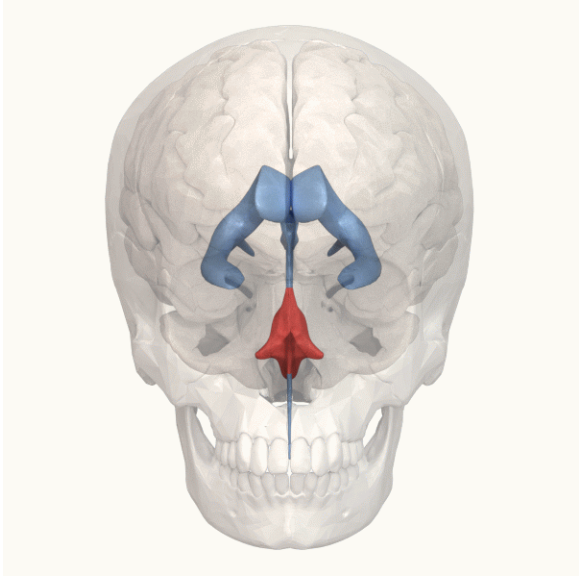


Figure 1.3.2: Human Ventricles (CC BY-SA 2.1; BodyParts3D by DBCLS via Wikimedia Commons)

During the Roman Empire, the Greek anatomist Galen (A.D. 130-200) dissected the brains of sheep, monkeys, dogs, pigs, among other non-human mammals (Carlson, 2014). He believed the brain to be the site of sensation and thought, and the controller of movement (Gross, 1987). He stated that spinal cord was an extension of the brain and chronicled the relationship between the spinal nerves and specific muscles each controlled. For the next advance in understanding spinal function, we must await Bell and Magendie in the 19th Century.

Middle Ages



Figure 1.3.3: Drawing of Ibn-Sina. (Public Domain; via Wikimedia Commons)

Avicenna (980-1037 C.E.) was a Persian physician who some regard as the father of modern medicine. He recognized biological psychology in his treatment of illnesses that involved emotions (Syed, 2002). In his book, *The Canon of Medicine (Qanun: Law of Medicine)*, Avicenna dedicated three chapters to neuropsychiatric disorders where he defined madness (Junun) as originating in the middle part of the brain. He discussed a condition similar to schizophrenia, which he called Junun Mufrit, characterized by agitation, behavioral and sleep disturbances, giving inappropriate answers to questions, and an occasional inability to speak. Avicenna also discovered the cerebellar vermis, which he simply called the vermis, and the caudate nucleus. Both terms are still used in neuroanatomy today (Mohamed, 2008). He further explained that "humidity" inside the head contributed to mood changes and when this moisture inside the brain goes beyond limits, the brain loses control over its rationality and mental disorders appear (Haque, 2004). Lastly he presented detailed knowledge about skull fractures and their surgical treatments (Aciduman, Arda, Ozakturk, and Telatar, 2009). He also discussed phenomena such as insomnia, mania, hallucinations, nightmares, dementia, epilepsy, stroke, paralysis, vertigo, melancholia, and tremors (Mohamed, 2008). He was also the first person to associate mental deficits with deficits in the brain's middle ventricle or frontal lobe (Mohamed, 2008).

Renaissance

By the beginning of the 16th century, Andreas Vesalius, founder of modern anatomy, rekindled interest in neuroscience (Gross, 1987). Through his dissection of human cadavers, Vesalius found problems with the Galenic view of anatomy (which emphasized three major systems--the heart, brain, and blood--and the importance of a balance between four bodily fluids--blood, phlegm, and black and yellow bile). Vesalius published seven books, with the fourth and seventh books devoted to the nervous system (Van Laere, 1993). Vesalius outlined seven pairs of 'brain nerves', each with a specialized function. In his seventh book which was solely devoted to the brain, he successfully describes the cerebral membranes, the ventricular system, and the cerebrum (Van Laere, 1993). Other scholars furthered Vesalius' work by adding their own detailed sketches of the human brain.

René Descartes (1596-1650) proposed the reflexive theory in terms of our behavior (Elias and Saucier, 2006). This theory explained reflexive behavior as an "external stimuli [that] would move the skin, in turn moving the filaments, releasing the animal spirits and innervating the muscles" (Elias and Saucier, 2006, p 6). His mechanical explanation of movement without conscious intervention allowed for scientific study of behavior. Furthermore, his theory encouraged using animal models to study biological bases of behavior (Cobb, 2002). He also studied the physiology of the brain, proposing the theory of dualism (the view that mind and brain are separate) to tackle the issue of the brain's relation to the mind. He suggested that the pineal gland was where the mind interacted with the body after recording the brain mechanisms responsible for circulating cerebrospinal fluid (Elias and Saucier, 2006).



Figure 1.3.4: Descartes Drawing - Reflexive role of pain in contracting muscle. (Public Domain; via Wikimedia Commons)

Discoveries of the 19th Century

Localization of Function

Starting in early 1800's, a series of researchers began to catalog different brain parts and their presumed role in behavior. In 1811, Jean-Cesar Legallois (1770-1840) discovered that when he destroyed tissue in the medulla, a procedure called lesioning, there was an immediate cessation of respiration (Elias and Saucier, 2006). Charles Bell (1774-1842) and Francois Magendie (1783-1840) discovered the different function of spinal cord nerves where the ventral roots transmitted motor impulses and posterior roots received sensory input (Bell-Magendie Law). Given the specialization found in spinal cord nerves, Bell recommended that further investigation of the the entire nervous system should examine functional and anatomical segregation (Elias and Saucier, 2006).

Taking on the challenge, Franz Joseph Gall (1758-1828) and Johann Spurzheim (1776-1832) formulated phrenology where measurement of the skull was used to determine personality characteristics of an individual. Gall made the claim that here were twenty-seven distinct cognitive abilities that could be localized on the cortex of the human brain (the cortex composing the outermost part of the brain). He believed that the design of the brain changed as each of us developed certain characteristics and this resulted in corresponding changes in the skull. Where the skull rises, one can see excellence in the human qualities associated with the underlying brain and where there were depressions in the skull, human defects were represented (Lau, Loi and Abdullah, 2021). Measuring the skull by using a technique called cranioscopy would allow the scientist to detect deformation and bumps on the skull which would outline the person's personality (Elias and Saucier, 2006).

In 1848, John Martyn Harlow treated Phineas Gage and documented his case. Gage, who was a railroad worker, had his frontal lobe pierced by an iron tamping rod in a blasting accident. He survived the trauma but suffered extensive damage to his left prefrontal cortex (Macmillan, 2001). Through Gage's case study, Harlow showed the connection between the prefrontal cortex damage, executive functioning, and personality changes.

In 1861, Paul Broca (1824-1880) presented a case where a young man had sustained damage to the left frontal lobe and as a result was unable to produce spoken speech. However, the patient was able to comprehend speech and had average intelligence. After his death, Broca performed an autopsy and determined that the patient had a lesion in the frontal lobe in the left cerebral hemisphere. Broca collected similar cases of damage to the left frontal lobe with the patient losing their ability to speak (Lau, Loi and Abdullah, 2021). One such case was Phineas Gage who lost his speech after his accident. Broca published his findings from the autopsies of twelve patients in 1865. Today, we recognize Broca's Area in the frontal lobe as a critical region in speech production. His work inspired others to perform careful autopsies with the aim of linking more brain regions to sensory and motor functions.

Carl Wernicke (1848-1904) further developed the theory of the specialization of specific brain structures in language comprehension and production. He wrote a paper in 1874, suggesting that housed in the left temporal lobe was an auditory comprehension center. He stated that when this area, now known as Wernicke's area, was damaged, the individual could not comprehend other's speech or use words correctly (Elias and Saucier, 2006). The concept of "localization of function", specific functions residing in specific parts of the brain, was established the end of the 19th century. Respiration and the medulla and the roles of Broca's and Wernicke's areas in language are examples of this concept.

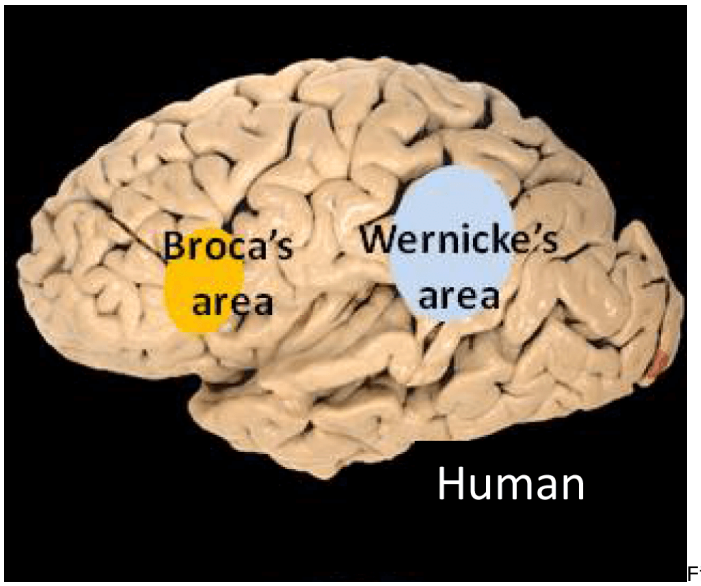


Figure 1.3.5: The two language areas of the brain. (Public Domain; via Wiki media Commons)

The Neuron

The last monumental neurological discovery of the 19th century was the identification of the specific structural unit responsible for these brain functions, the neuron. Studies of the brain became more sophisticated after the invention of the microscope and the development of a staining procedure by Camillo Golgi during late 1873 (Elias and Saucier, 2006). Golgi (1843-1926) was a histologist (one who studies the cellular structure of tissue) and a physician (Klein and Thorne, 2006). He used a silver chromate salt to reveal the intricate structures of single neurons (Elias and Saucier, 2006). Through this technique, he was able to reveal that the neuron has three distinct structures: dendrite, cell body, and axon (Elias and Saucier, 2006). Furthermore, he revealed that the axon can be short or very long, enabling the cell body to send messages to neurons far away. Therefore the axon must be the output carrier for the neuron. This technique is called the Golgi stain, named in his honor.

The Golgi stain technique was used by Santiago Ramón y Cajal to outline the neural connections in the brain (Elias and Saucier, 2006). While Golgi believed that neurons were fused together to form a continuous circuit, Cajal demonstrated that neurons are not physically connected but do have a mechanism for communicating (Elias and Saucier, 2006). This led to the formation of the **neuron doctrine**, the hypothesis that the functional unit of the brain is the neuron, also known as a nerve cell. Today, the field accepts neuronal theory which states that the nervous system is made up of individual nerve cells called neurons (Klein and Thorne, 2006).

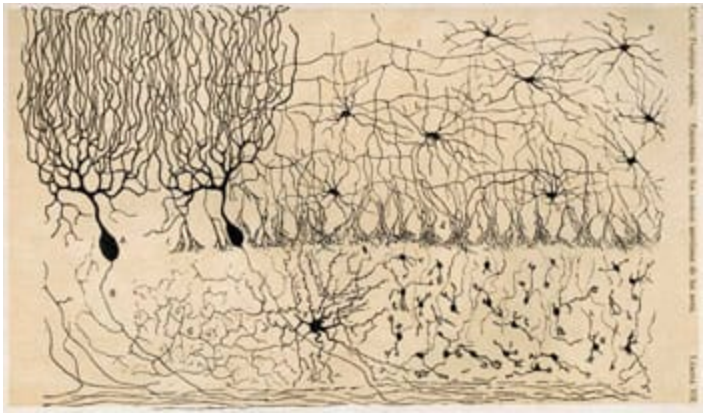


Figure 1.3.6: Ramon y Cajal's Drawing of A Neuron. (Public Domain; via Wikimedia Commons)

Golgi and Ramón y Cajal shared the Nobel Prize in Physiology or Medicine in 1906 for their extensive observations, descriptions, and categorizations of neurons throughout the brain. Golgi was praised for his staining technique and Cajal for developing the neuron doctrine.

One of the most important questions given Cajal's neuron doctrine was the mechanism for communication between neurons. The role of electricity in nerves and electrical communication between neurons was first observed in dissected frogs by Luigi Galvani. In 1780, he showed that an electrical stimulus applied to the motor nerve of a frog's nerve cell produced a twitch. This experiment suggested that electricity was an important functional element of the nervous system (Klein and Thorne, 2006).

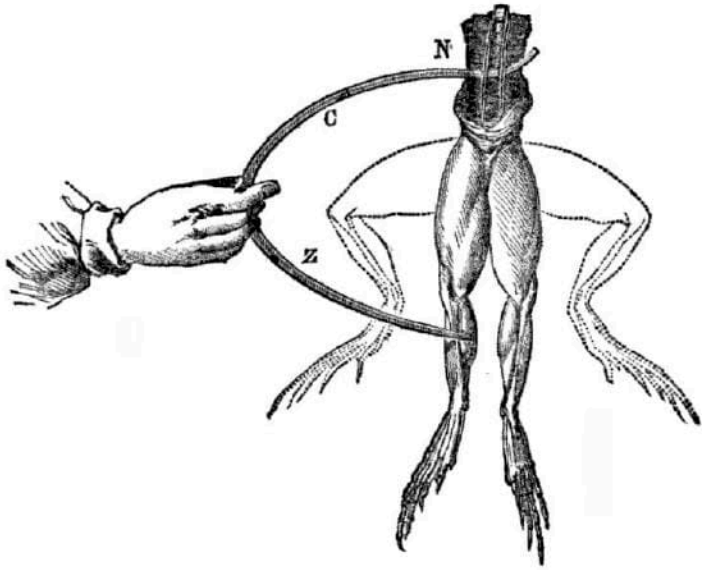


Figure 1.3.7: Drawing showing Galvani's Frog Leg Electricity Experiment. (Public Domain; via Wikimedia Commons)

Discoveries of the 20th Century

The Synapse

Charles Scott Sherrington (1857-1952) accepted Cajal's neuron doctrine and set out to discover the point of functional contact between neurons. He called this connection point the **synapse**, which means "binding together" (Klein and Thorne, 2006). His discovery was made by studying spinal reflexes in dogs. Confirming Galvani's electrical theory, he demonstrated the electrical transmission between neurons (Elias and Saucier, 2006). He received the Nobel Prize in 1932 for his research. A German pharmacologist and physician, Otto Loewi (1873-1961), investigated chemical communication between neurons. He removed the heart of two frogs and placed them in separate containers, each one filled with a chemical solution that allowed the hearts to continue to beat. He stimulated the vagus nerve of the first heart which slowed down its beating. He shared the solution from the first heart's container with the second heart and the beating of the second heart also slowed. He concluded that when he

stimulated the vagus nerve of the first heart, a chemical was released to slow down its beating and when the solution from the first heart's container was shared with the second heart, the chemical directed the second heart to also decrease its beating (Klein and Thorne, 2006). He originally called this chemical vagusstoff, referring to its secretion after the stimulation of vagus nerve. This chemical was later identified as a **neurotransmitter**, acetylcholine (ACh). ACh was originally identified in 1915 by Henry Hallett Dale. However, Loewi is credited with establishing its role in chemical communication between nerve cells (Klein and Thorne, 2006).

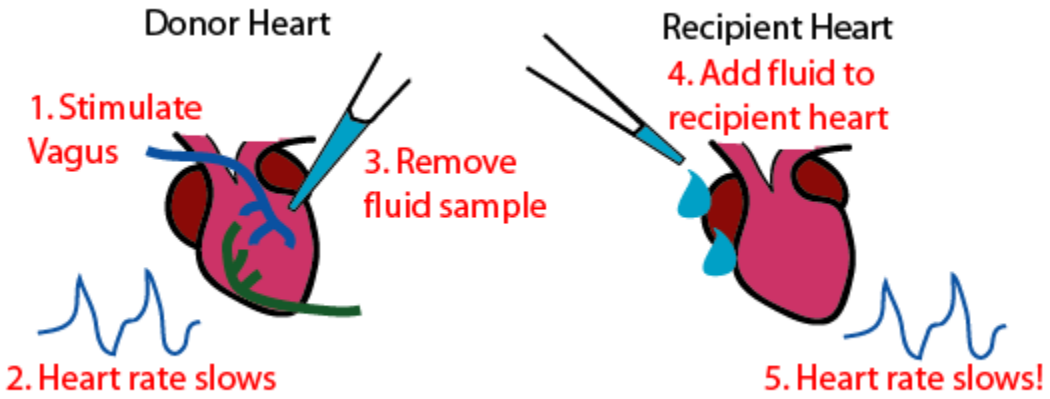


Figure 1.3.8: Loewi's experiment, describing the existence of Vagusstoff. (CC BY-SA 3.0; via Wikimedia Common)

Today, dozens of neurotransmitters have been identified in the brain. After acetylcholine, noradrenaline (now known as norepinephrine) was discovered in the 1940's, followed by dopamine and serotonin in the next decade and gamma-aminobutyric acid (GABA), glutamate, and glycine in the 1960's (Wickens, 2021). Later discoveries of neuropeptides, neuromodulators, and certain gases have added to the complexity of chemical communication in the brain. Our understanding of the impact and role of these chemical messengers and their effect on behavior and mental processes has given rise to the field of **psychopharmacology**.

Neural Conduction

Previous research had clearly demonstrated that electrical impulses played a role in neural communication. But the finer details of how this was occurring had not been discovered (Wickens, 2021). A series of discoveries led to our present understanding of neural conduction.

In 1902 and again in 1912, Julius Bernstein (1836-1917) was the first researcher to discover the **action potential** - the unique electrical signal traveling the length of an axon (Elias and Saucier, 2006). Additionally, he demonstrated that this electric conduction was due to change in **ionic concentration** of the cell's intracellular fluid. However, given the microscopic size of the cell, it was difficult to measure and study mammalian cells. In 1936, John Z. Young, an Oxford biologist, located a neuron in the body of a squid. The axon was nearly 1 mm in diameter which was 100 to 1,000 times larger than a mammalian axon and could be studied for about six hours after its dissection (Elias and Saucier, 2006). In 1952, two Cambridge University physiologists, Alan Hodgkin and Andrew Huxley published a set of papers describing their research on the **giant squid axon**. Much of our understanding of neural functioning came from the giant squid. Hodgkin and Huxley created a technique to measure electrical changes of the neuron by inserting an electrode inside and one positioned outside of the neuron without damaging it. This enabled them to measure **changes in electrical charge** when the neuron was at rest and when it produced an action potential (Wickens, 2021). A detailed discussion of both concepts, resting and action potential will follow in future chapters.

Studying Brain Activity and Brain Imaging

With the invention of machines such as the electroencephalograph (EEG), CT scan, and magnetic resonance imaging (MRI), scientists were able to peak into the activity and images of patients' brains while they were alive and engaged in mental activity. In 1924, Hans Berger recorded the first human brain EEG. This machine allowed researchers to study the overall electrical activity of the brain. In 1953, Kleitman and Aserinsky discovered Rapid Eye Movement (REM) using EEG on sleeping subjects. Today EEGs

are helpful in diagnosing epilepsy and sleep disorders. Many credit their work as the beginning of modern study of sleep. The first image of the brain by CT scan was in 1971 by Godfrey Hounsfield. He used the CT scan to locate a brain tumor (Wells, 2005). CT scans can be used to locate brain tumors, injury, or atrophy. However, the CT scan uses Xrays to provide an image of the brain which could pose risk to brain tissue. Magnetic resonance imaging (MRI) was also used in 1970's to give pictures of the brain. An MRI does not use Xrays and is therefore found to be a safer method for producing human brain scans.

In 1950, positron emission tomography (PET) scans were used to look at brain activity or communication in a living patient. Researchers were able to look at different parts of the brain in different situations. In other words, they could look at real time activity of the brain as the person laughed or was scared to see what ares of the brain lit up. This gave an indication of what areas of the brain maybe responsible for different emotions or behaviors. The problem with PET scans was that an individual receiving a PET scan had to drink or be injected with a mildly radioactive substance, called a tracer. Once in the bloodstream, the amount of tracer in any given region of the brain can be monitored. As brain areas become more active, more blood flows to that area. A computer monitors the movement of the tracer and creates a rough map of active and inactive areas of the brain during a given behavior. PET scans show little detail, are unable to pinpoint events precisely in time, and require that the brain be exposed to radiation. In 1990s, a group in Bell Laboratories invented functional Magnetic Resonance Imaging (fMRI). This machine shows changes in brain activity over time by tracking blood flow and oxygen levels. The fMRI provides more detailed images of the brain's structure, as well as better accuracy in time, than is possible in PET scans.

Today, these instruments have greatly contributed to our understanding of the brain and its function in behavior and cognition. With their high level of detail, MRI and fMRI are often used to compare the brains of healthy individuals to the brains of individuals diagnosed with psychological disorders. This comparison helps determine what structural and functional differences exist between these populations.

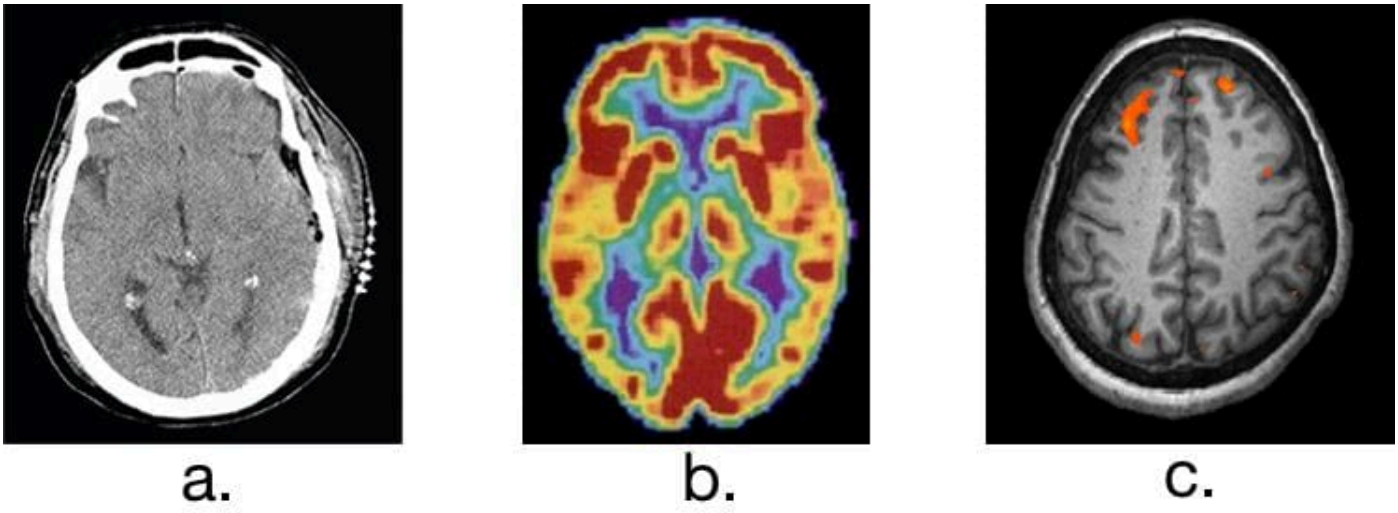


Figure 1.3.9: Images of brain using different instruments. a. CT scan; b. PET; c. fMRI (CC BY 3.0; via Wikimedia Commons)

Today

In April 2013, the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative was launched. The focus of this initiative was to advance our understanding of the human brain. In the fiscal year 2020, 10.1 billion U.S. dollars has been allocated to neuroscience studies (Mikulic, 2021). Different institutions, agencies and foundations such as Food and Drug Administration, Defense Advanced Research Projects Agency, have joined in this effort.

References

Aciduman, Ahmet, Arda, Berna, Ozakturk, Fatma G., Telatar, Umit F. (2009). What does Al-Qanun Fi Al-Tibb (the Canon of Medicine) say on head injuries?. *Neurosurgical Review, 32* (3), 255-263.

Carlson, Neil R. (2014). Foundations of Behavioral Neuroscience, 9th Edition. Pearson Publishing.

Cobb, Matthew (2002). Timeline: Exorcizing the animal spirits: Jan Swammerdam on nerve function. *Nature Reviews*

Neuroscience, 3 (5), 395-400.

Gross, Charles G. (1987). Neuroscience, Early History of. In Adelman, George (ed.), Encyclopedia of Neuroscience, Kirkhauswer Verlag AG, pp. 843-847.

Haque, Amber (2004). Psychology from Islamic perspective: Contributions of early Muslim scholars and challenges to contemporary Muslim psychologists. *Journal of Religion and Health, 43* (4), 357-377.

Klein, Stephen B. and Thorne, B. Michael (2006). Biological Psychology. Worth Publishers.

Lau, Yoke Lian, Loi, Chek Kim and bin Abdullah, Mohd Nor Azan (2021). The Historical Development of the study of Broca's Aphasia. *Malang Neurology Journal, 7* (2), 125-128.

Macmillan, Malcolm (2001). John Martyn Harlow: Obscure country physician? *Journal of the History of Neurosciences: Basic and Clinical Perspectives, 10* (2), 149-162.

Mikulic, Matej (2021). Total neuroscience funding by the National Institutes for Health (NIH). Statica.com. https://www.statista.com/statistics/...isticContainer

Mohamed, Wael MY (2008). History of Neuroscience: Arab and Muslim contributions to modern neuroscience. *IBRO History of Neuroscience*: 255.

Syed, Ibrahim B. (2002). Islamic medicine: 1000 years ahead of its times. *Journal of the International Society for the History of Islamic Medicine 2,* 2-9.

Van Laere J. Vesalius en het zenuwstelsel [Vesalius and the nervous system]. Verh K Acad Geneeskd Belg. 1993;55(6):533-76. Dutch. PMID: 8209578.

Wells, P. N. T. (2005). “Sir Godfrey Newbold Hounsfield KT CBE. 28 August 1919 – 12 August 2004: Elected F.R.S. 1975”. Biographical Memoirs of Fellows of the Royal Society. **51**: 221–235. doi:10.1098/rsbm.2005.0014.

Wickens, A. P. (2021). Introduction to Biopsychology. United Kingdom: SAGE Publications.

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1.4: Applications of Biological Psychology

Biological psychology and related neuroscience fields are highly active areas of research. Billions of dollars are invested annually and tens of thousands of researchers study the brain and behavior. The vast endeavor to understand the brain will help unravel the mysteries of human nature and our human experience. Brain research also has impactful applications—it helps to heal brain damage and psychological disorders and guides the development of artificial intelligence and brain-compatible social policies (Eagleman & Downar, 2016).

Healing the brain. Brain damage and psychological disorders affect tens of millions of people each year. Basic brain science enhances patient care and treatment. Research on cellular and molecular mechanisms in the brain can lead to new drugs, ways to regrow neurons, and increased neural plasticity. Researchers have developed groundbreaking new technology like transcranial magnetic stimulation that stimulates the brain with magnetic pulses and can treat depression, or deep brain stimulation that uses brain implants to treat diseases like Parkinson's. Brain-computer interfaces pick up brain signals, analyze them, and translate them into commands for devices like wheelchairs or robotic arms. These can help people regain movement who have neuromuscular disorders including amyotrophic lateral sclerosis (ALS), spinal cord injury, or stroke (Figure 4).

Figure 4. Components of a typical Brain-Computer Interface system that picks up brain signals, analyzes them, and translates them into commands to an external output device like a wheelchair or robotic arm.

Guiding Artificial Intelligence. Neuroscience is intertwined with artificial intelligence (AI). Understanding biological brains is important for building artificial brains and neuroscience has inspired the design of AI systems (Hassabis et al., 2017). Like neurons in the human brain, artificial neural networks have many interconnected units that work in parallel. Neuroscience provided early guidance for AI-system architecture (e.g., units organized in many layers) and algorithms (e.g., a "backpropagation algorithm" that adjusts the connections between units across multiple layers to enable learning). Another example of neuroscience-inspired AI is in attention—until recently artificial neural networks processed an entire image or video frame with equal priority given to all pixels. Conversely, humans focus on one small aspect at a time and strategically shift our "spotlight of attention." By incorporating a biologically-inspired approach with prioritized focus, AI-image processing improved performance and efficiency (Hassabis et al., 2017).

AI has recently made dramatic advances thanks to breakthroughs in "deep learning" and "reinforcement learning" methods (wherein learning is optimized by reinforcing or rewarding when desired outcomes occur). By incorporating principles from neuroscience, AI researchers have improved the efficiency and accuracy of AI algorithms, resulting in significant advances in areas like computer vision, decision-making, and natural language processing. Popular AI tools for text generation (like ChatGPT, Claude, and LLaMa) and image creation (like Stable Diffusion and DALL-E) are built on principles derived from neuroscience. Finally, advances in AI that were inspired by neuroscience are now being applied back to neuroscience as tools to understand the brain. For example, AI and deep learning approaches can analyze neuroimaging data, build computational models to simulate and study the brain, and predict the trajectory of psychological disorders or diseases like Alzheimer's (Kreigeskorte & Douglas, 2018; Colliot, 2023).

Computer generated image of a brain.

Figure 5. AI-generated image from DALL-E 3 using the prompt "Artificial Intelligence computer system inspired by neurons and brains."

Brain-compatible social policies. As outlined by Eagleman and Downar (2016), brain science can also have payoffs in guiding brain-compatible social policies. For example, psychology and neuroscience research has implications for how to view and address drug addiction. Advances in psychopharmacology and neuroscience reveal that addiction is driven by brain processes. As a result, policies that attack only drug *supply* are typically unsuccessful—if one point of supply is busted, another will pop up soon because the demand remains. Instead, policies should focus on attacking the demand for drugs. Treatments rooted in disrupting the brain circuits driving addiction will be more effective than an incarceration-focused approach.

Finally, a large portion of the prison population in the U.S. is mentally ill. The prevalence of serious mental illness in jail inmates is around 15% for men and 31% for women (Steadman et al., 2009). Jails and prisons have become mental health care facilities. For example, the Rikers Island prison is New York's largest mental institution (Ransom & Harris, 2023), and more mentally ill persons are in jails and prisons than are in hospitals (Torrey et al., 2010). Brain science demonstrates that psychological disorders are rooted in the brain, so one must ask whether policies that support and treat those with mental-health problems might keep them from committing crimes, and whether a treatment approach could be more humane and cost-effective (Eagleman & Downar, 2016).

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1.5: Research with Animals

To understand the human brain and human psychology, ideally we would only study humans. But some research cannot be conducted with humans, so biopsych researchers also perform research with animals. Most psychological research using animals is now conducted with rats, mice, and birds, as the use of other animals such as non-human primates is declining (National Research Council, 2011; Thomas & Blackman, 1992). Like research with humans, all research plans with animals must be reviewed by ethics boards to ensure that they meet important ethical principles such as:

- Use animals in research *only if* there is a reasonable expectation that the research will provide some benefit such as increasing understanding of the structures and processes underlying behavior or benefiting the health and welfare of humans or other animals.
- Use a procedure that subjects animals to pain or stress *only if* an alternative procedure is not available and the research goals are justified by its prospective scientific, educational, or applied value.
- Make every effort to minimize discomfort, illness, and pain of the animals.

People naturally disagree about the practice of using animals in research. Although many people accept the value of such research (Plous, 1996), a minority of people, including some animal-rights activists, believe that it is ethically wrong to conduct research on animals because animals are living creatures just as humans are, so no harm should be done to them.

Most scientists, however, argue that such beliefs ignore the benefits that can come from animal research (Stangor et al., 2019). For instance, drugs to prevent or treat polio, diabetes, smallpox, cancer, or Alzheimer's disease may first be tested on animals, and surgery that can save human lives may first be practiced on animals. Research on animals has also led to a better understanding of the physiological causes of depression, phobias, and stress, among other illnesses. Many scientists believe that because there are many possible benefits from animal research, such research should continue as long as the animals are treated humanely and ethical principles mentioned above are met. The animal-research debate is complex, not a simple yes-or-no issue. Animal-rights advocacy has improved lab-animal welfare and conditions.

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1.6: Diversity in Biological Psychology

While biological psychology is diverse in the approaches to study the brain, historically the people involved in the research have not been especially diverse. Most early research was done by men of European descent due to social and cultural factors, systemic barriers, and unconscious biases. The field has been getting more diverse in the last decades and many leading labs are headed by women and historically underrepresented minorities. Diversity both across and within labs contributes to better quality science. If everyone has the same background and viewpoint, innovation lags because novel ideas are generated less often and new ideas may be derided and viewed as dissenting. Unique perspectives advance science, and research shows that more diverse groups outperform less diverse groups in many settings (Page, 2008). Diversity in science can be increased with policies and programs that address bias, harassment, mentorship, work-life balance, and educational and training opportunities, so that all have equal opportunity to succeed (Greider et al., 2019; National Academies of Sciences, Engineers, and Medicine, 2023).

Another area lacking diversity in biological psychology is in the research subjects. The vast majority of research subjects in psychology studies (96% by one estimate) are from Western, Educated, Industrialized, Rich, and Democratic ("WEIRD") societies. These WEIRD subjects represent a very narrow slice of humankind, and research findings from them don't necessarily generalize to other populations or serve the goal of understanding *human* psychology (Henrich et al., 2008).

Likewise, most participants in mental health studies, such as those looking at genetic risk in psychiatric disorders, have been of European ancestry. It is unclear how those studies benefit people of differing ethnicities who may have different mental health needs and respond differently to treatments (Gordon, 2018). Research on diverse populations is crucial considering the long-standing disparities in mental health care—individuals from racial and ethnic minority groups, those with lower socioeconomic status, and residents of rural areas, are more likely to receive lower-quality mental health care (Agency for Healthcare Research and Quality, 2016). Funding agencies, including the National Institute of Mental Health (NIMH), are increasingly paying attention to the importance of including people from diverse backgrounds when developing funding mechanisms and reviewing grant proposals, which ultimately shapes the direction of the science.

In sum, biological psychology benefits from researchers and participants with different backgrounds to enrich the quality and creativity of the science, and make the findings and field more relevant and applicable for all.

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2: ANATOMY OF THE NERVOUS SYSTEM

2.1: Visualizing and Navigating the Human Brain
2.2: The Nervous System
2.3: The Peripheral Nervous System
2.4: Cranial Nerves
2.5: The Central Nervous System
2.6: The Brain
2.7: Non-Neuronal Structures in the Central Nervous System
2.8: Meninges and Protection of the Central Nervous System

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2.1: Visualizing and Navigating the Human Brain

Before diving into nervous system organization, we present some important anatomical terms for visualizing and navigating the brain. The brain is a three-dimensional (3-D) structure that can be visualized in two-dimensional (2-D) slices. There are three standard anatomical planes for visualizing the brain: 1) the coronal or frontal plane; 2) the sagittal plane; and 3) the horizontal or axial plane (Figure 1). The coronal or frontal plane is a vertical plane and splits the brain into front and back sections. The sagittal plane is a vertical plane which splits the brain into left and right sections. The horizontal or axial plane is a horizontal plane which splits the brain into upper and lower sections.

Image of slices of the human brain; three possible 2-D cuts through the brain: a coronal or frontal slice (top image), a sagittal slice (middle), and a horizontal slice (bottom), which is also known as a transverse or axial slice.

Figure 1: Slices of the human brain. Three possible 2-D cuts through the brain: a coronal or frontal slice (top image), a sagittal slice (middle), and a transverse, horizontal or axial slice (bottom).

Conventional terms describe locations and directions in the brain and are helpful for navigating around the brain.

- *Anterior* means toward the front of the brain; *Posterior* means toward the back of the brain.
- *Rostral* means toward the front or the “beak”; *Caudal* means toward the tail end.
- *Superior* means toward the top; *Inferior* means toward the bottom.
- *Dorsal* means toward the top or back (think dorsal fin); V*entral* means toward the belly.
- *Medial* means toward the middle; *Lateral* toward the side.
- *Contralateral* means on the opposite (left/right) side; *Ipsilateral* means on the same side.

You’ll hear these terms a lot as you learn about the brain.

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2.2: The Nervous System

The **nervous system** can be thought of as the body's command center and communication network; it processes information, relays sensory input, and coordinates actions by transmitting signals to and from other body parts (Ahmad, 2023). The nervous system is divided into the **central nervous system** (CNS) and the **peripheral nervous system** (PNS) (**Figure 2**). The central nervous system consists of the brain and spinal cord. The peripheral nervous system consists of nerves outside the brain and spinal cord and forms the communication network between the CNS and other body parts. The PNS has several subdivisions that we explore in more detail in the following section.

Figure 2. The human nervous system. The Central Nervous System (CNS), shown in yellow, is made up of the brain and spinal cord. The Peripheral Nervous System (PNS), shown in blue, is made up of nerves that connect the brain and spinal cord to the rest of the body.

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definition

Complex network of nerves and cells that transmit information between the brain and the rest of the body.

×Close definition

The portion of the nervous system that includes the brain and spinal cord.

×Close definition

All of the nerve cells that connect the central nervous system to all the other parts of the body.

×Close definition

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2.3: The Peripheral Nervous System

The **peripheral nervous system** (PNS) connects the central nervous system with the rest of the body. It serves as a communication relay between the CNS and muscles, organs, and glands. The peripheral nervous system includes nerves that are connected to the brain (cranial nerves) and the spinal cord (spinal nerves). Unlike the CNS, the PNS is not protected by the bone of the skull and spine. Nor does it have a barrier between itself and the blood (like the blood-brain barrier), leaving it exposed to toxins and mechanical injuries .

The PNS can be divided into the **autonomic nervous system**, which controls bodily functions without conscious control, and the **somatic nervous system**, which transmits sensory information from the skin, muscles, and sensory organs to the CNS and also sends motor commands from the CNS to the muscles (Figure 3).

Figure 3: Components of the peripheral nervous system.

The Autonomic Nervous System

The autonomic nervous system serves as the relay between the CNS and the internal organs. It controls the lungs, the heart, smooth muscle, and exocrine and endocrine glands. The autonomic nervous system controls these organs largely without conscious control. It can continuously monitor the conditions of these different systems and implement changes as needed. There are two divisions of the autonomic nervous system that often have opposing effects: the **sympathetic nervous system** and the **parasympathetic nervous system**.

The Sympathetic Nervous System. The sympathetic nervous system is responsible for the "fight or flight" response that occurs when an animal encounters a dangerous situation. One way to remember this is to think of the surprise a person feels when encountering a snake ("snake" and "sympathetic" both begin with "s"). Examples of functions controlled by the sympathetic nervous system include an accelerated heart rate and inhibited digestion. These functions help prepare an organism's body for the physical strain required to escape a potentially dangerous situation or to fend off a predator.

The Parasympathetic Nervous System. While the sympathetic nervous system is activated in stressful situations, the parasympathetic nervous system allows an animal to "rest and digest." One way to remember this is to think that during a restful situation like a picnic, the parasympathetic nervous system is in control ("picnic" and "parasympathetic" both start with "p"). The parasympathetic nervous system resets organ function after the sympathetic nervous system is activated (the common adrenaline dump you feel after a 'fight-or-flight' event). Thus the sympathetic and parasympathetic nervous systems work in a push–pull manner (**Figure 4**). Examples of functions controlled by the parasympathetic nervous system include slowing of heart rate, lowered blood pressure, and stimulation of digestion.

Diagram of the sympathetic and parasympathetic nervous systems.

Figure 4. The sympathetic and parasympathetic nervous systems often have opposing effects on target organs.

The Somatic Nervous System

The somatic nervous system manages external interactions: sensing the environment via sensory neurons and sending commands to skeletal muscles via motor neurons. It often governs voluntary behaviors initiated by complex brain processes. For example, you hear your name, interpret the speech, and turn your head towards the sound.

The somatic nervous system is made up of cranial and spinal nerves and contains both sensory and motor neurons. Sensory neurons transmit sensory information from the skin, skeletal muscle, and sensory organs to the CNS. Motor neurons transmit messages about desired movement from the CNS to skeletal muscles to make them contract. Without a somatic nervous system, an animal would be unable to process any information about its environment (what it sees, feels, hears, etc.) and could not control motor movements.

Cranial nerves. Humans have 12 cranial nerves; these nerves emerge from the skull (cranium), as opposed to the spinal nerves, which emerge from the vertebral column. Each cranial nerve is accorded a name, as shown in **Figure 5**. Some cranial nerves transmit only sensory information. For example, the olfactory nerve transmits information about smells from the nose to olfactory

regions in the brain. Other cranial nerves transmit almost solely motor information. For example, the oculomotor nerve controls the opening and closing of the eyelid and some eye movements. Other cranial nerves contain a mix of sensory and motor fibers. For example, the glossopharyngeal nerve has a role in both taste (sensory) and swallowing (motor).

Illustration shows the underside of the brain. The twelve cranial nerves cluster around the brain stem, and are symmetrically located on each side. The olfactory nerve is short and lobe-like, and is located closest to the front. Directly behind this is the optic nerve, then the oculomotor nerve. All these nerves are located in front of the brain stem. The trigeminal nerve, which is the thickest, is located on either side of the brain stem. It forms three branches shortly after leaving the brain. The trochlear nerve is a small nerve in front of the trigeminal nerve. Behind the brain stem are the smaller facial, vestibulocochlear, glossopharyngeal and hypoglossal nerves. The nerve furthest back is the accessory nerve.

Figure 5. Inferior view (from below) of the human brain showing the 12 cranial nerves in orange. Cranial nerves receive sensory input and control motor output for the head and neck.

Spinal nerves. Spinal nerves transmit sensory and motor information between the spinal cord and the rest of the body. Each of the 31 spinal nerves in humans contains both sensory and motor axons. The sensory neuron cell bodies are grouped in structures called dorsal root ganglia (dorsal = toward back) (**Figure 6**). Each sensory neuron projects from a sensory receptor in skin, muscle, or sensory organs to a synapse with a neuron in the dorsal spinal cord. Motor neurons have cell bodies in the ventral gray matter of the spinal cord that project to muscle through the ventral root (ventral = toward belly). These neurons are usually stimulated by interneurons within the spinal cord but are sometimes directly stimulated by sensory neurons (as in a reflex arc). Each spinal nerve corresponds to different body regions—for example, spinal nerves that exit near the top of the spine correspond to the shoulders and arms, whereas spinal nerves that exit near the bottom of the spine correspond to legs and feet (**Figure 7**).

Illustration shows a cross section of the spinal cord. The gray matter forms an X inside the white matter. A spinal nerve extends from the left arm of the X, and another extends from the left leg of the X. The two nerves join together to the left of the spine. The right arm and leg of the X form a symmetrical nerve. The part of the nerve that exits from the leg of the X is called the ventral root, and the part that exists from the arm of the X is called the dorsal root. The ventral root is on the belly side, and the dorsal root is on the back side. The dorsal root ganglion is a bulge halfway between where the nerve leaves the spine and where the dorsal and ventral roots join. Sensory neuron somas cluster in the dorsal root. Motor neuron somas cluster in the gray matter in the leg of the X. Motor neuron axons are bundled in the ventral root.

Figure 6. Spinal nerves contain both sensory and motor axons. The somas (cell bodies) of sensory neurons are located in dorsal root ganglia. The somas of motor neurons are found in the ventral portion of the gray matter of the spinal cord.

Figure 7. Spinal nerves exit the spinal cord through notches in the vertebrae. This figure illustrates the spinal cord segments in the vertebral column (cervical, thoracic, lumbar, sacral), and how each spinal nerve relates to different regions of the body.

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definition

All of the nerve cells that connect the central nervous system to all the other parts of the body.

×Close definition

A part of the peripheral nervous system that connects to glands and smooth muscles. Consists of sympathetic and parasympathetic divisions.

×Close definition

A part of the peripheral nervous system that uses cranial and spinal nerves in volitional actions.

×Close definition

A division of the autonomic nervous system, that is faster than its counterpart that is the parasympathetic nervous system and works in opposition to it. Generally engaged in “fight or flight” functions.

×Close definition

A division of the autonomic nervous system that is slower than its counterpart—that is, the sympathetic nervous system—and works in opposition to it. Generally engaged in “rest and digest” functions.

×Close definition

A set of 12 paired nerves that emerge directly from the brain and relay information between the brain and parts of the body; primarily to the head and neck regions.

×Close definition

Mixed nerves that carry sensory and motor information between the spinal cord and rest of the body.

×Close definition

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2.4: Cranial Nerves

Cranial Nerves

Cranial nerves (Figure 2.4.3) are in the head and neck and connect directly to the brainstem. There are twelve cranial nerves, which are designated CN I through CN XII (the "CN" stands for “Cranial Nerve”) using the Roman numerals for 1 through 12, based on their anatomical location on the inferior view of the brain, from anterior to posterior. Sensory cranial nerves sense smells, tastes, light, sounds, and body position and sensations. Motor cranial nerves control muscles of the face, tongue, eyeballs, throat, head, and shoulders. The motor nerves also control the salivary glands and swallowing. Four of the 12 cranial nerves participate in both sensory and motor functions as mixed nerves, having both sensory and motor functions. See Table 2.4.1 for a brief summary of the functions of each cranial nerve.

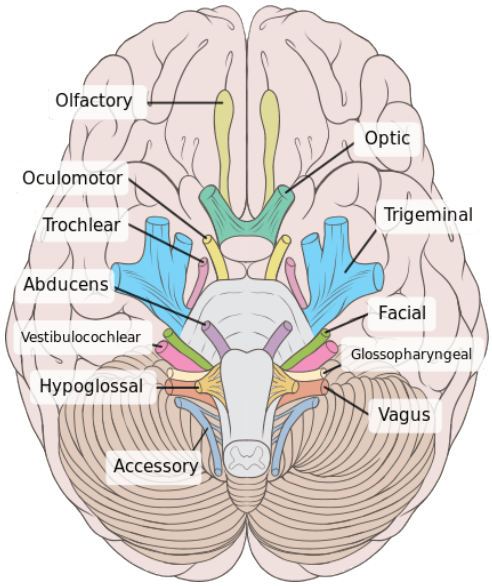


Figure 2.4.3: The twelve pairs of cranial nerves are located on the inferior aspect of the human brain.

Table 2.4.1: Cranial Nerves

Mnemonic	#	Name	Function (Sensory/Motor/Both)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
On	I	Olfactory	Smell (S)	Olfactory bulb	Olfactory epithelium
Old	II	Optic	Vision (S)	Hypothalamus/ thalamus/ midbrain	Retina (retinal ganglion cells)
Olympus’	III	Oculomotor	Eye movements; lens and pupil movements (M)	Oculomotor nucleus	Four of the extraocular muscles; levator palpebrae superioris; ciliary ganglion (autonomic)
Towering	IV	Trochlear	Eye movements (M)	Trochlear nucleus	Superior oblique muscle (eyeball)
Tops	V	Trigeminal	Sensory/ motor – face (B)	Trigeminal nuclei in the midbrain, pons, and medulla	Trigeminal
A	VI	Abducens	Eye movements (M)	Abducens nucleus	Lateral rectus muscle (eyeball)

Mnemonic	#	Name	Function (Sensory/Motor/Both)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
Finn	VII	Facial	Motor – face; Taste (B)	Facial nucleus, solitary nucleus, superior salivatory nucleus	Facial muscles; Geniculate ganglion; Pterygopalatine ganglion (autonomic)
And	VIII	Auditory (Vestibulocochlear)	Hearing/ balance (S)	Cochlear nucleus, Vestibular nucleus/ cerebellum	Spiral ganglion (hearing); Vestibular ganglion (balance)
German	IX	Glossopharyngeal	Motor – throat; Taste (B)	Solitary nucleus, inferior salivatory nucleus, nucleus ambiguus	Pharyngeal muscles; Geniculate ganglion; Otic ganglion (autonomic)
Viewed	X	Vagus	Motor/ sensory – viscera (autonomic) (B)	Medulla	Terminal ganglia serving thoracic and upper abdominal organs (heart and small intestines)
Some	XI	(Spinal) Accessory	Motor – head and neck (M)	Spinal accessory nucleus	Neck muscles
Hops	XII	Hypoglossal	Motor – lower throat (M)	Hypoglossal nucleus	Muscles of the larynx and lower pharynx

Attributions

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2.5: The Central Nervous System

The **central nervous system** is made up of the brain and spinal cord. The brain and spinal cord are enclosed in three layers of protective coverings called meninges (from the Greek word for membrane) **(Figure 8**). The outermost layer is the dura mater (Latin for “hard mother”)—a thick layer that protects the brain and spinal cord and contains large blood vessels. The middle layer is the web-like arachnoid mater. The innermost layer is the pia mater (Latin for “soft mother”), which directly contacts and covers the brain and spinal cord like plastic wrap. The subarachnoid space between the arachnoid and pia maters is filled with cerebrospinal fluid (CSF), a fluid that helps cushion and protect the brain and spinal cord. We examine CSF more in the next section on The Brain.

Figure 8. The cerebral cortex is covered by three layers of meninges: the dura, arachnoid, and pia maters (Credit: modification of work by Gray’s Anatomy). The cerebral cortex © OpenStax is licensed under a CC BY-NC-SA (Attribution NonCommercial ShareAlike) license

The Spinal Cord

The spinal cord is the major bundle of nervous tissues that extends from the brainstem down the backbone to the lumbar region of the spine. The spinal cord transmits information from the skin, muscles, and internal organs to the brain, and vice versa. Information that travels from the bodily periphery *toward* the brain (or deeper centrally within the brain) is called an **afferent** signal. Information that travels *away* from the brain, such as a motor command to a muscle, is called an **efferent** signal.

In addition to sending information to and from the brain, the spinal cord controls some simple reflexive movements like removing your hand from a hot object and the knee reflex. These reflexive movements are very fast because the sensory signal is processed and the motor command is initiated directly in the spinal cord. Processing in the spinal cord avoids the time-consuming signal transmission to and from the brain, saving hundreds of milliseconds to protect our tissue from damage.

The spinal cord also houses central pattern generators that control some simple rhythmic movements such as walking. Experiments with cats have shown that even after severing the spinal cord (thereby cutting off motor commands from the brain), cats can still produce relatively normal walking on a treadmill (Duysens & Van de Crommert, 1998).

The spinal cord is protected by the bony vertebrae in the backbone and cushioned by cerebrospinal fluid. However spinal cord injuries still can occur and are very serious. In the United States, around 10,000 spinal cord injuries occur each year. Because the spinal cord is the information superhighway connecting the brain with the body, damage to the spinal cord can lead to paralysis. The extent of the paralysis depends on the location of the injury along the spinal cord and whether the spinal cord was completely severed. For example, if the spinal cord is damaged at the level of the neck, it can cause paralysis from the neck down, whereas damage further down the spinal column may limit paralysis to the legs. Spinal cord injuries are notoriously difficult to treat because spinal nerves do not regenerate, although ongoing research suggests that stem-cell transplants may be able to act as a bridge to reconnect severed nerves.

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definition

The portion of the nervous system that includes the brain and spinal cord.

×Close definition

Signals that travel from the periphery *toward* the central nervous system and brain, or travel deeper centrally within the brain

×Close definition

Signals that travel away from the central nervous system or brain to the periphery, such as motor command

×Close definition

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2.6: The Brain

The brain is the most complex part of the human body, consisting of 86 billion neurons, each of which may connect with 1000s of other neurons. It is the center of higher-order processes like planning, memory, problem solving, and consciousness, and coordinates voluntary and involuntary movements and bodily functions. This section provides an introductory overview of the brain and some basic neuroanatomy.

The mammalian brain can be subdivided in many ways, resulting in some inconsistent and ambiguous naming conventions over the history of neuroanatomy (Swanson, 2000). One way to think about brain organization reflects brain development in the embryo. The human nervous system starts as a simple neural tube, and 3-4 weeks after conception, the tube expands into three primary vesicles—the forebrain, midbrain, and hindbrain. After a few more weeks, these primary vesicles give rise to secondary vesicles that eventually develop into the components of the adult nervous system (more detail on brain development in Chapter 7). As seen in **Figure 9**, the forebrain vesicle develops into a) the **cerebrum**, which includes the cerebral cortex (frontal, temporal, parietal, and occipital lobes) and underlying **subcortical** structures (e.g., the hippocampus, amygdala, and basal ganglia), and b) the **diencephalon**, which includes the thalamus and hypothalamus. The midbrain primary vesicle develops into part of the brainstem, including the superior and inferior colliculi. The hindbrain develops into the cerebellum and other brainstem regions including the pons and medulla oblongata. We introduce these brain structures in the section below.

Figure 9: The central nervous system and its various major subdivisions.

Cerebral Cortex

The **cerebral cortex** is a thin sheet of neurons that makes up the outermost layer of the **cerebral hemispheres**. The term **cortex,** derived from the Latin for “bark,” refers to a thin sheet of neurons; in contrast, the term **nucleus** (plural: nuclei) in neuroanatomy refers to a cluster of neurons. The cerebral cortex is made up of **gray matter**, a type of tissue named for its color that consists largely of neuronal cell bodies and short-range connections. Conversely, **white matter** tissue consists largely of axons covered in myelin, a fatty white substance that insulates axons to speed the transmission of neural signals. White-matter fiber tracts underlie the gray matter of the cerebral cortex and send signals to more distant brain regions (**Figure 10**).

Figure 10. Coronal tissue slice from the brain of a macaque monkey. The gray matter of the cerebral cortex is the outer layer depicted in dark violet. The underlying white matter fiber tracts are shown in lighter color.

The cerebral cortex ‘bark’ is only 2-4 mm across, but most cortex consists of 6 layers. Each layer has characteristic cell types and connectivity—the innermost layers 5 and 6 send signals out of cortex, layer 4 receives input from the thalamus, layers 2 and 3 project to nearby regions within cortex, and layer 1 has very few cell bodies and mostly contains the tips of dendrites and axons (Hall, 2023).

The thin cortex has a surprisingly large surface area—the human cortex is about 1800 cm^2, making the cortex in each hemisphere about the size of medium thin-crust pizza (minus the sauce, cheese, and toppings) (Van Essen et al., 2018) (**Figure 11**). This large surface area fits into the small volume of the cranium, because the human cortex is extensively folded (most other animals including small mammals have a smooth cortex). Folding maximizes the surface-to-volume ratio, and improves packaging and communication efficiency (Shipp, 2007).

Hybrid picture of a brain and peperoni pizza

Figure 11. The thin outermost layer of each cerebral hemisphere, the cerebral cortex, is about the size of a medium thin-crust pizza–minus the sauce, cheese, and toppings.

The folding of the cortex also gives the brain its bumpy appearance. The bumps are called **gyri** (singular: **gyrus**) and the valleys between gyri are called **sulci** (singular: **sulcus**). Larger and deeper sulci are called **fissures**. Major gyri, sulci, and fissures are used as landmarks to separate the cortex into its major regions, including the frontal, temporal, parietal, and occipital lobes (**Figure 12**). The **central sulcus** marks the border between the frontal and parietal lobes. The **lateral sulcus** (also called the Sylvian fissure), separates the temporal lobe from the frontal and parietal lobes. The occipital lobe has no obvious anatomical border on the outer surface of the brain. However, from the medial (inner) surface, an obvious landmark, the **parieto-occipital sulcus**, separates the parietal and occipital lobes.

Figure 12: The lobes of the brain and the major sulci that mark the borders. The central sulcus separates the frontal and parietal lobes. The lateral sulcus marks the upper border of the temporal lobe. And the parieto-occipital sulcus (which is more clearly seen on the medial surface) separates the parietal and occipital lobes.

Another prominent landmark, the **longitudinal fissure**, runs down the brain's midline and separates the left and right cerebral hemispheres. The two cerebral hemispheres are connected to each other via the **corpus callosum**, a large white matter tract that passes information between hemispheres. The left and right hemispheres are structurally symmetrical and often have overlapping and redundant functions, but there is some **lateralization** of function, where some brain functions are processed more in one hemisphere than the other. For example, touch signals and motor commands for each side of the body are processed in the contralateral (opposite) side of the brain, and language for most people is processed more in the left hemisphere.

Finally, smaller subregions of the cerebral cortex are associated with particular functions, a concept known as **localization of function**. In the early 1900s, a German neuroscientist named Korbinian Brodmann extensively studied the microscopic anatomy, or **cytoarchitecture**, of the cerebral cortex and divided the cortex into 52 separate regions based on the microscopic tissue structure. These "Brodmann areas" are still used today to describe anatomical regions within the cortex (**Figure 13)**. Brodmann's anatomical maps align well with the particular functions within the cortex. For example, Brodmann area 4 (as defined based on the microscopic tissue structure) aligns with the primary motor cortex that sends motor commands to the spinal cord.[1]

Figure 13. Brodmann's maps from 1909 that he built based on the cytoarchitecture or microscopic tissue structure and organization. Several important Brodmann areas are shown on the brain's lateral surface (left) and the medial surface (right).

Frontal Lobe

The **frontal lobe**, located in the front of the brain (where else?), is involved in planning and implementing movement, as well as higher-order cognitive processes such as attention, language, reasoning, problem solving, and abstract thought. The frontal lobe is made up of subregions that perform specialized functions. At the back of the frontal lobe is the precentral gyrus (the *gyrus* or bump directly *pre-* or anterior to the *central* sulcus); this region is the primary motor cortex, which contains neurons that send commands to the spinal cord to move skeletal muscles. Areas within the primary motor cortex map to different muscle groups in an ordered manner (**Figure 14**). Body parts that require especially fine motor control, like the fingers, lips, and tongue, occupy more "neural real estate" on the motor cortex than, say, the shoulder or trunk. Anterior to the primary motor cortex are other areas associated with movement, including the premotor area (involved in movement planning) and the frontal eye fields (involved in eliciting eye movements and visual attention).

image of the brain central sulcus

Figure 14. The primary motor cortex on the precentral gyrus is directly anterior to the central sulcus. It is organized so certain areas of the motor strip send signals to specific body parts like the tongue or fingers.

Anterior to the motor and premotor cortex is the prefrontal cortex (PFC), which is involved in many cognitive and executive functions (**Figure 15**). In the inferior prefrontal cortex (usually left lateralized) lies Broca's area (**Figure 16**), a region involved in language production. Broca's area is named after a French physician, Paul Broca, who in 1861, documented that damage here impaired speech production. Other major subregions of the prefrontal cortex include the dorsolateral PFC (dorsal=upper, lateral=outer) involved in working memory, planning, inhibiting responses, and cognitive flexibility, and the orbitofrontal cortex at the very front (by the orbits of the eye), which is involved in complex decision making, encoding value, emotion, sociality, and predicting the consequences of our actions (Rudebeck & Rich, 2018).

In general, more anterior regions in the brain and within the frontal lobe are roughly associated with 'higher' cognitive function, such as rule learning at higher levels of abstraction. High-level abstract thought, executive function (such as maintaining goal-directed behavior), language, and navigating complex social contexts are crucial for what we consider "human" cognition. Indeed, the corresponding prefrontal regions are disproportionately large in humans and have expanded or reorganized in humans compared to other species, especially compared to species more distant on the evolutionary tree (Van Essen et al., 2018)

Humans with frontal lobe damage can have a variety of impairments depending on the location and extent of the damage. These impairments include changes in personality, cognition, learning, decision making, risk assessment, behavioral inhibition, and social function.[2]

lateral view of the front part of the brain showing the prefrontal cortex and subregions. Details in text and caption.

Figure 15. Prefrontal cortex in blue-ish colors. Subregions include: Broca's area marked by its Brodmann areas (BA) numbers 44 and 45; the dorsolateral prefrontal cortex [BA 9 and 46], and the orbitofrontal cortex [BA 10 and 11].

Temporal Lobe

The **temporal lobe** is located in the lateral portion of each hemisphere under the temples (hence "temporal"). It is involved in processing auditory information, understanding language, recognizing visual objects, and memory. The auditory cortex, which processes auditory information, is located in the superior temporal lobe. In the posterior part of the superior temporal lobe lies **Wernicke's area**, a region involved in language comprehension. Wernicke's area connects to the frontal Broca's area (involved in language production) through a white-matter fiber tract called the **arcuate fasciculus**, **(Figure 16**).

In addition to processing sound and language, the temporal lobe is critical for visual object recognition and memory. The ventral (bottom) surface of the temporal lobe receives visual signals from the visual cortex. It contains subregions specialized to perceive and recognize faces (the fusiform face area) and places and scenes (the parahippocampal place area). Damage to these regions, from a stroke for example, can impair specific abilities; inferior temporal lobe lesions may lead to prosopagnosia, the inability to recognize and identify faces (Kanwisher & Yovel, 2008). Finally, the medial temporal lobes are important for encoding long-term memory.[3]

Image of the Wernicke's area

Figure 16. Broca's area in the left frontal gyrus; Wernicke's area in the superior temporal gyrus; and the arcuate fasciculus, a white matter tract that connects the caudal temporal cortex with the inferior frontal lobe.

Parietal Lobe

The **parietal lobe**, located above the temporal lobe and behind the frontal lobe, processes touch, bodily and spatial maps, and integrates senses. The postcentral gyrus (directly behind the central sulcus) houses the **primary somatosensory cortex (S1)**. This region processes the tactile senses, including touch, pressure, pain, itch, and vibration, as well as more general bodily senses of proprioception (body position) and kinesthesia (movement sense). The somatosensory cortex is organized topographically: adjacent skin areas are represented by adjacent cortical regions. Sensitive body parts have more nerve receptors on the skin and occupy larger cortical areas than less sensitive parts. For example as seen in **Figure 17**, the highly sensitive fingers and lips occupy much more somatosensory cortex than the leg and trunk.

Figure 17. A coronal brain slice showing the somatosensory cortex and its topographic organization. More sensitive body parts, like the face and hands, are processed by larger regions of the somatosensory cortex, compared to less sensitive regions like the leg and trunk.

While the anterior parietal cortex processes body senses, the posterior parietal cortex is an "associative" region, meaning it is neither strictly sensory nor motor. Rather it integrates inputs from touch, proprioception, vision, audition, as well as from motor and prefrontal regions (Whitlock, 2017). This integration is crucial for making spatial maps that guide attention and movement. In order to grasp an object, that object's location must be translated from its retinotopic coordinates (i.e., where it lands on the retina) into coordinates in space; this translation depends on the direction the eyes and head are pointed. Parietal maps of the locations of body parts and objects in space are critical for planning and executing movements to manipulate objects. These spatial maps output to frontal motor regions for planning body movement and to the frontal eye fields for directing eye movements and attention.

Damage to the posterior parietal lobe can impair visually guided reaching movements and spatial perception (Karnath, 1997). In light of its role in attention and awareness, damage here can also lead to a condition called **hemispatial neglect**, wherein a patient loses awareness of one side of space. For example, a stroke in the right posterior parietal lobe can lead to the inability to perceive the left visual field, causing the patient to act as if the left side of space doesn't exist (they might ignore food on the left side of their plate, or when asked to copy a picture, they might only draw the right half). Ultimately, the parietal lobe is critical for processing and integrating sensory information and transmitting this information to brain areas that control attention and movement.[4]

Occipital Lobe

The **occipital lobe**, located at the back of the brain, contains the visual cortex that processes visual information. Visual input from the eyes travels along the optic nerves to the **lateral geniculate nucleus (LGN)** in the thalamus, and continues to the visual cortex. Visual input enters the cortex at the most posterior portion of the occipital lobe—the primary visual cortex (V1). V1 (and other regions in the visual system) is organized retinotopically, meaning that adjacent regions of the retina (and visual field) are represented by adjacent parts of visual cortex. From V1, visual signals are sent to different brain regions (in the visual cortex and beyond) that specialize in processing different image features such as color, edges, orientation, texture, and movement. Visual regions are highly interconnected and recurrent, sending feedforward signals "up" the processing hierarchy, as well as feedback signals "back down" the processing chain (Van Essen et al., 1992). There are two main visual processing pathways—the lower ventral or "what" pathway proceeds to the inferior temporal lobe for object recognition, and the upper dorsal or "where" pathway proceeds to parietal regions for mapping object location, especially for eye or hand movements.[5]

Insula

The **insula** is part of the cerebral cortex tucked deep into the lateral sulcus. It lies underneath parts of the frontal, temporal, and parietal lobes (**Figure 18**). It is sometimes called the insular lobe, a fifth lobe of the cerebral cortex, but it remains less understood than the four cortical lobes visible on the brain's surface. The insula has been implicated in a dizzying array of functions, including sensory processing (e.g., taste and interoceptive processing of bodily states like hunger, pain, and arousal), representing emotions, motor control, self-awareness, empathy, risk prediction, cognitive functioning, consciousness, etc. (Gogolla, 2017). The insula's diverse functions and extensive connectivity to other brain regions highlight its role as a hub linking large-scale brain systems. The insula is thought to be involved in many psychological and neurological conditions including anxiety and depressive disorders, emotion dysregulation, autism spectrum disorders, and addiction. While the insula is considered one of the least understood cortical structures, a surge of recent research interest is making headway (Gogolla, 2017; Kortz & Lillehei, 2023).

Figure 18. Anatomical illustration of the right insula from the 1908 edition of Sobotta's Anatomy Atlas. The insula is exposed here by removing portions of the overlying frontal, parietal, and temporal regions (these overlying areas are termed the "operculum").

Limbic System

The **limbic system** is a collection of highly specialized neural structures, both subcortical and cortical, that sit at the top of the brainstem (**Figure 19**). The limbic system was originally defined by Paul Broca (1880) as a series of structures near the border between the brainstem and the cerebral hemispheres ("limbus" is Latin for border). The limbic system is involved in many functions including memory, emotion, behavior, motivation, and olfaction. Given advances in neuroscience, the definition of which structures are included in the limbic system has gone through many iterations (Torrico & Abdijadid, 2019). Major components of the limbic system include the **hippocampus**, the **amygdala**, and the **cingulate cortex**.

Figure 19: A midsagittal plane showing the interior of the brain and the locations of several limbic-system structures, including the hippocampus, amygdala, and cingulate cortex.

Hippocampus. The hippocampus is a seahorse-shaped structure involved in memory, learning, and spatial processing (**Figures 19 and 20**). The hippocampus is richly connected to many cortical and subcortical regions. During learning, the connection strengths of hippocampal neurons change, and those changes are important for particular aspects of memory, particularly the ability to remember more of an event or stimulus when exposed to only part of it (pattern completion), and to remember events or stimuli as distinct from each other (pattern separation). Damage to the hippocampus produces memory deficits. Hippocampus damage occurs early in Alzheimer's disease, and extensive damage can lead to anterograde amnesia (the inability to form new memories). The hippocampus is also important for spatial navigation. As discovered in rats and mice, many neurons in the hippocampus respond as "place cells," meaning that they fire bursts of action potentials when the animal passes through a specific place in its environment.

Figure 20. Location of the hippocampus in red.

Amygdala. The amygdala, named for its almond shape, lies next to the hippocampus beneath the cerebral cortex (**Figure 19**). It processes emotions, generating responses like fear, anxiety, and aggression, and facilitates emotional learning such as fear conditioning.

The amygdala receives input from sensory and prefrontal cortex, hippocampus, and brainstem, allowing it to integrate situational, contextual, memory, and bodily information. The amygdala sends output signals to regions throughout the brain, including the frontal lobes, hippocampus, basal ganglia, thalamus, and hypothalamus. This connectivity allows it to produce emotional responses appropriate to a given situation. For example, a punishment-associated stimulus can trigger a fear response by altering hormone release via the hypothalamus, triggering freezing behaviors, and activating the sympathetic nervous system via the brainstem. Amygdala damage can lead to reduced emotional behavior ("flat affect") and impaired learning about emotional or frightening stimuli.[6]

Basal Ganglia

The **basal ganglia** **(Figure 21)** are a group of subcortical nuclei (i.e., clusters of cell bodies that lie below the cerebral cortex) that are critical for regulating and selecting voluntary movement. In particular, the basal ganglia are traditionally defined as the **caudate nucleus**, **putamen**, and **globus pallidus**, but are known to rely on engagement with related nuclei, such as the **subthalamic nucleus** and **substantia nigra,** to initiate voluntary movement (Lanciego et al., 2012).

Information flows from widespread areas of the cerebral cortex, through the basal ganglia and thalamus, and back to the cerebral cortex.

These cortico-basal ganglia-thalamo-cortical loops are crucial for selecting motor actions, initiating and stopping behaviors, and aspects of motivated behavior, including action selection based on potential outcomes. The loops include excitatory and inhibitory pathways, the balance of which is important for initiating or inhibiting motor outputs. Disruptions to this circuitry can cause an imbalance between these excitatory and inhibitory effects, as is seen in a number of neurological conditions including Parkinson's disease and Huntington's disease, as well as schizophrenia, Tourette's syndrome, obsessive-compulsive disorder, and addiction.[7]

Image of the Basal Ganglia and related structures

Figure 21: Basal Ganglia and related structures.

Thalamus

The **thalamus** is an information hub that relays information from and to widespread brain areas (**Figure 22A)**. Nerve fibers project from the thalamus to the cerebral cortex in all directions, allowing it to act as an information hub. The thalamus is organized into specialized regions or nuclei that process specific modalities. All sensory systems, except smell, have a thalamic nucleus that receives sensory signals and sends them to their primary cortical areas. For example, the lateral geniculate nucleus of the thalamus receives visual information from the eye via the optic nerve and sends projections to primary visual cortex (**Figure 22B**); the medial geniculate nucleus receives auditory information from the ear via the inferior colliculus and projects to auditory cortex. Thalamic nuclei don't just relay information "upward" (to cortex), they also receive "descending" input from cortex, forming circuits termed thalamo-cortical loops.

Thalamocortical loops are not limited to sensory processing, but also play important roles in memory, attention, motor control, and decision making. These loops demonstrate that the 'input-computation-output' function of the nervous system is not simply in one direction. Instead, outputs from a given region often feed back to structures that provide inputs to that region, as well as sending outputs to 'upstream' brain areas. Finally, because of its role as informational/sensory hub, the thalamus plays a role in transitioning between sleep and wakefulness, as well as modulating alertness and attention (Portas et al., 1998).[8]

rotating image showing the location of the thalamus in red.

Figure 22A. Location of the thalamus in red.

Diagram of the visual pathway from the eyes through the thalamus to the visual cortex.

Figure 22B. Visual pathway from the eyes through the thalamus to the visual cortex. Visual information is sent from the retinas at the back of the eyeballs, along the optic nerve to the lateral geniculate nucleus (LGN) of the thalamus, then to the primary visual cortex. Blue color represents the path of information from the left visual field; red from the right visual field.

Hypothalamus

The **hypothalamus** is located below the thalamus (hence its name) and is primarily responsible for regulating endocrine hormones in conjunction with the **pituitary gland** that extends from the hypothalamus (**Figure 17**). Endocrine hormones are important for controlling mood, development, growth, and reproduction. Given its central location in the brain, the hypothalamus connects to the brainstem, cerebral cortex, hippocampus, amygdala, and thalamus (Bear et al., 2018). As a result, the hypothalamus, both by trafficking sensory and motor information and secreting endocrine hormones across different brain regions, is well-positioned to regulate drives and motivations.

Cerebellum

The **cerebellum** (Latin for "little brain") is the distinctive structure at the back of the brain (Beck & Tapia, 2023). In **Figure 23,** you can see the cerebellar white matter (arbor vitae) and the cerebellum's tightly folded surface. The cerebellum is critical for coordinated movement and posture. It does not initiate motor commands, but contributes to movement precision, timing, and fine-tuning (based on sensory feedback), as well as motor learning. In addition to the cerebellum's role in motor control, neuroimaging studies have implicated it in many cognitive functions, including language and attention. The cerebellum's influence beyond movement aligns with its anatomy: it contains ~80% of the brain's neurons (most of its neurons are tiny and densely packed granule cells, van Essen et al., 2018) and largely maps to cerebral brain networks involved in cognition (Buckner, 2013).[9]

Figure 23. Image shows the location of the cerebellum at the bottom of the brain. Illustrated in white on the medial view are the cerebellar white matter tracts, the arbor vitae (their name stems from their branching, tree-like structure). On the lateral view, you can see the cerebellum's tightly folded surface.

Brainstem

The brainstem (or brain stem) is sometimes referred to as the "trunk" of the brain (Beck & Tapia, 2023). It contains many white matter tracts carrying information to and from the spinal cord, cranial nerves, and the rest of the brain. The brainstem is responsible for many neural functions that keep us alive, including regulating breathing, heart rate, and digestion. In keeping with its function, if a patient sustains severe damage to the brainstem they will often require life-support machines to keep them alive. The brainstem can be divided into multiple sections in descending order: midbrain, pons, and medulla oblongata (Figure 24). At the top of the brainstem is the midbrain, which houses dopamine-producing cells, regulates movement, and includes the superior and inferior colliculi, which process and relay visual and auditory information, respectively. Below the midbrain lies the pons which processes and relays sensory and motor information. By employing the cranial nerves, the pons serves as a bridge that connects the cerebral cortex with the medulla and exchanges information between the brain and the spinal cord. The lowest portion of the brainstem, the medulla oblongata, processes breathing, digestion, heart and blood vessel function, swallowing, and sneezing. Collectively, these regions are involved in body regulation, the sleep–wake cycle, and sensory and motor function.[10]

Image of the brainstem and its component substructures

Figure 24. Brainstem and its component substructures, in descending order: the midbrain, pons, and medulla.

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10. This section contains material adapted from: Beck, D. & Tapia, E. (2024). The brain. In R. Biswas-Diener & E. Diener (Eds), Noba textbook series: Psychology. Access for free at http://noba.to/jx7268sd License: CC BY-NC-SA 4.0 DEED 2.06: The Brain#return-footnote-90-10

definition

Usually refers to the cerebral cortex and associated white matter, but in some texts includes the subcortical structures.

×Close definition

Structures that lie beneath the cerebral cortex, but above the brainstem.

×Close definition

Neural structure located deep in the brain that includes the thalamus and hypothalamus. Connects the midbrain to the forebrain.

×Close definition

The outermost layer of gray matter of the cerebral hemispheres.

×Close definition

The cerebral cortex, underlying white matter, and subcortical structures.

×Close definition

In neuroanatomy, cortex refers to a thin sheet of neurons

×Close definition

(plural: nuclei)
In neuroanatomy, nucleus or nuclei refers to a cluster of neurons.

Collection of nerve cells found in the brain which typically serve a specific function.

×Close definition

Composes the bark or the cortex of the cerebrum and consists of the cell bodies of the neurons (see also white matter).

×Close definition

Regions of the nervous system that represent the axons of the nerve cells; whitish in color because of myelination of the nerve cells.

×Close definition

(plural) Folds between sulci in the cortex.

×Close definition

(plural: gyri)
A fold between sulci in the cortex.

×Close definition

(plural) Grooves separating folds of the cortex.

×Close definition

(plural: sulci)
A groove separating folds of the cortex.

×Close definition
×Close definition

The major fissure that divides the frontal and the parietal lobes.

×Close definition

The major fissure that delineates the temporal lobe below the frontal and the parietal lobes.

×Close definition

Deep sulcus that divides the parietal lobe from the occipital lobe.

×Close definition

Deep groove that separates the two cerebral hemispheres of the brain.

×Close definition

Primary bundle of white matter tracts that connect the left and right cerebral hemispheres.

×Close definition

Refers to the idea that specific functions may reside primarily in one hemisphere or the other (e.g., for the majority of individuals, the left hemisphere is most responsible for language).

×Close definition

Different brain functions are processed in or localized to specific brain areas

×Close definition

The study of the cellular composition of the central nervous system's tissues, with a focus on the arrangement, structure, and function of cells.

×Close definition

The front most (anterior) part of the cerebrum; anterior to the central sulcus and responsible for motor output and planning, language, judgment, and decision-making.

×Close definition

The part of the cerebrum in front of (anterior to) the occipital lobe and below the lateral fissure; involved in vision, auditory processing, memory, and integrating vision and audition.

×Close definition

A language area in the temporal lobe where linguistic information is comprehended (Also see Broca's area).

×Close definition

A fiber tract that connects Wernicke's and Broca's areas

×Close definition

The part of the cerebrum between the frontal and occipital lobes; involved in bodily sensations, visual attention, and integrating the senses.

×Close definition

Located on the postcentral gyrus of the parietal lobe; primarily responsible for processing sensory information from the body.

×Close definition

Neuropsychological condition in which damage to the parietal lobe impairs attention and awareness of one side of space. Damage to the left hemisphere would lead to neglect of the right visual field.

×Close definition

The back most (posterior) part of the cerebrum; involved in vision.

×Close definition

(or LGN) A nucleus in the thalamus that is innervated by the optic nerves and sends signals to the visual cortex in the occipital lobe.

×Close definition

Region in the cerebral cortex tucked deep into the lateral sulcus. The insula is Involved in many functions and serves as a hub that links large-scale brain systems.

×Close definition

Involved in learning and emotion. Includes the subcortical structures of the amygdala and hippocampal formation as well as some cortical structures, such as the cingulate cortex. Responsible for aversion and gratification.

×Close definition

(plural form, hippocampi)
A nucleus inside (medial) the temporal lobe implicated in learning and memory.

×Close definition

Almond-shaped neural structure that is primarily responsible for regulating emotional responses, especially fear.

×Close definition

A medial cortical brain region that is a part of the limbic system and is Involved in emotion, motivation, learning, and memory.

×Close definition

Subcortical structures of the cerebral hemispheres involved in voluntary movement.

×Close definition

A “C” shaped subcortical structure located near the thalamus that contributes to the formation of the basal ganglia. There is a caudate nucleus located in each cerebral hemisphere.

×Close definition

A subcortical structure that contributes to the formation of the basal ganglia. Involved in learning and motor control.

×Close definition

A nucleus of the basal ganglia.

×Close definition

A small lens-shaped nucleus located within the diencephalon. Interacts with the basal ganglia to facilitate motor regulation.

×Close definition

Involved in transferring chemical signals related to reward. Interacts with the basal ganglia to facilitate motor and reward

processes.

×Close definition

A part of the diencephalon that works as a gateway for incoming and outgoing information.

×Close definition

Part of the diencephalon. Regulates biological drives with pituitary gland.

×Close definition

Small pea-sized gland that produces and secretes hormones as part of the endocrine system. Interacts with the hypothalamus to monitor the regulation of growth, development, and metabolism.

×Close definition

The distinctive structure at the back of the brain between the cerebrum and brainstem. Important for muscle control, such as balance and movement.

×Close definition

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2.7: Non-Neuronal Structures in the Central Nervous System

Ventricular System and Cerebrospinal Fluid

The **cerebral ventricular system** is a set of interconnected cavities known as cerebral ventricles that produce and transport **cerebrospinal fluid (CSF)** (Shenoy & Lui, 2022). This ventricular system consists of 4 main ventricles—2 lateral ventricles, the third ventricle, the fourth ventricle, and the cerebral aqueduct (**Figure 25**). CSF is produced in the ventricles by a tissue called choroid plexus. It drains through sinuses around the brain and through lymphatic vessels. CSF fills the subarachnoid space around the brain, so the brain is suspended in CSF. CSF thus acts as a shock absorber to cushion and protect the brain. Additionally, floating in CSF reduces the effective weight of the brain from around 1500 grams to around 50 grams (Wright et al., 2012). Without CSF, the brain's own weight would cut off blood supply and kill neurons especially in its lower regions. Finally, CSF circulates nutrients throughout the brain and helps clear waste products away from the brain.

The cerebrospinal fluid (CSF) system. CSF is produced in four ventricles (e.g., two lateral ventricles, the third ventricle, and the fourth ventricle) via a tissue known as choroid plexus. By filling in the subarachnoid space surrounding the brain, the brain is essentially suspended by CSF and afforded an additional layer of protection from potential injuries to the skull.

Figure 25: A) The cerebral ventricular system showing the 4 major ventricles.

Rotating 3D rendering of the ventricles.

Figure 25: B) Rotating 3D rendering of the ventricles.

Vasculature

The brain is an energetically demanding organ. It is only 2% of the body's mass, but uses 20% of its energy when the body is resting (i.e., when muscles are not active). It relies on a constant supply of oxygen and glucose in the blood to sustain neurons—a disruption of blood flow to the brain leads to a loss of consciousness within 10 seconds. To deliver a constant flow of oxygenated blood, the brain has a complex and tightly regulated vasculature that directs blood to the most active brain regions. Four arteries feed the brain with oxygenated blood, forming a circle known as the circle of Willis. Major arteries branch off the circle of Willis to supply different regions of the brain. Branches of these arteries form progressively smaller arteries and arterioles that pass through the subarachnoid space and enter the brain. Inside the brain, they branch further to form a dense capillary network (**Figure 26**). A mind-blowing 1 to 2 meters of capillaries exist in every cubic millimeter of brain tissue. These capillaries are less than 10 microns in diameter, so occupy only 2% of brain volume. In the cerebral cortex, a capillary is typically within 10-20 microns from a given neuron. This dense vascular network allows efficient oxygen and glucose delivery to active neurons.

The blood supply is finely adjusted according to the needs of each brain region. Active neurons produce molecules that dilate smooth muscle cells and pericytes on local arterioles and capillaries, increasing blood flow in active regions. Increased blood flow to active brain regions typically exceeds oxygen demand, resulting in elevated local blood oxygen levels. The BOLD (blood oxygen level dependent) signal can be detected using magnetic resonance imaging and serves as a proxy for neuronal activity in experiments on brain function (see Chapter 4–Research Methods).

A cast of the brain's vasculature.

Figure 26. A cast of the brain's vasculature.

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definition

Interconnected cavities within the brain tissue that produce and secrete cerebrospinal fluid to protect the brain

×Close definition

Cerebrospinal fluid is an ultrafiltrate of plasma that surrounds the brain and spinal cord.

×Close definition

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2.8: Meninges and Protection of the Central Nervous System

Protective Coverings of the Central Nervous System

The central nervous system (CNS) is crucial to the operation of the body and any compromise of function in the brain and spinal cord can lead to severe difficulties. Both the brain and spinal cord are protected by multiple structures. First, the bones of the skull enclose and house the brain, and the bones of the vertebral column enclose and protect the spinal cord. Figure 2.8.6 shows a segment of the spinal cord within its protective vertebra.

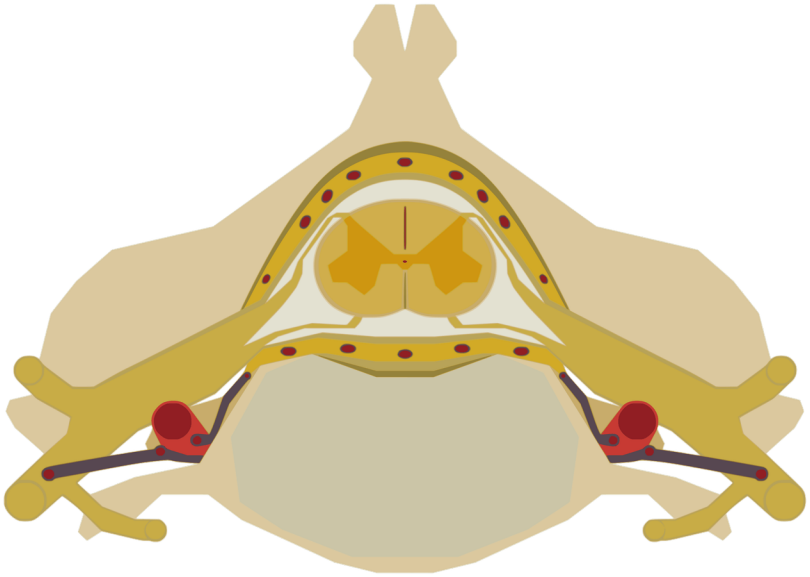


Figure 2.8.6: Cross-section of a spinal cord segment shown encased in its vertebra. The back of the person is at the top of the image.

Underneath the skeletal structures, the brain and spinal cord are surrounded and protected by tough **meninges**, a three-layer protective sheath made of connective tissue that surrounds, supports, stabilizes and partitions the nervous tissue. The meninges also contain cushioning **cerebrospinal fluid** (CSF). The three meningeal layers are the **dura mater**, the **arachnoid mater**, and the **pia mater**. Figure 2.8.7 shows the three layers of meninges covering the spinal cord and Figure 2.8.8 shows all the protective structures of the brain. The subdural cavity of the spinal cord and the subdural space of the brain lie between the dura mater and the arachnoid mater, whereas the subarachnoid cavity of the spinal cord and the subarachnoid space of the brain lie between the arachnoid mater and the pia mater. The **superior sagittal sinus** is a space between layers of dura mater immediately superior to the **longitudinal fissure** (the separation between the left and right hemispheres) of the brain.

In the spinal cord, the posterior (/dorsal) and anterior (/ventral) roots converge to form the **spinal nerve**. The **spinal ganglion** (also known as the **dorsal root ganglion**), an enlargement of the posterior (/dorsal) root, encases sensory neuron cell bodies.

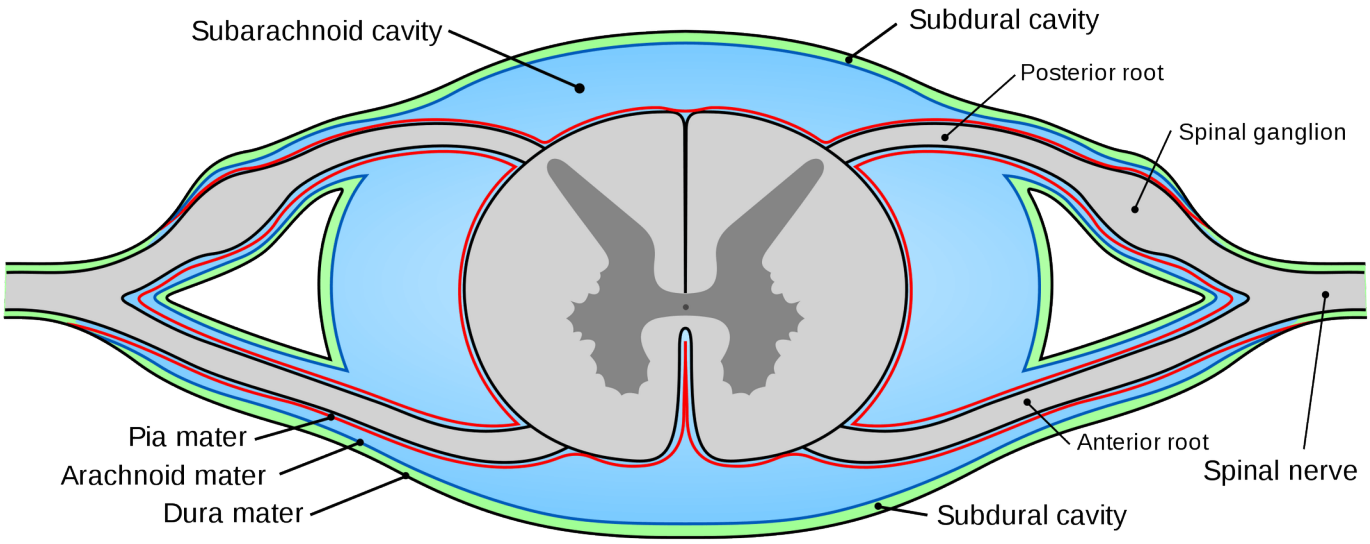


Figure 2.8.7: Cross-section of a spinal cord segment with the meninges and other structures labeled.

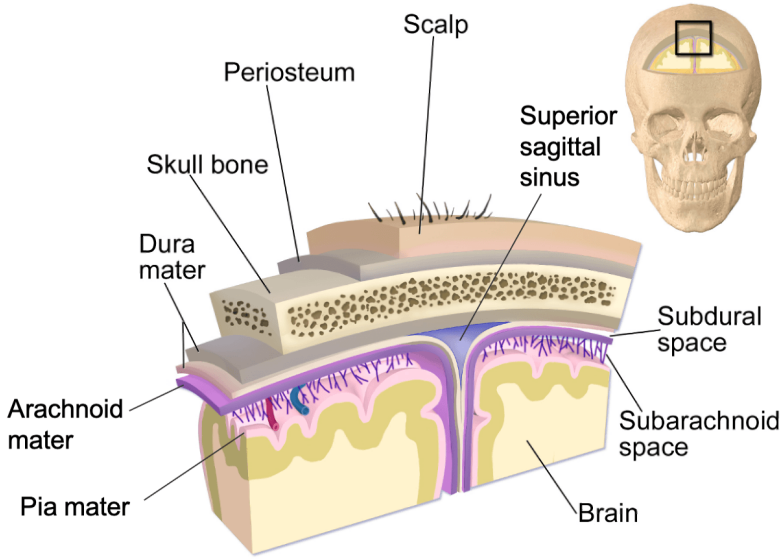


Figure 2.8.8: Protective structures of the brain. Superficially, the skin of the scalp and components of the skull bone create the first layer of protection. Deep to these layers, the meninges (the dura mater, arachnoid mater and pia mater) cover and partition the brain.

References

Basinger H., & Hogg, J.P. (2021) Neuroanatomy, Brainstem. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544297/

Additional Resources

If you are curious about anatomical terms used to describe different areas of the body, see "Anatomical Vocabulary" on: " Anatomical Position and Planes" by LibreTexts, licensed under CC BY-SA .

For more detail on the embryological development of the brain and the primary and secondary brain vesicles, see: " The Embryologic Perspective" by OpenStax, LibreTexts, licensed under CC BY .

For more detail on the meninges and the ventricles, see: " Support and Protection of the Brain" by Whitney Menefee, Julie Jenks, Chiara Mazzasette, & Kim-Leiloni Nguyen, LibreTexts, licensed under CC BY and " Circulation and the Central Nervous System" by OpenStax, LibreTexts, licensed under CC BY .

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3: NEURAL CONDUCTION, SYNAPSES, AND NEUROTRANSMITTERS

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3.1: Introduction to the Neuron

Imagine trying to string words together into a meaningful sentence without knowing the meaning of each word or its function (i.e., Is it a verb, noun, or adjective?). Similarly, to appreciate how groups of cells work together in the brain, we must first understand how individual cells in the brain function. Much like words, brain cells, called *neurons,* have an underlying structure that provides the foundation for their functional purpose. Have you ever seen a neuron? Did you know that the basic structure of a neuron is the same whether it is from the brain of a rat or a human? How do the billions of neurons in our brain allow us to do all the things we enjoy, such as chatting with a friend, cheering on a sports team, or laughing?

Figure 1. Three drawings by Santiago Ramón y Cajal, taken from "Comparative study of the sensory areas of the human cortex", pages 314, 361, and 363. Left: Nissl-stained visual cortex of a human adult. Middle: Nissl-stained motor cortex of a human adult. Right: Golgi-stained cortex of a 1 1/2 month old infant. Cajal cortex drawings © Santiago Ramón via wikimedia is licensed under a Public Domain license

Our journey into these questions begins more than 100 years ago with a scientist named Santiago Ramón y Cajal. Cajal (1911) boldly concluded that discrete individual neurons are the structural and functional units of the nervous system. He based his conclusion on the numerous drawings he made of Golgi-stained tissue, a stain named after the scientist who discovered it, Camillo Golgi. Scientists use several types of stains to visualize cells. Each stain works in a unique way, which causes them to look different when viewed under a microscope. For example, a Nissl stain labels only the main part of the cell (i.e., the cell body; see left and middle panels of Figure 1). In contrast, a Golgi stain fills the cell body and all the processes that extend from it (right panel of Figure 1). Most notably, a Golgi stain only stains approximately 1–2% of neurons (Pasternak & Woolsey, 1975; Smit & Colon, 1969), permitting the observer to distinguish one cell from another. These qualities allowed Cajal to examine the full anatomical structure of individual neurons for the first time. This significantly enhanced the appreciation of the intricate networks their processes form. Based on his observation of Golgi-stained tissue, Cajal suggested neurons were distinct individual units rather than continuous structures. This opposed the dominant theory at the time proposed by Joseph von Gerlach, which stated that the nervous system was composed of a network of long continuous fibers, like telegraph wires (for review see Lopez-Munoz et al., 2006). Camillo Golgi himself had been an avid supporter of Gerlach's theory. Despite their scientific disagreement, Cajal and Camillo Golgi shared the Nobel Prize for Medicine in 1906 for their combined contribution to our understanding of neurons. This seminal work paved the way for our current understanding of the basic structure of the nervous system described in this chapter (for reviews see: De Carlos & Borrell, 2007; Grant, 2007).

This chapter first introduces some basic terminology and the anatomy of neurons in the section "The Structure of the Neuron." The remainder of the chapter focuses on the electrochemical signals through which neurons communicate. While the electrochemical process might sound intimidating, it is broken down into manageable sections. The first subsection, "Resting Membrane Potential," describes what occurs in a neuron at rest, when it is theoretically not receiving or sending signals. Building upon this, we examine the electrical conductance within a single neuron when it receives signals. Finally, the chapter concludes with a description of the electrical conductance, which results in communication between neurons through a release of chemicals. At the end of the chapter, you should have a broad understanding of how neurons send and receive information by electrical and chemical signals.

A note of encouragement: This chapter introduces a vast amount of terminology that at times may feel overwhelming. Do not get discouraged or bogged down in the details. Utilize the book's glossary, which contains all terms in **bold typing**. On your first read of this chapter, try focusing on the broader concepts and functional aspects of the terms instead of trying to commit all the terminology to memory. I suggest reading this chapter at least twice, once before *and* once after the course lecture on this material. Repetition is the best way to gain clarity and commit to memory the challenging concepts and detailed vocabulary presented here.

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3.2: The Structure of the Neuron

Basic Nomenclature

There are approximately 86 billion neurons in the human brain (Herculano-Houzel, 2009). Each neuron has three main components: dendrites, the soma, and the axon (see **Figure 2**). **Dendrites** are processes that extend outward from the **soma**, or cell body of a neuron, and typically branch several times. Dendrites receive information from thousands of other neurons and are the main source of input of the neuron. The **nucleus**, which is located within the soma, contains genetic information, directs protein synthesis, and supplies the energy and the resources the neuron needs to function. The main source of output of the neuron is the **axon**. The axon extends away from the soma and carries an important signal called an action potential to another neuron. The place at which the axon of one neuron approaches the dendrite of another neuron is a **synapse** (**Figures 2 and 3**). Typically, the axon of a neuron is covered with an insulating substance called a **myelin sheath** that allows the signal of one neuron to travel rapidly to another neuron.

Figure 2. Basic structure of a neuron. Basic structure of neuron © Noba is licensed under a CC BY-NC-SA (Attribution NonCommercial ShareAlike) license

The axon splits many times so it can communicate, or synapse, with several other neurons (see **Figure 2**). At the end of the axon is a **terminal button**, which forms synapses with **spines**, or protrusions, on the dendrites of neurons. Synapses form between the *presynaptic* terminal button (neuron sending the signal) and the *postsynaptic* membrane (neuron receiving the signal; see **Figure 3**). Here we will focus specifically on synapses between the terminal button of an axon and a dendritic spine; however, synapses can also form between the terminal button of an axon and the soma or the axon of another neuron.

A tiny space called a **synaptic gap**, approximately 5 nm (nanometers), exists between the presynaptic terminal button and the postsynaptic dendritic spine. To give you a better idea of the size, the thickness of a dime is 1.35 mm (millimeters) or 1,350,000 nm. In the presynaptic terminal button, **synaptic vesicles** package together groups of chemicals called **neurotransmitters** (see **Figure 3**). Neurotransmitters are released from the presynaptic terminal button, travel across the synaptic gap, and activate ion channels on the postsynaptic spine by binding to *receptor sites*. We will discuss the role of receptors in more detail later in the chapter.

Figure 3. Characteristics of a synapse. synapse © Noba is licensed under a CC BY-NC-SA (Attribution NonCommercial ShareAlike) license

definition

Part of a neuron that extends away from the cell body and is the main input to the neuron.

×Close definition

Cell body of a neuron that contains the nucleus and genetic information and directs protein synthesis.

×Close definition

(plural: nuclei)
In neuroanatomy, nucleus or nuclei refers to a cluster of neurons.

Collection of nerve cells found in the brain which typically serve a specific function.

×Close definition

Part of the neuron that extends off the soma, splitting several times to connect with other neurons; main output of the neuron.

×Close definition

The tiny space separating neurons

×Close definition

Substance around the axon of a neuron that serves as insulation to allow the action potential to conduct rapidly toward the terminal buttons.

×Close definition

The part of the end of the axon that forms synapses with postsynaptic dendrite, axon, or soma.

×Close definition

Protrusions on the dendrite of a neuron that form synapses with terminal buttons of the presynaptic axon.

×Close definition

Also known as the synaptic cleft; the small space between the presynaptic terminal button and the postsynaptic dendritic spine, axon, or soma.

×Close definition

Groups of neurotransmitters packaged together and located within the terminal button.

×Close definition

Chemical substance released by the presynaptic terminal button that acts on the postsynaptic cell.

×Close definition

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3.3: Types of Cells in the Brain

Not all neurons are created equal. *Sensory* neurons help us receive information about the world around us. *Motor* neurons allow us to initiate movement and behavior, ultimately allowing us to interact with the world around us. *Interneurons* process sensory input from our environment into meaningful representations, plan behavioral responses, and connect to the motor neurons to execute these behavioral plans.

The main categories of neurons are defined by their specific structure. The structures support their unique functions. *Unipolar neurons* are structured in a way that is ideal for relaying information forward, so they have one neurite (axon) and no dendrites (**Figure 4**). They are involved in transmission of physiological information from the body's periphery such as communicating body temperature through the spinal cord up to the brain. *Bipolar neurons* are involved in sensory processing such as sensing light in the eye's retina. They have one axon and one dendrite which help acquire and pass sensory information to various regions in the brain. Finally, *multipolar neurons* are most common and communicate sensory and motor information in the brain. Multipolar neurons have one axon and many dendrites which allows them to communicate with other neurons. One of the most prominent neurons is a pyramidal neuron, which falls under the multipolar category. It gets its name from the triangular or pyramidal shape of its soma (for examples see, Furtak et al., 2007).

Illustrations of the Types of Neurons: (1) unipolar, (2) bipolar, (3) multipolar, and (4) pseudounipolar.

Figure 4. Types of Neurons: Neurons are broadly divided into a few main types based on the number and placement of axons: (1) unipolar, (2) bipolar, (3) multipolar, and (4) pseudounipolar.

In addition to neurons, non-neuronal cells in the nervous system called **glia** or *neuroglia* provide support and play essential roles in the functioning of neurons. Glial cells have several functions, just a few of which we will discuss here. One type of glial cell, called *oligodendroglia*, forms the myelin sheaths that insulate axons (Simons & Trotter, 2007; see Figures 5). In the central nervous system (CNS), oligodendroglia wrap their dendritic processes around the axons of neurons many times to form the myelin sheath. One cell will form the myelin sheath on several axons. In the peripheral nervous system (PNS), Schwann cells, another type of glial cell, form the myelin sheath for neurons. One cell will wrap around a singular axon in the PNS. Other types of glial cells, such as *microglia* and *astrocytes*, digest debris of dead neurons, carry nutritional support from blood vessels to neuron, and help to regulate the ionic composition of the extracellular fluid. Glial cells are essential for neuronal support, but unlike neurons, they do not conduct electrical signals or engage in cell-to-cell communication.

Drawing of the Oligodendrocyte

Figure 5. An oligodendrocyte myelinating several axons in the central nervous system.

Drawing of the peripheral nervous system (PNS) has myelinating Schwann cells

Figure 6. The peripheral nervous system (PNS) has myelinating Schwann cells.

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definition

Non-neuronal cells in the nervous system that play a wide range of supporting roles in the nervous system.

×Close definition

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3.4: Communication Within and Between Neurons

Thus far, we have described the main characteristics of neurons, including how their processes come in close contact to form *synapses*. In this section, we consider the conduction of communication within a neuron and how this signal is transmitted to the next neuron. There are two stages of this electrochemical action in neurons. The first stage is the electrical conduction of dendritic input to the initiation of an action potential within a neuron. The second stage is a chemical transmission across the synaptic gap between the presynaptic neuron and the postsynaptic neuron of the synapse. To understand these processes, we first need to consider what occurs within a neuron at its steady state, called *resting membrane potential*.

Resting Membrane Potential

The intracellular (inside the cell) fluid and extracellular (outside the cell) fluid of neurons is composed of a combination of ions (electrically charged molecules; Figure 7). Cations are positively charged ions, and anions are negatively charged ions. The composition of intracellular and extracellular fluid is similar to salt water, containing sodium (Na+), potassium (K+), chloride (Cl–), and anions (A–).

The **cell membrane**, which is composed of a lipid bilayer of fat molecules, separates the cell from the surrounding extracellular fluid. Proteins span the membrane, forming **ion channels** that allow particular ions to pass between the intracellular and extracellular fluid (**Figure 7**). These ions are in different concentrations inside the cell relative to outside the cell, and the ions have different electrical charges. Due to this difference in concentration and charge, two forces act to maintain a steady state when the cell is at rest: diffusion and electrostatic pressure. **Diffusion** is the force on molecules to move from areas of high concentration to areas of low concentration. **Electrostatic pressure** is the repulsive force between similarly charged ions and the attractive force between oppositely charged ions. Remember the saying “opposites attract”?

Figure 7. Representation of ion concentrations inside (intracellular) and outside (extracellular) a neuron in the unmyelinated segment of the axon.

There is a membrane potential at which the force of diffusion is equal and opposite to the force of electrostatic pressure. This voltage, called the *equilibrium potential*, is the voltage at which no ions flow. Since several ions can permeate the cell’s membrane, the baseline electrical charge inside the cell compared with outside the cell, referred to as **resting membrane potential**, is based on the collective drive of force on several ions. Relative to the extracellular fluid, the membrane potential of a neuron at rest is negatively charged at approximately -70 millivolts (mV). These voltages are tiny compared to those of batteries and electrical outlets, which are measured in volts, not millivolts, and range from 1.5 to 240 volts.

Let us see how these two forces, diffusion and electrostatic pressure, act on the four groups of ions mentioned above.

1. ***Anions (A-)***: Anions are highly concentrated inside the cell and contribute to the negative charge of the resting membrane potential. Diffusion and electrostatic pressure are not forces that determine A– concentration because Anions are impermeable to the cell membrane. There are no ion channels that allow for A– to move between the intracellular and extracellular fluid.
2. ***Potassium (K+)***: The cell membrane is permeable to potassium at rest, but potassium remains in high concentrations inside the cell. Diffusion pushes K+ outside the cell because it is in high concentration inside the cell. However, electrostatic pressure pushes K+ inside the cell because the positive charge of K+ is attracted to the negative charge inside the cell. In combination, these forces oppose one another with respect to K+.
3. ***Chloride (Cl-)***: The cell membrane is also very permeable to chloride at rest, but chloride remains in high concentration outside the cell. Diffusion pushes Cl– inside the cell because it is in high concentration outside the cell. However, electrostatic pressure pushes Cl- outside the cell because the negative charge of Cl– is attracted to the positive charge outside the cell. These forces on Cl- oppose one another.
4. ***Sodium (Na+)***: The cell membrane is not very permeable to sodium at rest. Diffusion pushes Na+ inside the cell because it is in high concentration outside the cell. Electrostatic pressure also pushes Na+ inside the cell because the positive charge of Na+ is attracted to the negative charge inside the cell. Both of these forces push Na+ inside the cell; however, Na+ cannot permeate the cell membrane and remains in high concentration outside the cell. The small amounts of Na+ inside the cell are removed by a **sodium-potassium pump**, which uses the neuron’s energy (adenosine triphosphate, ATP) to pump 3 Na+ ions out of the cell in exchange for bringing 2 K+ ions inside the cell.

Action Potential

Now that we have considered what occurs in a neuron at rest, let us consider what changes occur to the resting membrane potential when a neuron receives input from the presynaptic terminal button of another neuron. Our understanding of the electrical signals or potentials within a neuron results from the seminal work of Hodgkin and Huxley that began in the 1930s at a well-known marine biology lab in Woods Hole, MA. Their work, for which they won the Nobel Prize in Medicine in 1963, resulted in the general model of electrochemical transduction described here (Hodgkin & Huxley, 1952). Hodgkin and Huxley studied a very large axon in the squid, a common species for that region of the United States. The squid's axon is roughly 100 times larger than axons in the mammalian brain, making it much easier to work with. Activation of the giant axon, whose large size allows for rapid electrical signal transmission, triggers a swift withdrawal response that enables the squid to escape from predators.

While studying this species, Hodgkin and Huxley noticed that if they applied an electrical stimulus to the axon, a large, transient electrical current conducted down the axon. This transient electrical current is known as an **action potential** (**Figure 8**). An action potential is an all-or-nothing response that occurs when there is a change in the charge or potential of the cell from its resting membrane potential (-70 mV) in a more positive direction, which is a *depolarization* (**Figure 8**). An all-or-nothing response parallels the binary code used in computers, where only two possibilities exist: 0 or 1. There are no intermediate values; 0.5, for example, doesn't exist in binary code. Similarly, an action potential either occurs or doesn't occur, with no partial activation. This all-or-nothing principle applies to both binary code and action potentials: they are either triggered fully or not at all.

There is a specific membrane potential that the neuron must reach to initiate an action potential. This membrane potential, called the **threshold of excitation**, is typically around -50 mV. If the threshold of excitation is reached, then an action potential is triggered.

Drawing showing the changes in membrane potentials of neurons.

Figure 8. Changes in membrane potentials of neurons.

How is an action potential initiated? At any one time, each neuron may receive hundreds of inputs from the cells that synapse with it. These inputs can cause several types of fluctuations in the neuron's membrane potentials (**Figure 8**):

1. **Excitatory postsynaptic potentials** (EPSPs): a *depolarizing* current that causes the membrane potential to become more positive and closer to the threshold of excitation
2. **Inhibitory postsynaptic potentials** (IPSPs): a *hyperpolarizing* current that causes the membrane potential to become more negative and further away from the threshold of excitation

These postsynaptic potentials, EPSPs and IPSPs, *summate* or add together in time and space. The (inhibitory) IPSPs make the membrane potential more negative, but how much so depends on their strength. The (excitatory) EPSPs make the membrane potential more positive; again, how much more positive depends on their strength. If you have two small EPSPs at the same time and same synapse, then the result will be a large EPSP. If you have a small EPSP and a small IPSP at the same time and same synapse, then they will cancel each other out. Unlike the action potential, which is an all-or-nothing response, IPSPs and EPSPs are smaller and *graded* potentials, varying in strength. The change in voltage during an action potential is approximately 100 mV. In comparison, EPSPs and IPSPs are changes in voltage between 0.1 to 40 mV. They can be different strengths, or gradients, and they are measured by how far the membrane potentials diverge from the resting membrane potential.

The concept of summation can be confusing. As a child, I used to play a game with a very large parachute where you would try to knock balls out of the center of the parachute. This game illustrates the properties of summation. In this game, a group of children next to one another would work together to produce waves in the parachute in order to cause a wave large enough to knock the ball out of the parachute. The children would initiate the waves at the same time and in the same direction. The additive result was a larger wave in the parachute, and the balls would bounce out of the parachute. However, if the waves they initiated occurred in the opposite direction or with the wrong timing, the waves would cancel each other out, and the balls would remain in the center of the parachute. EPSPs or IPSPs in a neuron work in the same fashion; they either add or cancel each other out. If you have two EPSPs, then they sum together and become a larger depolarization. Similarly, if two IPSPs come into the cell at the same time, they will sum and become a larger hyperpolarization in membrane potential. However, if two inputs were opposing one another, moving the potential in opposite directions, such as an EPSP and an IPSP, their sum would cancel each other out.

At any moment, each cell is receiving mixed messages, both EPSPs and IPSPs. If the summation of EPSPs is strong enough to depolarize the membrane potential to reach the threshold of excitation, then it initiates an action potential. The action potential then travels down the axon, away from the soma, until it reaches the ends of the axon (the terminal button). In the terminal button, the action potential triggers the release of neurotransmitters from the presynaptic terminal button into the synaptic gap.

These neurotransmitters, in turn, cause EPSPs and IPSPs in the postsynaptic dendritic spines of the next cell (Figure 9). The neurotransmitter released from the presynaptic terminal button binds with **ionotropic receptors** in a lock-and-key fashion on the postsynaptic dendritic spine. Ionotropic receptors are receptors on ion channels that open, allowing some ions to enter or exit the cell, depending upon the presence of a particular neurotransmitter. The type of neurotransmitter and the permeability of the ion channel it activates will determine if an EPSP or IPSP occurs in the dendrite of the postsynaptic cell. These EPSPs and IPSPs summate as described above and the entire process occurs again in another cell.

The Change in Membrane Potential During an Action Potential

We discussed previously which ions are involved in maintaining the resting membrane potential. Not surprisingly, some of these same ions are involved in the action potential. When the cell becomes depolarized (more positively charged) and reaches the threshold of excitation, this opens a voltage-dependent Na+ channel. A voltage-dependent ion channel is a channel that opens, allowing some ions to enter or exit the cell, depending upon when the cell reaches a particular membrane potential. When the cell is at resting membrane potential, these voltage-dependent Na+ channels are closed. As we learned earlier, both diffusion and electrostatic pressure are pushing Na+ inside the cells. However, Na+ cannot permeate the membrane when the cell is at rest. Now that these channels are open, Na+ rushes inside the cell, causing the cell to become very positively charged relative to the outside of the cell. This is responsible for the rising or depolarizing phase of the action potential (Figure 8). The inside of the cell becomes very positively charged, +40mV. At this point, the Na+ channels close and become *refractory.* This means the Na+ channels cannot reopen again until the cell returns to the resting membrane potential. Thus, a new action potential cannot occur during the refractory period. The refractory period also ensures the action potential can only move in one direction down the axon, away from the soma. As the cell becomes more depolarized, a second type of voltage-dependent channel opens; this channel is permeable to K+. With the cell depolarized (very positive relative to the outside of the cell) and the high concentration of K+ within the cell, the forces of both diffusion and electrostatic pressure drive K+ outside of the cell. The movement of K+ out of the cell causes the cell potential to return to the resting membrane potential, the falling or hyperpolarizing phase of the action potential (Figure 8). A short hyperpolarization occurs partially due to the gradual closing of the K+ channels. With the Na+ closed, electrostatic pressure continues to push K+ out of the cell. In addition, the sodium-potassium pump is pushing Na+ out of the cell. The cell returns to the resting membrane potential, and the excess extracellular K+ diffuses away. This exchange of Na+ and K+ ions happens very rapidly, in less than 1 millisecond. The action potential occurs in a wave-like motion down the axon until it reaches the terminal button. Only the ion channels in close proximity to the action potential are affected.

Drawing of the summary of the electrochemical communication within and between neurons.

Figure 9. Summary of the electrochemical communication within and between neurons.

Earlier you learned that axons are often covered in myelin. Let us consider how myelin speeds up the process of the action potential. There are gaps in the myelin sheaths called *nodes of Ranvier*. The myelin insulates the axon and does not allow any fluid between the myelin and cell membrane. Under the myelin, when the Na+ and K+ channels open, no ions flow between the intracellular and extracellular fluid. This saves the cell from having to expend the energy necessary to rectify or regain the resting membrane potential. (Remember, the pumps need ATP to run.) Under the myelin, the action potential degrades some, but still has a large enough potential to trigger a new action potential at the next node of Ranvier. Thus, the action potential jumps from node to node (Figure 10); this process is known as *saltatory conduction* (*Saltus* means “jump” in Latin).

Two neurons--with and without myelin. See caption for details.

Figure 10. Action potential propagation in myelinated neurons (right) is faster than in unmyelinated neurons (left) because of saltatory conduction.

In the presynaptic terminal button, the action potential triggers the release of neurotransmitters. Neurotransmitters cross the synaptic gap and open subtypes of receptors in a lock-and-key fashion (see Figure 9). Depending on the type of neurotransmitter, an EPSP or IPSP occurs in the dendrite of the postsynaptic cell. Neurotransmitters that open Na+ or calcium (Ca+) channels cause an EPSP; an example is the NMDA receptors, which are activated by glutamate (the main excitatory neurotransmitter in the brain). In contrast, neurotransmitters that open Cl- or K+ channels cause an IPSP; an example is gamma-aminobutyric acid (GABA) receptors, which are activated by GABA, the main inhibitory neurotransmitter in the brain. Once the EPSPs and IPSPs occur in the postsynaptic site, the process of communication within and between neurons cycles on (Figure 9). A neurotransmitter that does not bind to receptors is broken down and inactivated by enzymes or glial cells, or it is taken back into the presynaptic terminal button in a process called *reuptake*, which will be discussed further in the chapter on psychopharmacology.

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definition

A bi-lipid layer of molecules that separates the cell from the surrounding extracellular fluid.

×Close definition

Proteins that span the cell membrane, forming channels that specific ions can flow through between the intracellular and extracellular space.

×Close definition

The force on molecules to move from areas of high concentration to areas of low concentration.

×Close definition

The force on two ions with similar charge to repel each other; the force of two ions with opposite charge to attract to one another.

×Close definition

The voltage inside the cell relative to the voltage outside the cell while the cell is at rest (approximately -70 mV).

×Close definition

An ion channel that uses the neuron's energy (adenosine triphosphate, ATP) to pump three Na+ ions outside the cell in exchange for bringing two K+ ions inside the cell.

×Close definition

A transient all-or-nothing electrical current that is conducted down the axon when the membrane potential reaches the threshold of excitation.

×Close definition

Specific membrane potential that the neuron must reach to initiate an action potential.

×Close definition

A depolarizing postsynaptic current that causes the membrane potential to become more positive and move towards the threshold of excitation.

×Close definition

A hyperpolarizing postsynaptic current that causes the membrane potential to become more negative and move away from the threshold of excitation.

×Close definition

Ion channel that opens to allow ions to permeate the cell membrane under specific conditions, such as the presence of a neurotransmitter or a specific membrane potential.

×Close definition

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3.5: General Neurochemistry Principles

Learning Objectives

By the end of this section, you should be able to

- Explain the basic mechanisms that neurons use to produce and release neurotransmitters
- Describe the ways that neurotransmitters interact with receptors

In the following sections, you will learn general principles about brain chemistry. Neurons access nutrients from the diet, or from their own neuronal membranes, to produce the neurotransmitters that underlie behavior. These nutrients, including amino acids, fatty acids or sugar molecules, are taken inside a neuron or glial cell where they are acted upon by enzymes to produce a neurotransmitter that is stored in a vesicle and later released in response to specific intracellular signals. Neurons release the most recently produced neurotransmitter molecules first, thus guaranteeing that the communication between neurons is successful.

How do neurons produce neurotransmitters?

Neurotransmitters are produced inside neurons. Their production depends upon the neuron obtaining an adequate supply of precursors from the blood. This is not as easy as it sounds. The production of neurotransmitters requires a variety of amino acids, sugar, fats, vitamins, and minerals. These nutrients float around in the blood after each meal. Every cell in the body competes with the brain for access to these nutrients. The brain is at a distinct disadvantage because it sits behind a firewall called the blood-brain barrier. However, fortunately, the blood-brain barrier possesses a variety of specialized transporting mechanisms that can actively transfer nutrients into the brain (Step 1 in Figure 3.3). Once a nutrient crosses the blood-brain barrier it is usually transported to neurons with the assistance of astrocytes.

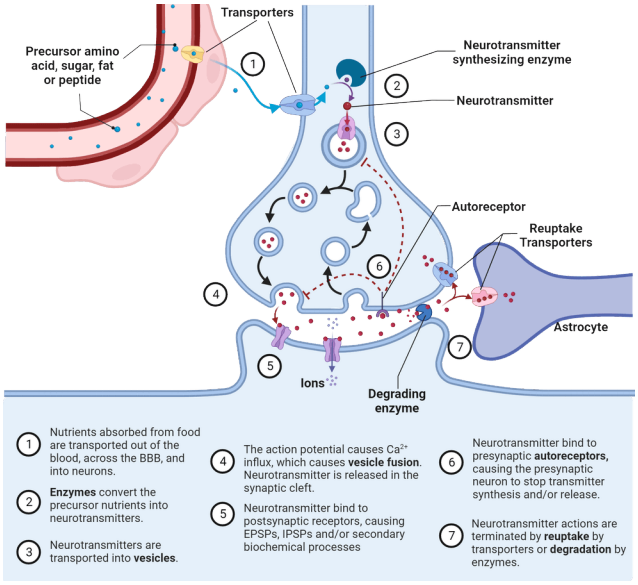


Figure 3.3 Neurotransmitter lifecycle

After an amino acid, fatty acid or sugar molecule is inside a neuron, it is generally acted upon by synthesizing enzymes (Step 2 in Figure 3.3). Enzymes are proteins that help build, breakdown or otherwise modify substances in our cells. The action of many of these enzymes uses metal ions as co-factors to assist with the conversion process. For example, neurons in the substantia nigra contain iron, neurons in the hippocampus contain zinc, neurons in the locus coeruleus contain copper, and neurons in the red nucleus contain cobalt. The presence of these metals is critical for normal neurotransmitter metabolism.

Brains demonstrate a degree of energy efficiency in terms of which of these transmitters it utilizes most extensively. For

example, GABA and glutamate are simple amino acids and are the most abundant neurotransmitters in the human brain. They require only single-step enzymatic modification. Four amine neurotransmitters (dopamine, norepinephrine, epinephrine, and serotonin) require enzymatic modification of dietary amino acids to produce and inactivate. The brain contains 1000-fold fewer of these amine-releasing neurons, as compared to glutamate and GABA, probably because they require more energy to function. Finally, the other, far less abundant neurotransmitters, such as the neuropeptides (which are a string of amino acids) require a considerable amount of energy by the neuron to produce and inactivate. Neuropeptides occur roughly one-million-fold lower concentration in the brain than glutamate and GABA. These neurotransmitters, as well as the fat-derived neurotransmitters endocannabinoids and prostaglandins, all utilize the DNA in the nucleus to produce the necessary enzymes and precursors. The endogenous levels of these two fat-derived are kept quite low and are produced only when needed.

How are neurotransmitters stored and released?

Once synthesized, most neurotransmitter molecules are then actively transported into synaptic vesicles (step 3 Figure 3.3); these are very tiny spheres clustered at the presynaptic terminal with hollow centers into which approximately 10,000 molecules of a typical neurotransmitter can be stored for later release from a neuron. Neurons pay attention to the shelf life of their neurotransmitters; they prefer to release the most recently produced neurotransmitter molecules first. This means that the freshest products are released first, thus guaranteeing that the communication between neurons is successful. Many neurons produce two (and rarely three) different neurotransmitters; each is stored inside different vesicles and are released independently of each other.

The arrival of the action potential at the end of the axon opens a group of voltage-dependent calcium channels that allows the entry of calcium ions. The elevated intracellular concentration of calcium ions initiates the next step in the communication of one neuron with the next: A synaptic vesicle either merges into its cell wall (both are made of lipids so imagine two soap bubbles coming together), or opens a small pore into the neuronal membrane, and releases the neurotransmitter into the small space between neurons, called a synaptic cleft (step 4 Figure 3.3). Figure 3.4 shows the process of vesicle fusion in more detail. The junction at which two neurons communicate via the release of a neurotransmitter molecule is called a synapse. Because the synapse is such a small space, the concentration of neurotransmitter molecules in the synapse following release becomes very high for a brief period.

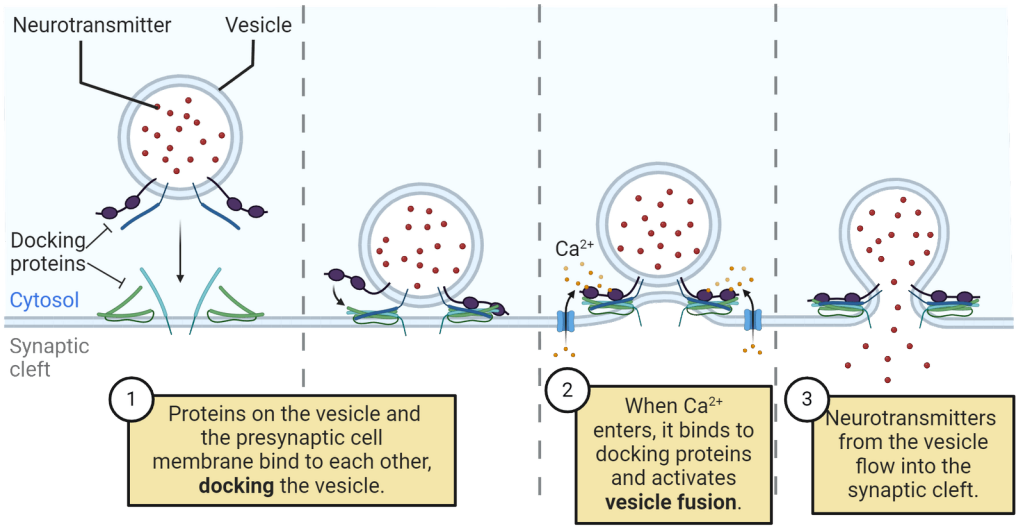


Figure 3.4 Vesicle fusion

Post-synaptic actions of neurotransmitters

Once released into the synapse, neurotransmitter molecules briefly interact or bind with a protein, called a receptor, that is (usually) located on the surface of the neuron on the other side of the synapse (step 5 in Figure 3.3). These receptors are divided into two general types: either ionotropic or metabotropic receptors (Figure 3.5). Ionotropic receptors are transmembrane molecules that can “open” or “close” a channel that would allow smaller particles to travel in and out of the cell. Ionotropic receptors allow different kinds of ions to travel in and out of the cell. Ionotropic receptors are not opened (or closed) all the time.

They are generally closed until another small molecule (called a ligand — in our case, a neurotransmitter) binds to the receptor. As soon as the ligand binds to the receptor (step 1 in the left side of Figure 3.5), the receptor changes conformation (the protein that makes up the channel changes shape), and, as they do so, they create a small opening that is big enough for ions to travel through (step 2 in the left side of Figure 3.5). Therefore, ionotropic receptors are called "ligand-gated transmembrane ion channels". The abrupt change in concentration of these ions induces secondary biochemical processes which may have either short-term or long-term consequences on the post-synaptic neuron's behavior.

Metabotropic receptors do not have a "channel" that opens or closes. Instead, they are linked to another small chemical called a "G-protein." As soon as a ligand binds the metabotropic receptor (step 1 in the right side of Figure 3.5), the receptor "activates" the G-protein (it basically changes the G-protein shape). Once activated, the G-protein itself goes on and activates another molecule (step 2 in the right side of Figure 3.5). This new molecule is called a "secondary messenger." A secondary messenger is a chemical whose function is to go and activate other particles. So far, this process is common to all metabotropic receptors. What happens from there on is different for every metabotropic receptor. In some cases, the secondary messenger travel until it binds to and opens ion channels located somewhere else on the membrane (step 3 in the right side of Figure 3.5). In some cases, the secondary messenger will go and activate other intermediate molecules inside the cell. The important thing to remember is that metabotropic receptors do not have ion channels, and binding of a ligand may or may not result in the opening of ion channels at different sites on the membrane. But they will always activate a G-protein that will in turn activate secondary messengers. G-protein coupled receptors are a large group of evolutionarily related proteins that are very common in the brain and body; over eight hundred human genes are devoted to producing these proteins.

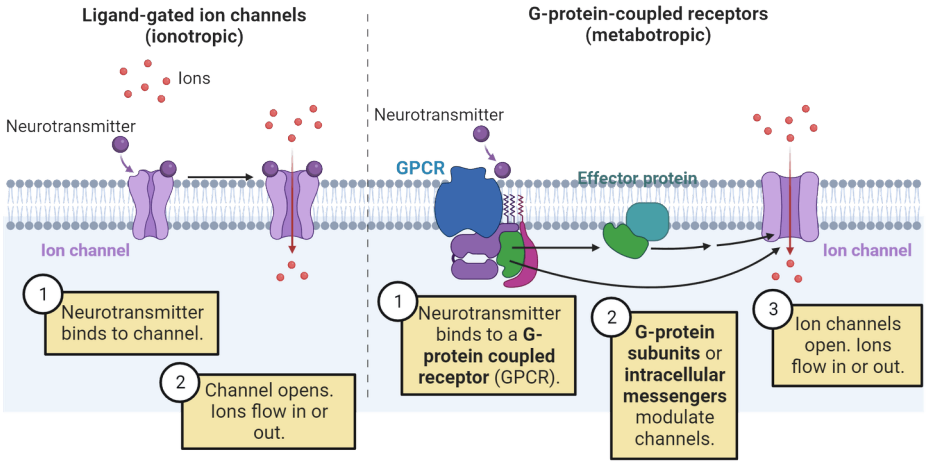


Figure 3.5 Metabotropic vs ionotropic receptors

Despite many safeguards, the synaptic communication processes described above often fail because the vesicles are empty or do not fuse properly, or the neurotransmitters are oxidized and therefore inactive (Linden, 2007). Neural systems have a built-in redundancy that allows them to compensate for failures in single neurons. Brains try to be energy efficient and not waste neurotransmitters. Many, but not all, neurotransmitters, or components of them after enzymatic inactivation, are re-absorbed by the axon terminal and re-used. Finally, although neurons utilize components of the diet to produce neurotransmitters, the production of neurotransmitters is rarely significantly enhanced by dietary supplements.

Ending neurotransmitter action

After most neurotransmitters are released into the synaptic cleft they need to be inactivated. The primary mechanism for inactivation is reuptake (step 7 in Figure 3.3). Reuptake is the reabsorption of a neurotransmitter via a protein transporter located on the (pre-synaptic) membrane of the axon terminal. Reuptake allows for the recycling of neurotransmitters. Because neurotransmitter molecules are large and hydrophilic, they cannot simply diffuse through the membrane; this is why specific transporter proteins are necessary.

Neurons benefit from feedback on how much neurotransmitter they are releasing at their axonal terminals. This feedback is provided by a special type of protein receptor called an autoreceptor (step 6 in Figure 3.3). Autoreceptors are located on the

membranes of nerve cells. They may be located on the cell body or the axonal terminal. These receptors are only sensitive to the neurotransmitters released by the neuron on which the autoreceptor sits. Activation of an autoreceptor usually leads to a reduction in the rate of release of the cell's neurotransmitter.

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3.6: Neurotransmitters Made from Amino Acids

Learning Objectives

By the end of this section, you should be able to

- Identify the neurotransmitters produced from amino acids in the diet
- Describe the similarities and differences in the ways these neurotransmitters are produced, inactivated, and utilized to control behavior

Dopamine, norepinephrine, and epinephrine.

Dopamine (often abbreviated DA), norepinephrine (often abbreviated NE), and epinephrine are sequentially synthesized from the same dietary amino acid precursor, tyrosine. Norepinephrine and epinephrine are also sometimes called noradrenaline and adrenaline, and the neurons that produce them are sometimes called noradrenergic and adrenergic. Understanding the sequence of biochemical steps that lead to the production, storage, release, and receptor interactions of these three neurotransmitters has allowed neuropharmacologists to design drugs that can either enhance or inhibit specific processes to treat neurological and psychiatric diseases.

Synthesis

Tyrosine is actively transported from the blood across the blood-brain barrier (Step 1 of Figure 3.6). Tyrosine is utilized by all the cells in the brain for a variety of purposes, not just for making these neurotransmitters. Dopamine, norepinephrine, and epinephrine neurons produce a series of enzymes that convert tyrosine into each of these neurotransmitters. The process begins inside the cytoplasm of the neuron with the conversion of tyrosine into L-DOPA by the addition of a hydroxy molecule to the benzene ring via the enzyme tyrosine hydroxylase (Step 2 of Figure 3.6). This enzyme requires the presence of iron ions to function properly. This enzyme does not work well in humans with severe anemia who have difficulty absorbing enough iron from their diet. Severe anemia is typically associated with feelings of depression and mental fatigue. These symptoms offer insight into the role of these neurotransmitters in normal brain function.

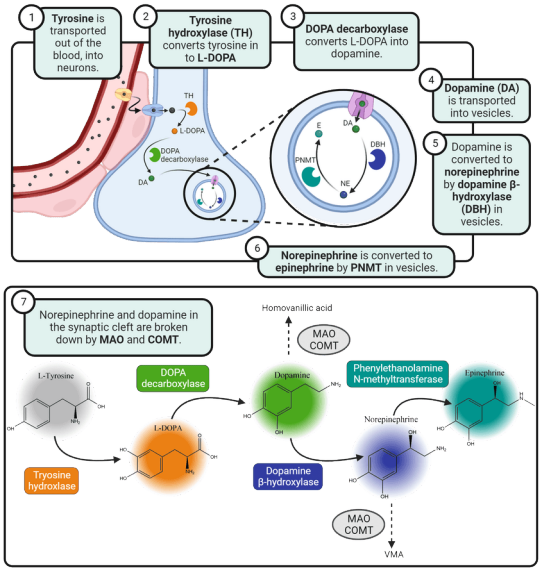


Figure 3.6

L-DOPA is converted into dopamine by the removal of a molecule of carbon dioxide via the enzyme aromatic amino acid decarboxylase, also called DOPA decarboxylase (Step 3 of Figure 3.6). This enzyme is extremely efficient, which may explain why

brain levels of L-DOPA tend to be very low and why providing exogenous L-DOPA to patients who lack sufficient dopamine—such as in patients with Parkinson's disease—leads to a dramatic increase in the production of dopamine. After synthesis, the dopamine is transported into a synaptic vesicle and stored until it is released from the axonal terminal (Step 4 of Figure 3.6).

In norepinephrine and epinephrine neurons, once dopamine is transported into the vesicle, it can be converted to norepinephrine by the vesicular enzyme, dopamine-beta-hydroxylase (Step 5 of Figure 3.6). In addition to dopamine-beta-hydroxylase, the vesicles contain copper. Copper is required for dopamine-beta-hydroxylase to function appropriately.

A very small group of neurons in the brainstem also express an enzyme, called phenolethanolamine-N-methyltransferase, that converts norepinephrine into the neurotransmitter epinephrine by adding a methyl group to the nitrogen atom (Step 6 of Figure 3.6). Epinephrine should be seen more as a hormone than intraneuronal signal. In addition to being released by neurons, it is also secreted by the medulla of the adrenal glands and does not enter the brain. It produces the peripheral manifestations of strong emotions such as fear or anger when it is released into the bloodstream.

Vesicles used for storage of dopamine, norepinephrine, and epinephrine.

Vesicles are very tiny lipid spheres with hollow centers. Neurotransmitters are actively transported into these vesicles. In Psychopharmacology, you will learn about drugs that can selectively inhibit this transfer process. Many vesicles also contain the antioxidant ascorbic acid, also known as Vitamin C. The Vitamin C maintains the integrity of these neurotransmitters within the vesicle in the same way that ascorbic acid added to processed meats, such as hotdogs, lengthens the shelf life of these products. Neurons require anti-oxidants such as Vitamin C because they are continually exposed to oxygen from the blood. Without Vitamin C, most neurotransmitters oxidize easily and become inactive while in storage inside the vesicles.

Receptors

Neurotransmitters relay their messages by traveling between cells and attaching to specific receptors on target cells. When a neurotransmitter attaches to a receptor, it triggers an action in the target cells. Receptors, even for a single neurotransmitter, exist as many different types that are differentially distributed and produce unique post-synaptic effects. Norepinephrine binds to three main G-protein-linked receptors: alpha1, alpha-2, and beta receptors that are located throughout the brain. Epinephrine can also stimulate all the adrenergic receptors including alpha and beta subtypes.

Dopamine binds to five different types of receptors, labelled D1-D5. Receptors have different, but often overlapping, functions. Figure 3.7 shows two different dopamine receptors that act via G-protein-linked receptors: one activates the enzyme adenylyl cyclase while the other inactivates this enzyme.

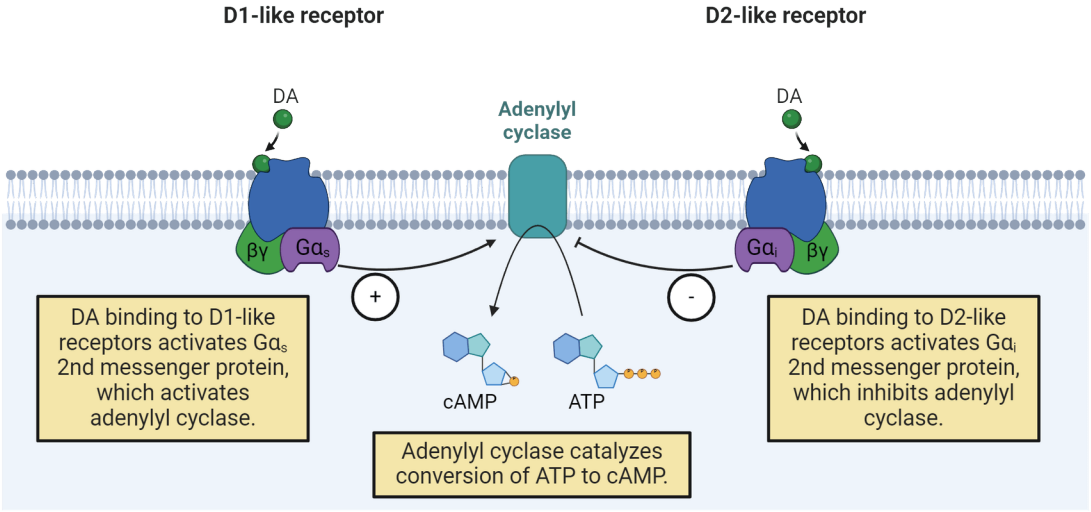


Figure 3.7 Dopamine receptors

Once again, notice that the function of any receptor depends upon which region of the brain the receptor is located and the nature of its second messenger, G-protein-linked systems.

Inactivation of dopamine, norepinephrine, and epinephrine

After dopamine, norepinephrine or epinephrine are released from the axonal terminal, they bind to specialized protein receptors on both the pre- and post-synaptic membranes. Most of the dopamine, norepinephrine, and epinephrine molecules are re-absorbed by the axonal terminal, a process called re-uptake, by low-capacity, high-affinity transporters or by either of the high-capacity, low-affinity organic cation transporters or plasma membrane monoamine transporters. Drugs, mostly anti-depressants, have been developed that selectively target each of these reuptake transporters. These neurotransmitter molecules are then re-packaged in vesicles and re-released again. The dopamine and norepinephrine molecules remaining in the synaptic cleft are catabolized by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (Step 7 of Figure 3.6).Under normal aerobic conditions, the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) are transported out of the brain and can be measured in the cerebrospinal fluid and urine as an indirect indicator of the health of these neural systems.

The functions of dopamine, norepinephrine, and epinephrine

The functions of dopamine and norepinephrine depend entirely on the function of the structures in which they are located. Consider the basal ganglia, a collection of nuclei that are responsible for producing normal movement. The level of the neurotransmitter dopamine in these nuclei is one hundred times higher than in the surrounding brain regions. Therefore, scientists have concluded that dopamine within the basal ganglia is involved in the control of movement. Furthermore, if we expose your brain to a drug that impairs the function of dopamine or the neurons that produce and release it, then your ability to move will be impaired. However, it would be incorrect to assume that dopamine is only involved with movement—it is not. You can also find dopamine in the retina of your eye and in your hypothalamus, structures that have nothing to do with movement. The nucleus accumbens receives an input of dopamine axonal projections that originate in the midbrain. Drugs that enhance the release of dopamine in the nucleus accumbens induce considerable motor stimulation always toward the rewarding stimulus. Thus, dopamine sometimes has mixed actions that influence movement. The multiple roles played by dopamine in the brain have contributed to difficulty in developing drugs to treat specific psychological and neurological conditions due to unintended effects on other brain circuits that use the same neurotransmitter.

Similar to dopamine, the neurotransmitter norepinephrine influences the function of multiple brain systems. It can be found in the hippocampus, a structure critical for forming new memories. Thus, norepinephrine influences the formation of memories. However, norepinephrine also plays a role in other brain regions that have nothing to do with making memories. The take-away point is that there is no such thing as a specifically unique “dopamine function” or an exclusively distinct “norepinephrine function.” The brain region that the neurotransmitter is found within defines its function, not the neurotransmitter itself. This statement is true for all neurotransmitters. In fact, neurotransmitters exhibit a complex array of actions in different brain regions, and so we can rarely make a single universal statement about their role in brain function.

We know a lot about dopamine and norepinephrine primarily because so many drugs and nutrients have been discovered that can modify their function. Norepinephrine underlies the major components of arousal and behaviors that arise in association with increased arousal; dopamine is intimately related to the control of movement, aspects of consciousness, hormone release, visual image processing and the experience of reward.

In humans, almost all norepinephrine neurons are located within a region called the locus coeruleus (Latin for “blue area” due to the presence of so many copper ions) that lies in the floor of the 4th ventricle (Figure 3.8).

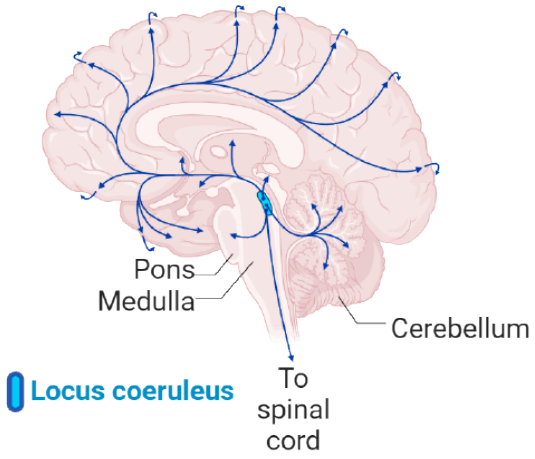


Figure 3.8 Norepinephrine system anatomy

The name of this region is related to the fact that these neurons concentrate copper into the pigmented polymer neuromelanin. Neuromelanin is synthesized from the precursor L-DOPA. Although copper is required for the synthesis of norepinephrine, the concentration of the copper in the locus coeruleus far exceeds what is necessary for neurotransmitter synthesis. Unfortunately, the presence of this metal makes these neurons vulnerable to oxygen, leading to oxidative stress, which poses a particular risk for these neurons. Norepinephrine neurons in the locus coeruleus project throughout the brain, mostly unilaterally. Their diffuse widespread projection into virtually all brain regions allows them to influence your level of arousal and almost every aspect of behavior.

Dopamine neurons are more numerous (by about five times) than norepinephrine neurons. However, they do not project as widely throughout the brain. Instead, these neurons, which originate in the ventral midbrain, send axonal projections forward primarily into basal ganglia and frontal lobes (Figure 3.9).

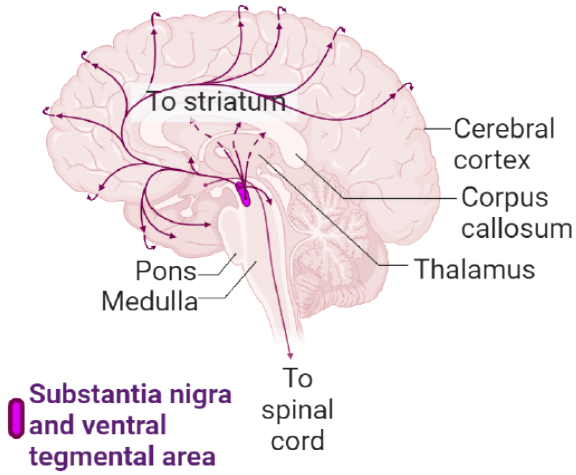


Figure 3.9 Dopamine system anatomy

One major dopamine pathway originates within the substantia nigra, or dark substance, so called because this region concentrates iron into neuromelanin. The oxidation of iron in the neuromelanin (you know this process as rusting) contributes a significant degree to the vulnerability of dopamine neurons to oxygen. Dopamine-containing neurons may be vulnerable to the presence of oxygen due to its original role in plants as an antioxidant; the dopamine molecule may sacrifice its molecular integrity during oxidative stress. Due to the presence of various toxins, mostly insecticides, in our environment and the oxygen that we

require for mitochondrial oxidative metabolism, these neurons are gradually lost with aging. In the US today, the greatest risk for developing Parkinson's disease is growing up in a rural environment around pesticides (Tanner et al., 2011).

Another pair of dopamine pathways originates in a region of the midbrain near the substantia nigra and ascends upward into the brain. One pathway projects to the limbic system, brain regions that are associated with the control of emotion. The other dopamine pathway projects to the frontal lobes and may play a critical role in the generation of pleasure and consciousness. For more than 50 years, scientists have speculated that both too little and too much activity in these pathways underlies the symptoms associated with psychosis. Currently, though, dysfunction of dopamine neurons is no longer considered the direct cause of psychosis. Instead, some recent studies suggest that dysfunction of glutamate NMDA receptors also play a role (Dong et al., 2023).

Generally, in a normal healthy person, the production of dopamine and norepinephrine is not easily affected by dietary supplements but can be negatively affected by a lack of nutrients. The reason is that the first enzyme in the production of dopamine and norepinephrine, tyrosine hydroxylase, is a rate-limiting step in the synthesis pathway. For example, consuming more tyrosine will not induce this enzyme to produce more dopamine.

History of neuroscience: Exciting discoveries that led to misleading conclusions

Sometimes, exciting discoveries lead to misleading conclusions about the function of a particular neurotransmitter. In 1817, James Parkinson wrote the first description of the disease that would be given his name. In the 1920s, scientists identified damage within the substantia nigra in the postmortem brains of Parkinson's disease patients. Then, in the 1960s, came the first reports of reduced dopamine as the cause of the symptoms. Parkinson recommended blood-letting from the neck as a potential therapy. Fortunately, it was discovered that precursor therapy using L-DOPA was considerably more effective, though it did not alleviate all symptoms of Parkinson's disease. This amazing discovery led a generation of scientists and physicians to search for other neurological disorders that could be treated with such simple targeted therapies. Every time this approach was attempted, it failed. The problem is that neurological and psychiatric disorders are far more complex. Even in the case of Parkinson's disease, many symptoms are due to a lack of dopamine, but a few others are due to deficits in other neurotransmitter systems in the brainstem. This may explain why simply replacing dopamine does not produce a removal of all the symptoms. The next time you read or hear someone state that such-and-such disease (for example, depression) is due to the dysfunction of a single neurotransmitter (such as serotonin) because we treat depressed people with serotonin-enhancing drugs, rest assured that those statements are both inaccurate and naïve.

Neurochemistry in the news: dopamine equals sex and love?

Dopamine has also been called the pleasure molecule. Is dopamine the "single chemical in the brain that drives love and sex," as many popular books and new articles claim. No. Such statements are naïve oversimplifications of the truth. Current evidence suggests that dopamine's role in the experience of pleasure is far more complicated. For example, some dopamine neurons cause a hedonic (positive) response to an anhedonic (negative) experience. Each process is regulated by specific dopamine circuits (Der-Avakian and Markou, 2012). In addition, some dopamine neurons become active prior to experiencing the reward. Dopamine neurons in the ventral tegmental area, the classic "pleasure center" of the popular literature, are actually involved in reward prediction. The dopamine neurons in this area facilitate "goal-seeking" behaviors; they fire faster when bigger rewards are expected and alter their firing in characteristic ways when the expected reward is smaller than expected. Furthermore, dopamine is not the only neurotransmitter in the brain that produces pleasure associated with a reward, food or sex. Serotonin, endocannabinoids, endorphins and the neuropeptide oxytocin also play important roles. Finally, as mentioned earlier, you can also find dopamine neurons in the retina of your eye and in your hypothalamus, where it controls release of the hormone prolactin; these actions have little to do with the experience of pleasure.

Serotonin

This section will describe the lifecycle and functions of serotonin (often abbreviated 5HT).

Synthesis

The neurotransmitter serotonin is built from a molecule of the amino acid tryptophan. Tryptophan is actively transported across the blood-brain barrier (step 1 in Figure 3.10). Tryptophan is utilized by all the cells in the brain to produce proteins for a variety of purposes that have nothing to do with neurotransmission. Serotonin neurons produce a series of enzymes that convert a small percentage (less than one tenth of one percent) of the tryptophan absorbed by the brain into serotonin. The process begins inside the cytoplasm of the serotonin neuron with the conversion of tryptophan into 5-hydroxytryptophan by the addition of a hydroxy molecule to the benzene ring via the enzyme tryptophan hydroxylase (step 2 in Figure 3.10). This enzyme is the rate-limiting step in the production of serotonin (Fernstrom, 2013). Unlike tyrosine hydroxylase, which is close to saturated with tyrosine under normal conditions, tryptophan hydroxylase is only half saturated with tryptophan (Young and Gauthier, 1981). Therefore, the entry of additional dietary tryptophan into the brain will lead to the production of more serotonin. Next, also occurring in the cytoplasm, 5-hydroxytryptophan is converted into serotonin by the removal of a carbon dioxide molecule via the enzyme aromatic amino acid decarboxylase, also often called 5-hydroxy-tryptophan decarboxylase (step 3 in Figure 3.10). Notice that the production of serotonin involves the same two chemical reactions, the addition of a hydroxy molecule and removal of a carbon dioxide molecule, that were used to produce the neurotransmitters dopamine and norepinephrine. The enzymes involved are also genetically similar to each other and likely evolved from genetic duplication.

Once produced in the cytoplasm, serotonin can either be stored in synaptic vesicles and released a fashion similar to dopamine and norepinephrine, or, despite having a positive charge, can cross cell membranes through a diffusion-like process (step 4 in Figure 3.10). Multiple low-affinity, high-capacity, sodium-independent transporters, widely expressed in the brain, allow the carrier-mediated diffusion of serotonin into forebrain neurons. The amount of serotonin crossing cell membranes through this mechanism under physiological conditions is considerable (Andrews et al., 2022).

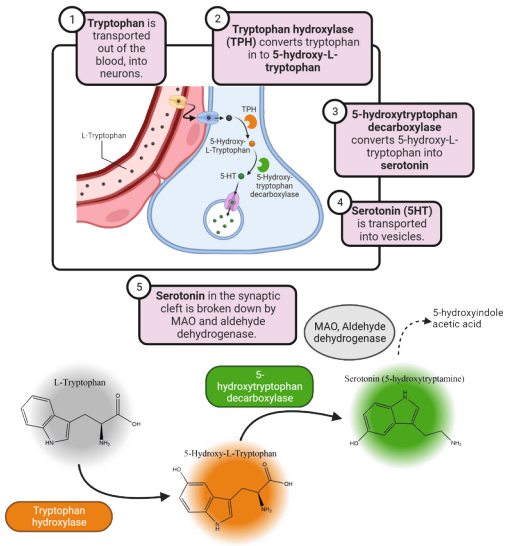


Figure 3.10 Serotonin synthesis

Receptors

Serotonin is one of the most ancient signaling molecules in nature. Bananas, single-celled paramecium, insects, and humans all synthesize it. The first primordial serotonin receptor is related to the rhodopsin protein found in the retina and may have first appeared almost one billion years ago; a time that likely predates the appearance of acetylcholine, dopamine, or norepinephrine. During this time, evolution greatly differentiated the serotonin receptors into a large and diverse group of proteins that are often less than 25% homologous with each other. This long evolutionary history underlies why serotonin plays a variety of roles throughout the brain, including behaviors such as aggression, appetite, sex, sleep, mood and cognitive function.

There are many different serotonin receptors in the brain and body (Table 3.1). It is difficult to assign a specific function to each receptor; once again, it depends on where the receptor is located, and the nature of the biochemical mechanisms activated by the receptor.

Receptor Subtypes	Signaling Mechanism	Distribution	Effects
5-HT_{1A}	Gi,↓cAMP	Raphe nuclei, hippocampus	Regulates sleep, feeding, and anxiety
5-HT_{1B}	Gi,↓cAMP	Substantia nigra, globus pallidus, basal ganglia	Neronal inhibition, behavioral changes
5-HT_{1D}	Gi,↓cAMP	Brain	Vasoconstriction
5-HT_{1E}	Gi,↓cAMP	Cortex, hippocampus	Memory
5-HT_{1F}	Gi,↓cAMP	Globus pallidus, putamen	Anxiety, vasoconstriction
5-HT_{2A}	Gq,↑IP_3	Platelets, cerebral cortex	Cellular excitation, muscle contraction
5-HT_{2B}	Gq,↑IP_3	Stomach	Appetite
5-HT_{2C}	Gq,↑IP_3	Hippocampus, substantia nigra	Anxiety
5-HT_3	Na^+-K^+ ion channel	Area postrema, enteric nerves	Vomiting
5-HT_4	Gs,↑$cAMP_3$	Cortex, smooth muscle	Gut motility
5-$HT_{5A,B}$	Gs,↓cAMP	Brain	Locomotion, sleep
5-HT_6	Gs,↑cAMP	Brain	Cognition, learning

Table 3.1

Consider one serotonin receptor called 5HT-1A. Studies of genetically altered mice and positron emission tomography studies on humans have been very useful in demonstrating the potential role of this receptor in the regulation of mood and anxiety. For example, mice and humans born with fewer serotonin type 5HT-1A receptors show more anxiety-like behavior (Olivier et al., 2001). Some of the newer anti-anxiety medications stimulate the 5HT-1A receptors. Interestingly, almost all the known hallucinogens stimulate at least two serotonin receptors, the 5HT-1A and 5HT-2A. More will be presented about anti-anxiety medications and hallucinogens in Psychopharmacology.

Inactivation of serotonin

After serotonin is released from the axonal terminal, and after it has interacted with receptors, one of two things can happen. 1) Most of the serotonin molecules are re-absorbed by the axonal terminal, repackaged into synaptic vesicles, and re-released again. 2) The serotonin molecules that are not removed by re-uptake are catabolized by the enzyme monoamine oxidase (step 5 in Figure 3.10). The product of this catabolism, 5-hydroxyindole acetic acid (5-HIAA), is ultimately removed from the brain and can be measured in the cerebrospinal fluid and urine.

Functions of serotonin

To understand the role of serotonin in the brain, one should first consider the entire body. Ninety percent of the total serotonin in the body is contained within the neurons of the gut. About 8% of the body's serotonin is found in the blood and is localized inside platelets and mast cells; in fact, serotonin was initially discovered in the serum and determined to have tonic (or constricting) effects on the vascular system—hence its name. About two percent of the body's serotonin is found in the pineal gland, which is located inside the skull but not considered part of the brain. The remaining one-half of one percent of the body's serotonin is found in the brain. The nuclei that contain serotonin neurons are in roughly the same anatomical location in the human brain as in every other vertebrate or invertebrate brain which implies a conservation of purpose across time (Berger and Gray, 2009). Despite the relative scarcity of serotonin neurons in your brain, drugs that alter serotonin function can produce profound changes in how you experience the world around you. Serotonin regulates various activities, including behavior, mood, memory, and gastrointestinal homeostasis.

Neurons that produce and release serotonin in the brain are organized into a series of nuclei that lie in a chain along the midline, or seam, of the brainstem; these are called the Raphe nuclei (raphe means "seam" in Latin) (Figure 3.10).

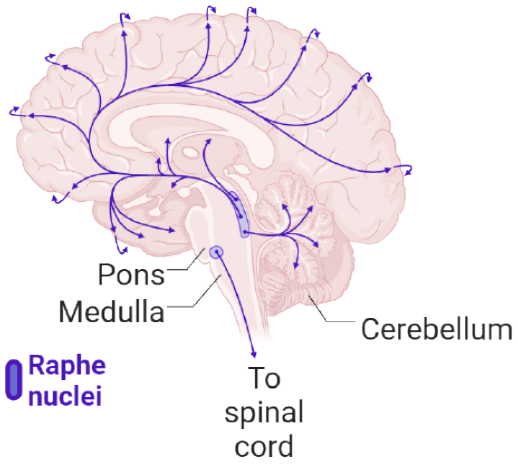


Figure 3.11 Serotonin system anatomy

These neurons project their axons to every part of the brain, and some of these axons form synaptic connections with small blood vessels. Serotonin controls the availability of blood to regions of the brain associated with its function. Another group of serotonin neurons project down-ward into the spinal cord to provide control over the autonomic nervous system and incoming pain signals.

If you were able to insert a recording device into the major raphe nuclei and "listen" to the activity of your serotonin neurons, you would discover that they have a regular, slow spontaneous level of activity that varies little while you are awake. When you fall asleep, the activity of these neurons slows. When you start to dream, these neurons temporarily cease their activity.

Neurochemistry in the news: getting a good sleep with serotonin

Some over-the-counter products claim that your mood and sleep will improve by consuming the amino acid precursor to serotonin. Consider what happens is you consume a pill containing 500 mg of tryptophan. (Don't bother with turkey meat, it is quite low in tryptophan levels.) First, the thousands of serotonin neurons in your gut feast on most of the tryptophan in the pill. The remaining tryptophan that is transported across the gut-blood barrier is then absorbed by one of the billions of platelets in the blood or by one of the trillions of cells in the body which utilize tryptophan to build proteins or hormones. The very small number of tryptophan molecules that do get transported across the blood-brain barrier are consumed by cells within the pineal gland for the production of melatonin or absorbed by one of the hundreds of billions of non-serotonergic cells that live within the brain. Finally, the few molecules of tryptophan that are still floating around in the extracellular space of the brain may be absorbed by a serotonin neuron in one of the raphe nuclei. Consuming tryptophan may ultimately lead to increased production of serotonin in the cytoplasm of serotonin neurons and improved mood in healthy adults (Asako et al., 2021).

Neuropeptides

The neuropeptide neurotransmitters can be quite small, only four or five amino acids strung together, or quite large, containing hundreds of amino acids folded into complex three-dimensional structures. Neurons that produce and release these neuropeptides are found throughout the brain. Neuropeptides may also be released along with the classical neurotransmitters, such as acetylcholine, dopamine and serotonin, from the same neuron. Which neurotransmitter is released is determined by the firing rate of the neuron; faster firing rates release neuropeptides.

Synthesis

Neuropeptide neurotransmitters are synthesized via a complicated, time consuming (about two to four weeks), and energy-demanding process of reading the DNA code to produce mRNA that can be translated into a long string of amino acids (step 1

in Figure 3.12). The process utilizes the rough endoplasmic reticulum and Golgi apparatus where the long string of amino acids, called a pre-pro-peptide at this point, is converted enzymatically into intermediate shorter versions called pro-peptides, until finally being enzymatically converted into an active neuropeptide that is then packaged in synaptic vesicles that are transported down the axon to await release (step 2 in Figure 3.12).

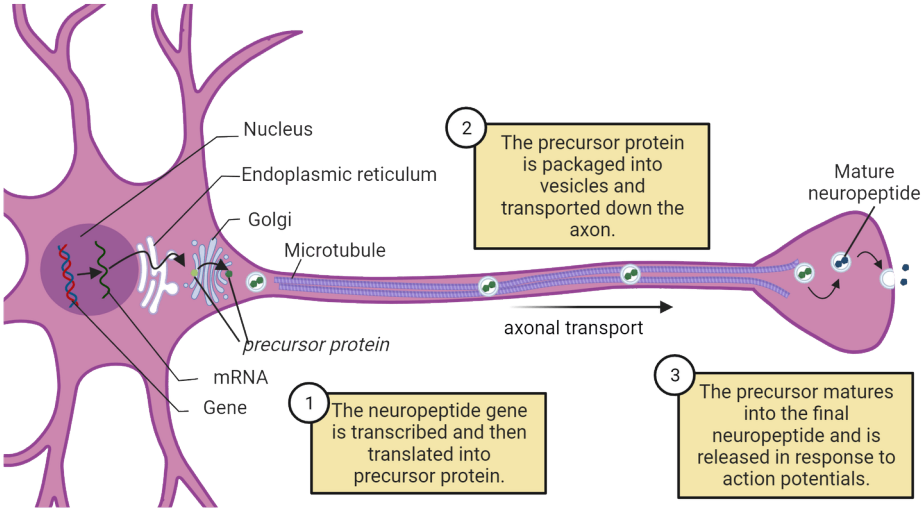


Figure 3.12 Synthesis of neuropeptides

After being released from the terminal axon (step 3 in Figure 3.12), the neuropeptide binds to its specific post-synaptic receptor and is then quickly inactivated by enzymatic degradation that generates not only biologically inactive fragments but also biologically active fragments that can modulate or even counteract the response of their parent peptides. Let's consider two of the best studied neuropeptides with considerable relevance, the endogenous morphine-like peptides called endorphins and oxytocin.

Endorphins

Endorphins are one of 4 families of endogenous opioids (thus, their name): endorphins, enkephalins, dynorphins, and endomorphins. Three of the most studied are shown in Table 3.2.

Family	Precursors	Peptides	Receptors
Endorphins	Proopiomelanocortin (POMC)	α-Endorphin β-Endorphin γ-Endorphin	μ-Opioid
Enkephalins	Proenkephalin (PENK)	Met-Enkephalin Leu-Enkephalin	Δ-Opioid μ-Opioid
Dynorphins	Prodynorphins (PDYN)	Dynorphin A Dynorphin B α-Neoendorphin β-Neoendorphin	κ-Opioid

Table 3.2

Each family has several opioid-like peptides within it. Endorphins have a diverse range of actions in the brain: they modulate the pain signals carried from the periphery to the higher centers of the brain, regulate numerous neuroendocrine or neuroimmune functions, and influence mood. Endorphins interact with families of various receptors. For example, when the "mu" opiate receptor is stimulated, it relieves pain and induces feelings of pleasure or euphoria. Endorphins are released in response to laughing, eating, intense exercising, listening to music, walking in the sunshine (it's the UV light), having sex, and so on. The emotional experience is ephemeral because endorphins have a very short life span once released; they are quickly catabolized by peptidases.

People behind the science: Candace Beebe Pert and endorphins

Candace Beebe Pert (June 26, 1946 – September 12, 2013) was an American neuroscientist, pharmacologist, and my dear friend, who discovered the opiate receptor, the cellular binding site for endorphins in the brain. Candice told me that she sampled her own blood during her pregnancy to monitor changes in blood-borne endorphins. While the discovery of the elusive endorphin receptor earned the coveted Albert Lasker Award (often a precursor to the Nobel Prize), the prize was awarded to the head of the laboratory, Dr. Solomon H. Snyder, without citing Candace. She wrote a letter to the head of the Lasker Foundation, claiming that her exclusion was due in part to being a woman. Ultimately, Dr. Pert became Chief of the Section on Brain Biochemistry at the National Institute of Mental Health. Candace was as brilliant as she was passionate about advancing women in science.

Oxytocin

Oxytocin is a neuropeptide that is synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus. It is synthesized as a large inactive precursor protein and progressively hydrolyzed into smaller fragments and stored in a vesicle. Oxytocin neurons send axons into the posterior pituitary gland as well as throughout the limbic system, olfactory bulb, nucleus accumbens (the brain's principal pleasure center), brainstem (to regulate pain), and cortex (Figure 3.13). Oxytocin receptors are G-protein-linked and are found on the presynaptic and postsynaptic membranes. Oxytocin also acts partially on vasopressin receptors, which complicates understanding its functions. It also indirectly modulates neurogenesis (the birth of new neurons) and synaptic plasticity via these receptors.

Oxytocin has several behavioral functions. In highly social animals, oxytocin, supported by actions of the endocannabinoid system, intensifies social attachment by conveying the social salience of environmental stimuli. Elevated levels of oxytocin via intranasal administration have been linked to a range of cognitive and behavioral effects including within-group conformity, trust, affiliation, and cooperation. Oxytocin also promotes aggression toward threatening out-group rivals and may underlie aspects of racism (Zhang et al.,2019). It appears to play a role in stimulating bonding between mother and child. Other studies have linked exposure to oxytocin with reduced social anxiety. Despite the many popular claims, there is no evidence that oxytocin has an aphrodisiac effect. Experiments with human couples sniffing oxytocin have not shown any increased tendency to fall in love.

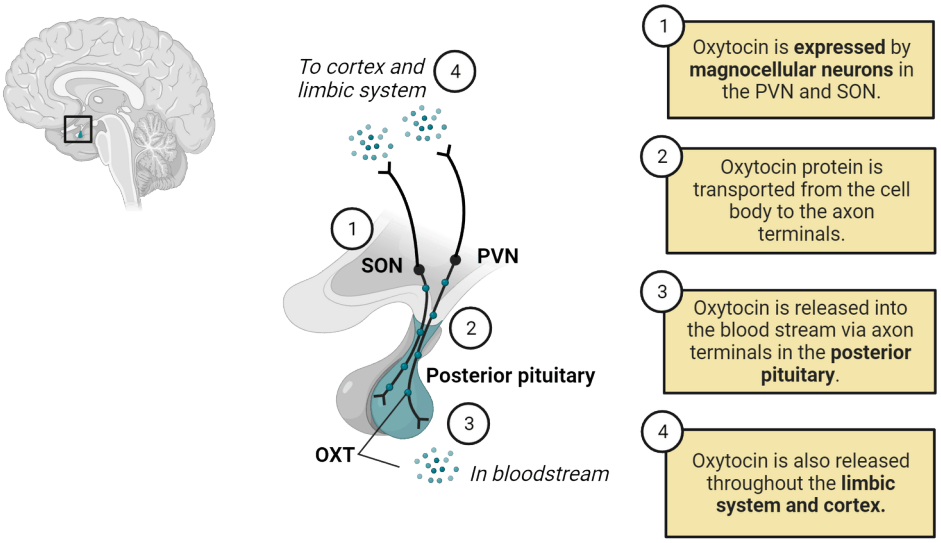


Figure 3.13 Oxytocin networks

Glutamate and GABA

These two amino acids are utilized by more neurons as a neurotransmitter than any other. Glutamate is the principal producer of excitation while GABA (gamma-amino butyric acid) is the principal producer of inhibition. The lifecycle of glutamate is shown in Figure 3.14. The lifecycle of GABA is shown in Figure 3.15. Because these lifecycles overlap substantially, we will discuss them in

tandem.

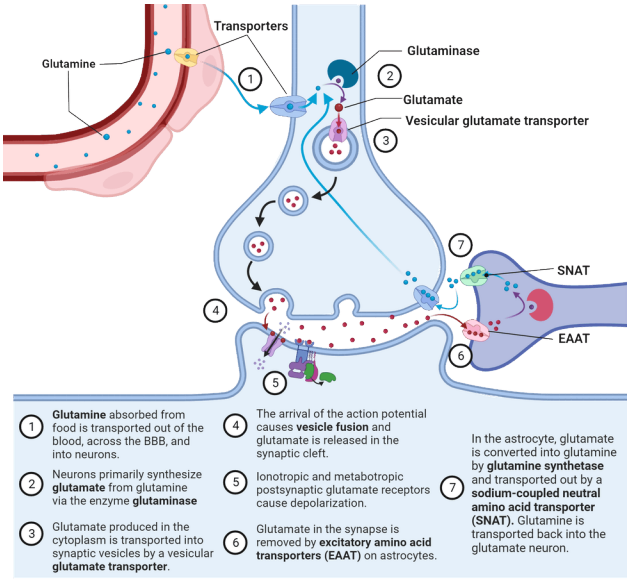


Figure 3.14 Glutamate lifecycle

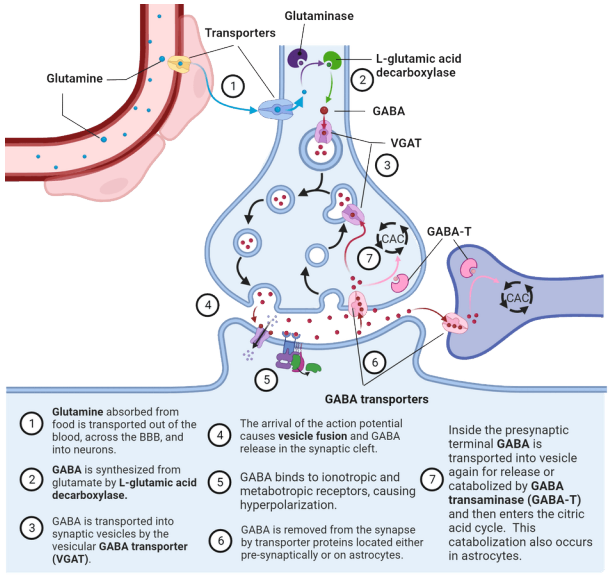


Figure 3.15 GABA lifecycle

Synthesis

The production of both neurotransmitters begins with the amino acid glutamine being transported across the blood brain barrier and requires the participation of an astrocyte (Step 1 in both Figure 3.14 and Figure 3.15). Glutamine is then converted into glutamate by the enzyme glutaminase inside the cytoplasm of both types of neurons (Step 2 in Figure 3.14). It is then packaged into vesicles, if the neuron is glutamatergic (Step 3 in Figure 3.14). If the neuron is GABAergic, glutamate undergoes conversion into GABA by glutamic acid decarboxylase, which requires pyridoxal phosphate (the active form of vitamin B6) as a cofactor and removes a molecule of carbon dioxide (Step 2 in Figure 3.15). The newly synthesized GABA is then transported by the vesicular GABA transporter (VGAT) protein into synaptic vesicles (Step 3 in Figure 3.15). GABA and glutamate are stored in vesicles until released by their respective neuronal terminals following the arrival of an action potential (Step 4 in both Figure 3.14 and Figure 3.15).

Receptors

Glutamate signaling activates a family of receptors consisting of metabotropic glutamate receptors and ionotropic glutamate receptors (Figure 3.16). Three of these receptors are ligand-gated ionotropic channels: NMDA receptors, AMPA receptors, or kainate receptors. These glutamate receptors were named after the agonists that activate them: NMDA (N-methyl-d-aspartate), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), and kainic acid. These ionotropic glutamate receptors are nonselective cation channels; they will allow the passage of Na+ and K+, and small amounts of Ca2+. AMPA, kainate, and NMDA receptor activation always produce excitatory postsynaptic responses. All three of these ionotropic receptors are formed from the association of several protein subunits. The metabotropic glutamate receptor, in contrast, is formed from a single protein and functions as a G-protein linked receptor that provides a mechanism for glutamate to modulate cell excitability and synaptic transmission via second messenger signaling pathways.

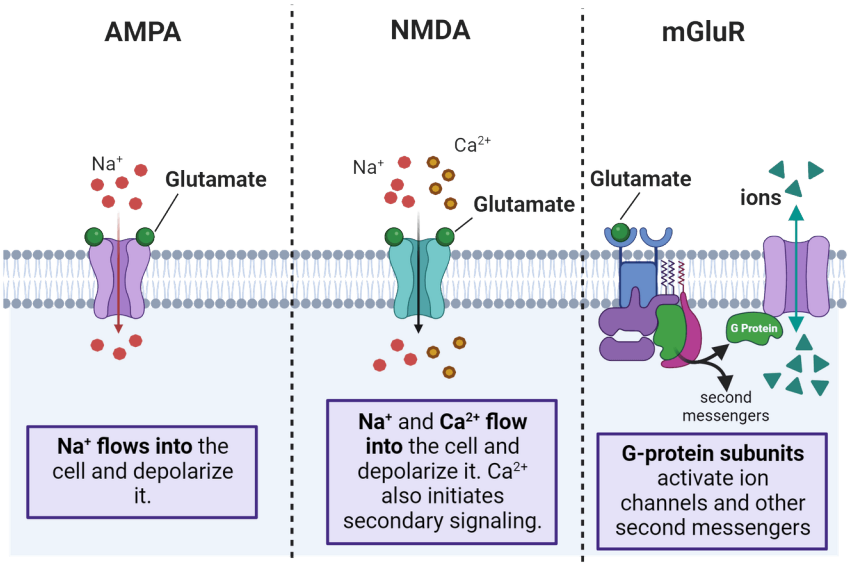


Figure 3.16 Glutamate receptors

GABA receptors are divided into GABA-A and GABA-B (Figure 3.17). Recently a GABA-C receptor was defined. Less is known about its function, but it appears, based on its sequence homology and structure, to have evolved from the nicotinic acetylcholine receptor. GABA-A is a fast-acting ligand-gated ion channel/inotropic receptor. The binding of GABA opens an ion pore to allow negatively charged chloride ions to move across the cell membrane into the cell, increasing the resting negative potential inside the cell. This is also known as hyperpolarization. GABA-A receptors are located throughout the central nervous system with a high concentration in the limbic system and cortex.

The GABA-B receptor is a G-protein linked receptor that leads to the opening of potassium channels, allowing the efflux of positive ions down their concentration gradient leading to the hyperpolarization of the cell membrane. Adenylyl cyclase is also activated, which prevents calcium entry; this action inhibits presynaptic release of other neurotransmitters. GABA-B receptors are slow-acting synaptic inhibitors and are in cortex and thalamic efferent pathways.

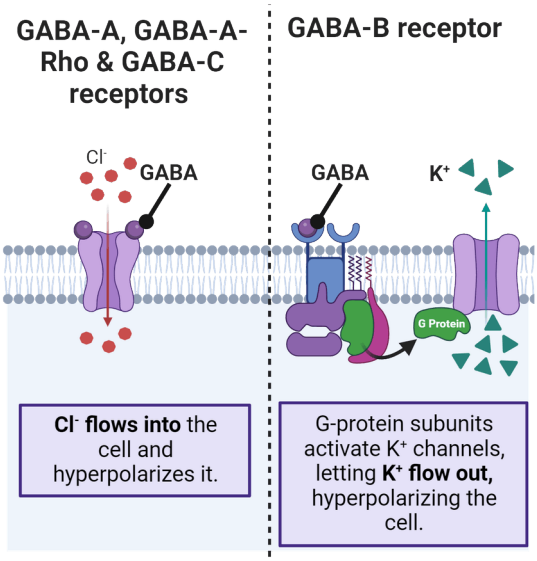


Figure 3.17 GABA receptors

Inactivation of glutamate and GABA

After interacting with their respective protein receptors in the synaptic space (Step 5 in both Figure 3.14 and Figure 3.15), released glutamate needs to be inactivated quickly, otherwise it may overstimulate the post-synaptic neuron and cause local degeneration. Fortunately, there are highly efficient transporters, called excitatory amino acid transporters (EAAT), that remove the glutamate in the synapse into astrocytes. Inside astrocytes, glutamate is converted into glutamine before being released into the extracellular space via the sodium-coupled neutral amino acid transporter (SNAT) (Step 6 and 7 in Figure 3.14). The extracellular glutamine is now available for re-use by glutamate neurons.

Released GABA is inactivated by being transported into astrocytes via GABA Transporters (GAT) (Step 6 in Figure 3.15). Inside the astrocyte, the GABA will be enzymatically converted initially into glutamate, which can then enter the citric acid cycle, or be further converted into glutamine before being released into the extracellular space for reuse by nearby glutamate or GABA neurons (Step 7 in Figure 3.15).

The functions of GABA and glutamate

GABA- and glutamate-releasing neurons are densely located throughout the brain. They tend to function competitively to induce a balance of excitation and inhibition. Neurons spontaneously fire off action potentials due to their tendency to constantly leak potassium ions. The brain takes advantage of this tendency and processes information primarily via the actions of GABA-induced inhibition.

Glutamate neurotransmission is critical for probably the most important physiological process in the brain: learning. This process is mediated through a two-step process shown in Figure 3.18 that begins with the glutamate-induced depolarization of the post-synaptic membrane via the activation of the AMPA ionotropic receptors. At resting membrane potentials, external magnesium (Mg2+) ions enter the NMDAR channel and bind tightly, preventing the influx of any ions. Mg2+ ions are present at millimolar concentrations in the external milieu of neurons, while intracellular Mg2+ concentrations are in the micromolar range, resulting in a net inward driving force for Mg2+ ions at negative membrane potentials. A depolarization of sufficient amplitude and duration by activation of nearby AMPA receptors is required to dislodge the Mg2+ ions from the channel, thereby allowing the influx of sodium and calcium ions. The increase in intracellular calcium ion concentration activates a complex cascade of biochemical changes that ultimately involve the genes of the neuron and that may change how the neuron behaves for the rest of your life. This process underlies the brain's ability to learn.

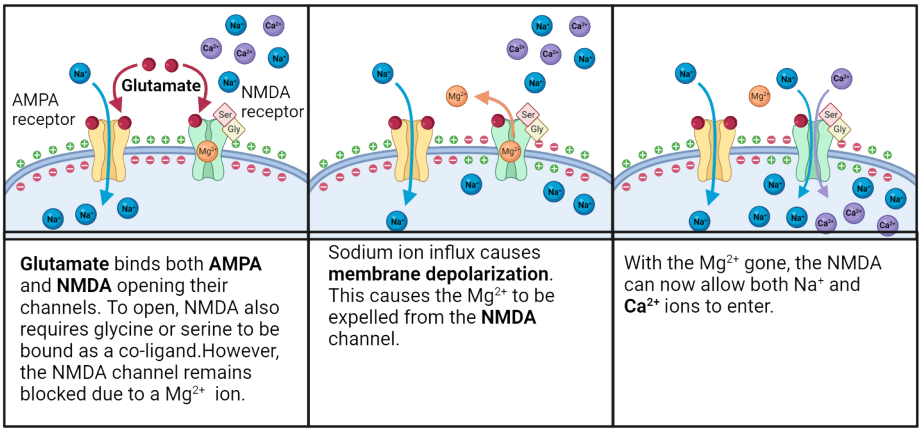


Figure 3.18 AMPA and NMDA functional interaction

Neuroscience in the news: eating GABA to calm the brain

A short search on the internet will uncover many different over-the-counter supplements containing GABA. The advertisements claim that this supplement will reduce stress and anxiety, and help you to fall asleep. Superficially, this makes sense. Anything that enhances GABA receptor function produces an overall decrease in the activity of neurons everywhere in your brain. This property of GABA has led to the development of highly effective anti-anxiety drugs that are GABA receptor agonists. Unfortunately, as is almost always true, the success of such claims about over-the-counter supplements depends upon the placebo effect. You cannot accomplish these effects simply by eating GABA-containing substances to increase the amount of GABA in your brain. While floating in the bloodstream, ingested GABA is mostly metabolized by the liver or consumed by the tissues of the body. Any remaining GABA molecules carry an electrical charge that prevents them from passing across the blood–brain barrier. Recall that the production of GABA begins with the amino acid glutamine being transported across the blood brain barrier, not GABA. Taking a few hundred milligrams of GABA every day, therefore, will not reduce your anxiety or help you sleep.

Histamine

Histamine neurons originate from the tuberomamillary nucleus of the posterior hypothalamus and send projections throughout the brain (Figure 3.19).

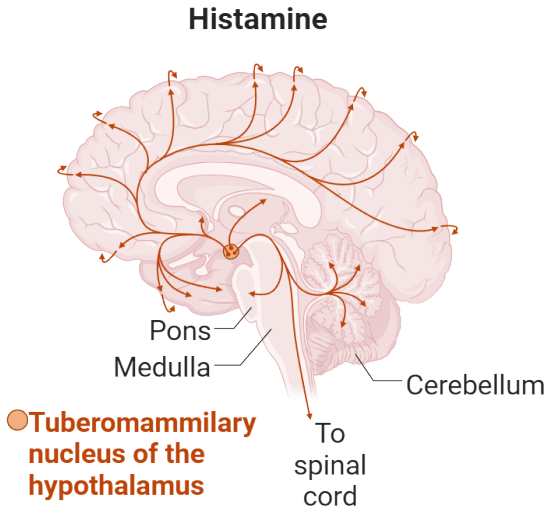


Figure 3.19 Histamine system anatomy

Histamine influences arousal, control of pituitary hormone secretion, suppression of eating and cognitive functions. I have included a discussion of this neurotransmitter because it is the target of so many different over the counter medications that are commonly overused.

Synthesis

Histamine is derived from the decarboxylation of the amino acid histidine, a reaction catalyzed by the enzyme L-histidine decarboxylase (step 1 and 2 in Figure 3.20). Once formed, histamine may be transported in vesicles by a plasma membrane monoamine transporter protein (step 3 in Figure 3.19).

Receptors

Histamine binds to G protein-coupled receptors, designated H1 through H4 (step 5 in Figure 3.20). The H1 and H2 receptors produce neuronal depolarization. The H3 receptor functions as an auto-receptor; it downregulates release of histamine, norepinephrine, acetylcholine, and serotonin (step 6 in Figure 3.20).

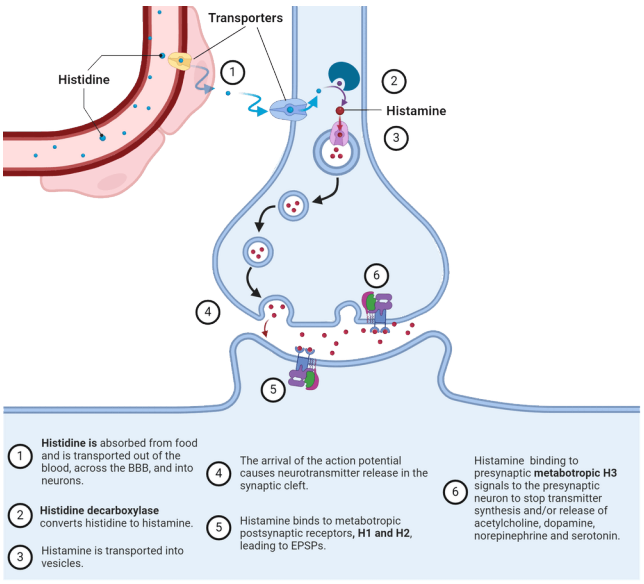


Figure 3.20 Histamine life cycle

Inactivation

Once released by fusion of synaptic vesicles, histamine is primarily catabolized by the enzyme histamine-N-methyltransferase. Unlike the other amino acid-derived neurotransmitters, neurons do not inactivate histamine by re-uptake.

Function of histamine

Histamine neurons, in tandem with neurons releasing norepinephrine, influence your level of arousal during the day. Any drug that reduces the actions of histamine will make you feel drowsy. You probably have taken antihistamines and experienced their adverse cognitive effects.

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3.7: Neurotransmitters Made from Fats

Learning Objectives

By the end of this section, you should be able to

- Describe how fat-derived neurotransmitters are produced and inactivated
- Define the function of each neurotransmitter discussed

The brain contains two important families of neurotransmitters that are physiologically active lipid compounds called either endocannabinoids or prostaglandins. They use related enzymatic systems for their production and inactivation. A third neurotransmitter, acetylcholine, is made from molecules of fat and acetate. Together, these three neurotransmitters influence mood, thinking and the experience of pain. This section will also introduce neurosteroids, a unique class of steroids that are synthesized in the brain and can rapidly modulate neuronal activity.

Endocannabinoids

This section will describe the lifecycle and functions of endocannabinoids.

Synthesis

The two currently best studied endocannabinoid neurotransmitters (there are at least seven) are anandamide and 2-AG (2-arachidonoyl-glycerol); 2-AG occurs at much higher levels in the brain than anandamide (Lu and Mackie, 2016). The production, synthesis and release of anandamide and 2-AG occur independently within the cell, suggesting that 2-AG and anandamide can be recruited differentially from the same postsynaptic neuron depending on the type of presynaptic signaling. The synthesis of both endocannabinoid neurotransmitters begins with phospholipid components of the neural membrane (Figure 3.21). Diacylglycerol (DAG) is produced first followed by enzymatic conversion into 2-AG via the enzyme diacylglycerol lipase (DAGL). A different membrane phospholipid is converted into N-arachidonoyl phosphatidylethanolamine (NAPE) which is then enzymatically converted into anandamide by the enzyme phospholipase D (PLD).

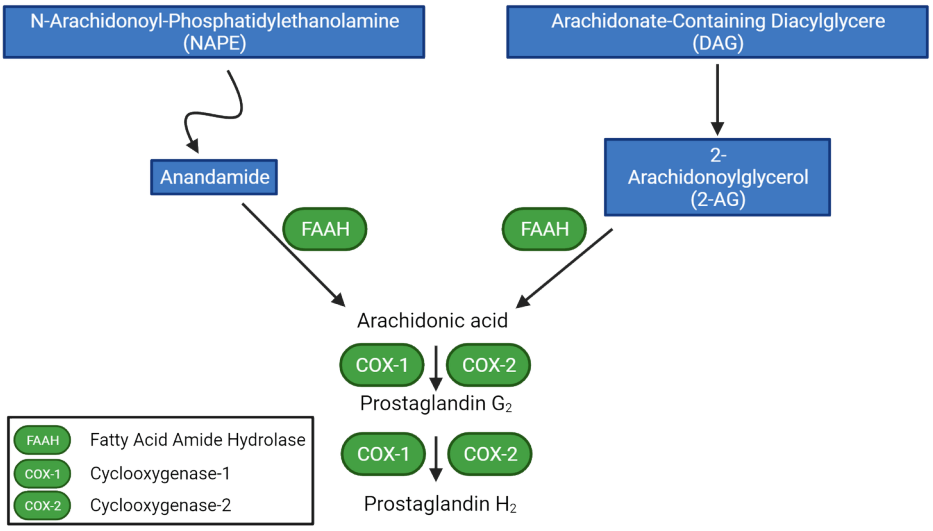


Figure 3.21 Synthesis of arachidonic acid and prostaglandins

Unlike the other neurotransmitters discussed thus far, these two endocannabinoids are not stored in synaptic vesicles. The depolarization of a postsynaptic neuron leads to Ca2+ influx through voltage-gated channels and causes the enzymatic de

novo generation and the release of endocannabinoids such as anandamide. Once produced they are released to flow in reverse direction (retrograde neurotransmission) across the synapse to find their receptors on the pre-synaptic side of the synapse (Figure 3.22).

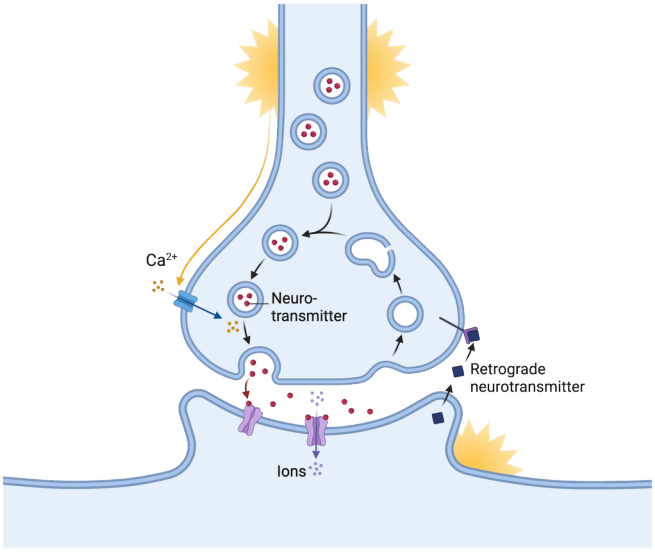


Figure 3.22 Retrograde neurotransmission Retrograde neurotransmitters are not packaged in vesicles. Instead, they are released by the postsynaptic cell and signal on receptors on the presynaptic cell.

Receptors

Two different types of endocannabinoid receptors are located throughout the brain and body. Anandamide binds best to CB1 receptors, while 2-AG binds best with the CB2 receptors (Figure 3.23).

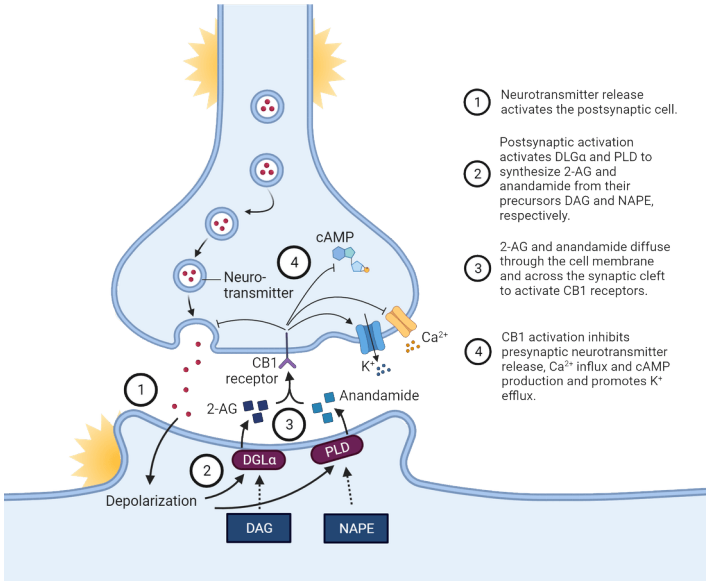


Figure 3.23 Function of endocannabinoid receptors

The type 1 receptors are densely distributed in several brain regions; the type 2 receptor is found at much lower levels in the brain. The type 1 receptor is among the most abundant G protein–coupled receptors in the brain. Anandamide and 2-AG also prevent the release of both glutamate and GABA, thus altering the balance of excitation and inhibition throughout the brain.

Inactivation of endocannabinoids

Anandamide is inactivated by either reuptake or catabolism by the enzyme fatty acid amide hydrolase (FAAH). 2-AG is inactivated by either reuptake or sequential catabolism by both FAAH and monoacylglycerol lipase (MAGL). The major product of this catabolism is arachidonic acid, which can be used to produce prostaglandins (see next section).

The functions of endocannabinoids

At the synaptic level, anandamide and 2-AG act retrogradely on pre-synaptic receptors to inhibit the release of a variety of neurotransmitters by altering the function of potassium and voltage-gated calcium channels. At the systems level, endocannabinoids influence appetite, mood, stress reduction, and the brain's inflammatory response. The endocannabinoids enhance goal-seeking behaviors by augmenting the actions of dopamine within the brain's pleasure centers in the ventral forebrain.

Prostaglandins

This section will describe the lifecycle and functions of prostaglandins.

Synthesis

Prostaglandins are synthesized from the fatty acid arachidonic acid via the enzyme cyclooxygenase (COX). Every prostaglandin contains 20 carbon atoms that includes a single 5-carbon ring. They are found throughout the body and brain. Like the endocannabinoids, prostaglandins are not stored in vesicles; they are produced on demand when they are needed and then released into the extracellular space via a specific protein transporter. Prostaglandins are not reused by the neurons. Prostaglandins are oxidized by NAD+-dependent 15-hydroxyprostaglandin dehydrogenase and then reduced by NADPH/NADH dependent delta13-15-ketoprostaglandin reductase.

Functions of prostaglandins

The variety of prostaglandins that exist and their wide distribution in the brain underlies their variety of functions. Glia release prostaglandins to activate pro-inflammatory cascades. Some prostaglandins are neuroprotective from the effects of hypoxia or ischemia. The sexual differentiation of the brain may depend on the actions of prostaglandins. Acutely, fever-producing agents induce the production of prostaglandins in the hypothalamus, altering body temperature regulation. In contrast, chronic inflammatory processes associated with prostaglandins may underlie the development of depression (Regulska et al., 2021). Generally, the level of most prostaglandins is kept quite low in the brain.

Acetylcholine

This section will describe the lifecycle and functions of acetylcholine.

Synthesis

Acetylcholine (commonly abbreviated ACh) is made by transferring a molecule of acetic acid on to a molecule of choline that is derived from the fatty acid lecithin (steps 1 and 2 in Figure 3.24). This conversion occurs via the action of an enzyme called choline acetyltransferase (Picciotto et al., 2012). The acetyl is derived from a molecule of sugar, usually glucose, that is initially modified inside the mitochondria. The brain needs sugar (usually in the form of glucose) to function normally. Once inside the brain, only a very small percentage of the dietary sugar is used to produce acetylcholine. The brain typically has a constant and ample supply of choline. Choline can be easily obtained from the diet, such as from eggs and baked goods. Despite this fact, many health foods stores sell choline powder to gullible customers, claiming that consuming more choline will somehow enable their brains to make more acetylcholine. Given the vital role of acetylcholine in learning and memory, this is an appealing claim. Regrettably, it has no basis in fact. For adults, the brain responds only to deficits in choline, not surpluses, in the diet. It has a ready source of choline in the diet or stored in the liver and, in fact, never develops a deficit in choline, even in patients with Alzheimer's disease. Thus, consuming extra choline does not induce your brain to make more acetylcholine. Instead, it only results in a gaseous by-product that you exhale and that smells like rotting fish. Rather than enhancing your cognitive abilities, choline

supplements merely generate a terrible case of bad breath.

Once acetylcholine is produced, it is transported into synaptic vesicles (step 3 in Figure 3.24). The vesicles containing acetylcholine fuse with the presynaptic membrane of the axon terminal in response to an action potential (step 4 in Figure 3.24). Each vesicle releases about 10,000 acetylcholine molecules into the synapse. Some of these acetylcholine molecules will bind to protein receptors on the surface of the nearby neuron (step 5 in Figure 3.24). Ultimately, all of them are inactivated by an enzyme.

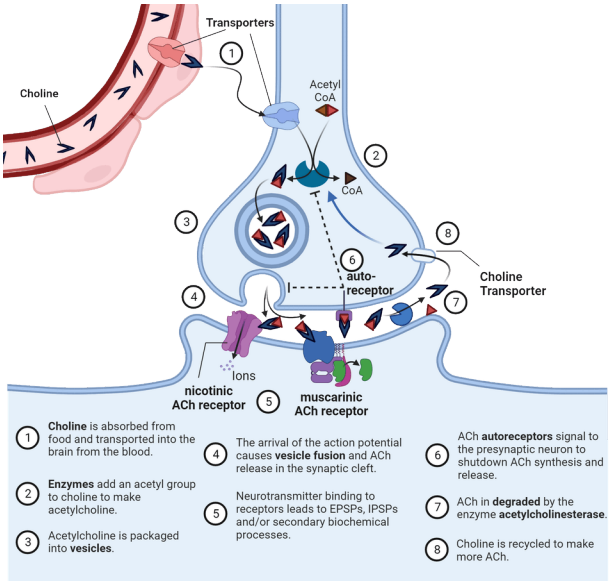


Figure 3.24 Acetylcholine lifecycle

Inactivation of Acetylcholine

Released acetylcholine molecules are quickly inactivated by the enzyme acetylcholinesterase (step 7 in Figure 3.24). Acetylcholinesterase has one of the fastest reaction rates of any of our enzymes, breaking up each molecule in about 80 microseconds (Taylor, 1991). Acetylcholinesterase breaks the acetylcholine into a molecule of acetate and choline. About forty percent of the choline will be reabsorbed into the axon terminal by specialized transport proteins and reused to produce more acetylcholine (step 8 in Figure 3.24). The remaining choline molecules and acetate will diffuse into the extracellular space and ultimately be removed from the brain. Knowledge about the chemistry and function of acetylcholinesterase led to the development of drugs that inhibit the enzyme acetylcholinesterase and greatly increase the amount of acetylcholine in the synapse. Today, acetylcholinesterase inhibitors are common treatments for Alzheimer's disease. In theory, the drugs should compensate for the loss of acetylcholine neurons in these patients; in practice, the drugs provide little clinical benefit because too few healthy acetylcholine neurons are still present in the brain.

Receptors

Once released into the synapse, the neurotransmitter acetylcholine can act on two quite different protein receptors that have been designated, as have most receptors, according to the compounds that were originally used to study them—in this case, muscarine and nicotine (Figure 3.25).

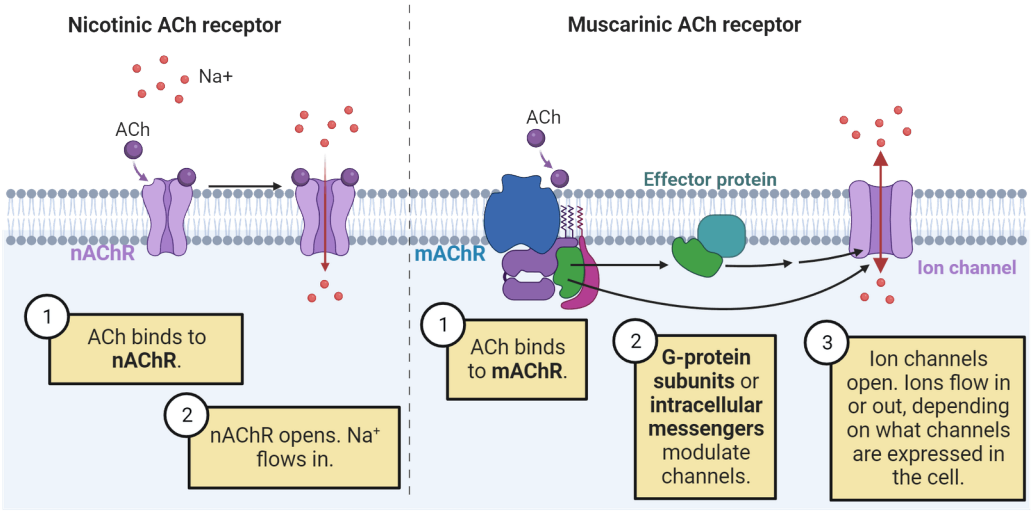


Figure 3.25 ACh channels

Most of the acetylcholine receptors in the brain are the muscarinic subtype, whereas less than 10% are nicotinic. They differ in size, structure, and mechanism of action; yet they both respond to acetylcholine. Nicotinic acetylcholine receptors are simple ligand-gated fast-opening ion channels that are also responsive to nicotine. Most of the nicotine receptors in the body live in the neuromuscular junction. Nicotine receptors allow the passage of sodium, potassium or calcium ions and typically produce depolarization. Muscarinic acetylcholine receptors are G-protein-linked receptors that activate other ionic channels via a second messenger cascade. These receptors are responsive to muscarine and can produce either depolarization or hyperpolarization depending on the nature of the ionic channel linked to the G-protein complex.

The functions of acetylcholine

Within the human brain are numerous acetylcholine pathways that influence the function of the cortex, hippocampus, and many other subcortical regions (Figure 3.26).

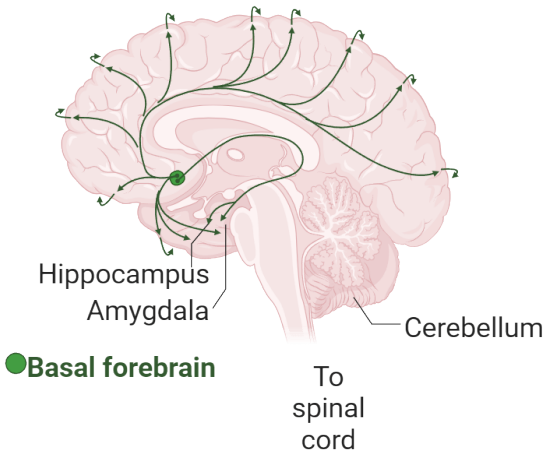


Figure 3.26 Acetylcholine system anatomy

Within these various regions, the actions of acetylcholine enable you to learn and remember, to regulate your attention and mood, and to control how well you can move. Thus, anything that affects the function of acetylcholine neurons has the potential to affect all these brain functions. Sometimes we can learn much about the role of a particular neurotransmitter system by investigating

what happens when it is injured or diseased. In the brains of people with Alzheimer's disease, for example, acetylcholine neurons that project into the hippocampus and cortex degenerate. The loss of normal acetylcholine function in the cortex may be why patients with Alzheimer's disease have difficulty paying attention to their environment. The loss of acetylcholine projections into the hippocampus may underlie the profoundly debilitating memory loss that is the hallmark of this disease.

History of Neuroscience: Otto Loewi and dreams of neuroscience

In 1902, a young German scientist named Otto Loewi at University College London began working with Henry Dale on how neurons communicate with each other. Loewi began thinking about ways that he might prove, or disprove, the chemical transmission hypothesis. According to Loewi, the idea of a viable experiment came to him in a dream a couple days after Easter Sunday in 1921. Unfortunately, his notes that night were illegible. Fortunately, the following night he had the dream again and he rushed off to the lab to test his ideas. Loewi determined that a substance was released by the vagus nerve that could communicate with other nervous tissues. Several years later this substance was isolated by Dale, who named it acetylcholine. Loewi and Dale shared the Nobel Prize for Physiology or Medicine in 1936 for their work on chemical neurotransmission.

Neurosteroids

Neurosteroids are produced from their precursor steroids by astrocytes and neurons (Maguire and Mennerick, 2024). Dietary cholesterol is converted into pregnenolone, an intermediate necessary for the synthesis of neurosteroids. Pregnenolone is then enzymatically converted into progesterone. Overall, neurosteroids are not themselves active at typical intracellular steroid receptors. They modulate brain excitability primarily by interaction with neuronal membrane receptors and ion channels. For example, progesterone is converted into allopregnanolone, which can enhance the function of GABA receptors and reduce seizure activity, anxiety and stress. Many neurosteroids are broad-spectrum anticonvulsant agents. In contrast, another neurosteroid, pregnenolone sulfate, is a negative GABA receptor modulator and tends to activate general brain activity and induce seizures. Neurosteroids are found at high levels in the cortex, hippocampus, and amygdala. Within these brain regions, neurosteroid synthetic enzymes are localized to glutamatergic principal neurons. Given their role in the control of neuronal excitability, neurosteroid analogs are now being considered for treatment of epilepsy, anxiety, depression, and stress-sensitive conditions.

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4: RESEARCH METHODS IN PHYSIOLOGICAL PSYCHOLOGY

4.1: Historical Methods – Studies of Brain Damage in Humans
4.2: Invasive Physiological Research Methods
4.3: Tools of Cognitive Neuroscience – EEG and MEG
4.4: Tools of Cognitive Neuroscience – Brain imaging, PET and MRI
4.5: Techniques that Modulate Brain Activity

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4.1: Historical Methods – Studies of Brain Damage in Humans

Early insights into brain-behavior links emerged from cases of brain damage. Prominent examples from the 19th century include Phineas Gage and the patients of physicians like Paul Broca and Carl Wernicke.

In the mid-1800s, the railroad worker Phineas Gage was responsible for setting explosive charges to blast through rock for railroad tracks. Using a 1-meter long tamping iron, he would tamp down the charges, but on one September afternoon, a spark set off the explosive prematurely. The tamping iron shot through the air like a rocket, entering the side of Gage's face, passing behind his left eye, exiting the top of his head, and landing 80 feet away (see Figure 1). Amazingly, he survived the accident and even was able to talk and walk away from it. Although he lost a portion of his left frontal lobe, he lived for another 12 years without apparent impairment in speech, motor abilities, memory, or intelligence (Damasio et al., 1994). However, what's fascinating about this incident from a biopsych perspective is that Gage's personality changed drastically as a result of the accident (Infantolino & Miller, 2023). Before the accident, Gage had been responsible and socially well-adapted, but afterward, he became irreverent, vulgar, impulsive, did not follow social conventions, and had difficulty executing plans.

A computerized tomography (CT) image reconstruction of the path of the tamping rod that entered Phineas Gage's mouth and blasted through his skull and left frontal lobe.

Figure 1: A computerized tomography (CT) image reconstruction of the path of the tamping rod that entered Phineas Gage's mouth and blasted through his skull and left frontal lobe. The bright colors represent White Matter fiber pathways likely intersected by the rod (Van Horn et al. 2012).

In another example from the 1800s, the French physician Paul Broca found that some patients who were unable to produce speech had brain damage to their left inferior frontal cortex. One of Broca's patients, nicknamed "Tan," could only produce the single syllable "tan" repeatedly. After Tan's death, Broca discovered a major lesion on Tan's left frontal lobe (see **Figure 2**). Another patient of Broca's was also severely aphasic (i.e., couldn't produce fluent speech) and had brain damage to the same portion of his left frontal lobe. This led Broca to surmise that speech production was localized to this region of the left inferior frontal lobe.

Around the same time, the German physician Carl Wernicke discovered that damage to a different brain region—the left superior temporal lobe—was associated with impaired speech *comprehension*. So together, this "double dissociation" showed that brain damage to specific locations is linked to specific types of behavioral impairments (Figure 3). (Here is a memory gem for distinguishing Broca's and Wernicke's brain areas: use the first three letters of each word: BROca's area = speech PROduction = FROntal; and WERnicke's area = speech PERception).

Photo of the brain of Broca's patient, Louis Victor Leborge ("Tan") preserved in jar in a museum in Paris.

Figure 2. The brain of Broca's patient, "Tan," preserved in a jar in a museum in Paris. Near the upper right side of the jar, you can see the damaged left inferior frontal lobe (associated with impaired speech production).

Drawing of Broca's Brain from the left side view.

Figure 3. BROca's area for Speech PROduction is located in the left FROntal lobe. WERnicke's area for Speech PERception is located in the left temporal lobe.

These and countless other examples show that brain damage can lead to behavioral and cognitive impairments. Such cases demonstrate **localization of function**—that certain brain regions perform specific functions (like the previous examples of impulse control, speech production, and perception). However, studies with human brain damage are a limited tool for understanding the brain. For example, when a patient suffers brain damage from force, trauma, a tumor, stroke, or a neurosyphilitic lesion (like Broca's patient Tan), that brain damage is a) unique to that patient making it difficult to extrapolate or generalize to others' brains, and b) rarely confined to just one brain area thus making it difficult to isolate the roles of specific brain structures. Creating controlled and localized damage to human brains in laboratory experiments is not possible, so researchers have resorted to creating carefully controlled brain damage or lesions in laboratory animals, such as mice and rats.

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definition

Different brain functions are processed in or localized to specific brain areas

×Close definition

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4.2: Invasive Physiological Research Methods

Invasive techniques, such as lesioning brain regions or implanting recording electrodes in the brain, are commonly used in biopsych research with non-human animals. For the experimental procedure, the animal undergoes surgery using a **stereotaxic unit** that allows precise positioning in the brain (see **Figure 4**). The stereotaxic unit has two main parts: a head holder to immobilize the head, and an electrode holder, which holds the device to be inserted. After the animal is anesthetized, its head is immobilized in the head holder. To locate target positions in the brain, researchers use a stereotaxic atlas (like a road atlas, but showing locations of brain regions instead of roads and cities). Then the researcher drills a small hole and performs the surgery. In some studies, researchers will lesion or remove a part of the brain; this is called ablation. The surgeon may use a surgical knife, a current-passing electrode, or an aspirating (suction) pipette. After the target region is carefully removed or inactivated, the animal's behavior is tested to determine the function of the lesioned structure. For example, researchers may remove (sub)components of the amygdala or hypothalamus and test how behavior changes. Studies will often include a control condition, in which control animals receive a *sham lesion,* wherein they undergo a similar surgical procedure but don't receive a lesion. This control condition allows researchers to more confidently interpret that the change in behavior stems from the lesioned brain area, rather than the handling, anesthesia, or other ancillary procedures. In other words, the direct manipulation of the brain, coupled with the control condition, allows researchers to make causal claims (something that cannot be done with correlational research methods). After the animal's death, its brain is often cut into thin slices and stained to highlight neuronal structures. These slices are then examined microscopically to verify the extent and precise location of the lesions.

As an alternative to *permanent* lesions, researchers can lesion brain regions *temporarily*. This can be achieved by cooling the target brain tissue or injecting it with an anesthetic. Additionally, electrical stimulation from implanted electrodes can temporarily inactivate or activate targeted brain regions.

Picture of the stereotaxic unit

Figure 4. A stereotaxic device used to perform surgeries on rodents. This unit would immobilize an anesthetized rat and allow precise placement of electrodes in the brain.

Picture of a laboratory rat.

Figure 5. A lab rat with a brain implant that was used to record neuronal activity while the rat performed a particular task (vibration discrimination in this case). In this picture, a scientist feeds the rat apple juice through a pipette.

In addition to manipulating brain function by damaging or stimulating brain regions, researchers learn about brain function by implanting recording devices directly in animal brains to 'listen in' on brain activity. The animal undergoes a stereotaxic surgery wherein a recording device or electrode is inserted into a target area then fixed into position on the skull (see **Figure 5**). Different types of invasive electrophysiological recording include: *intra*cellular unit recording, wherein a microelectrode is inserted *into* a single neuron to measure its electrical activity; *extra*cellular recordings that pick up the firing of one nearby neuron (single unit recording) or several adjacent neurons (multiunit recording); and invasive electroencephalography (EEG), wherein a large electrode picks up the electrical brain activity of a large swath of nearby neurons. These electrodes detect neural activity as the animal performs tasks, providing insight into the relationship between neural activity and behavior.

Directly recording from within *human* brains for research is rare, as invasively opening the skull cannot be ethically justified for research purposes alone. However, some patients who are already undergoing surgery for medical procedures, such as treatments for Parkinson's disease or epilepsy, might have electrodes placed directly on or in their brains. They occasionally participate in research. Such intracranial (meaning *within the skull*) electroencephalography (iEEG) or Electrocorticography (ECoG) is a valuable research tool because these direct recordings offer exceptionally clear and precise signals from the brain. However, these patients are rare, and the placement of electrodes is determined by the neurosurgeon and medical needs rather than the research question.

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definition

A surgical device that immobilizes an animal's head and allows precise positioning in an animal's brain using a three-dimensional coordinate system.

×Close definition

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4.3: Tools of Cognitive Neuroscience – EEG and MEG

Advances in technology have led to increasingly sophisticated brain recording techniques. Just as X-rays allow us to peer inside the body, neuroimaging techniques enable us to view the working brain (Raichle, 1994). Biopsychology employs various noninvasive methods to study human brain function, each with its own advantages and disadvantages. It's crucial to recognize that each technique offers a unique perspective on brain activity. Understanding these methods is essential, as our comprehension of the brain is closely tied to available technologies. As new techniques develop, we can anticipate an even deeper understanding of brain function (Biswas-Diener, 2023).

Electroencephalography (EEG) measures the electrical activity of the brain and has been used for a century (e.g., Berger, 1929). When large populations of neurons are active, they create a small electrical voltage that passes through the skull and scalp. Electrodes on the participant's head pick up the voltages, which are amplified and recorded. Researchers can record the voltages from brain activity as the participant performs a task.

The electrical signals generated in the brain become distorted as they travel through brain tissue, skin, and bone. As a result, researchers can only approximate the original source of these signals within the brain. This uncertainty is especially pronounced for signals originating deep within the brain (even with advanced tools such as structural brain scans, high-density electrode coverage from a cap with 256 electrodes, and sophisticated analysis algorithms for localization). Thus, EEG's ***spatial* resolution**—its ability to pinpoint *where* activity occurs in the brain—is relatively low. Conversely, EEG's ***temporal* resolution** is excellent and indicates *when* something happens in the brain with millisecond precision. EEG's superior temporal resolution makes it ideal for examining the brain's rapid response to a stimulus event, or the event-related potentials (ERP). In a typical ERP experiment, researchers might play a visual or auditory event like a word, and measure the corresponding voltage changes that unfold in the brain over the next few hundred milliseconds. The amplitude, timing, and topography (position) of the EEG signal capture the underlying neural/mental processes.

The high temporal resolution and continuous recording of EEG allows it to capture different frequency brain waves, such as theta waves (oscillating at 4-7 Hertz (Hz), i.e., cycles per second), alpha waves (at 8-13 Hz), and beta waves (at 14-30 Hz). Brain oscillations, reflecting the combined activity of millions of neurons, capture attentional and conscious states. These oscillations play a crucial role in information encoding and attention modulation in the brain (da Silva, 2013). In addition to research applications, EEG plays a crucial role in clinical diagnosis, particularly in identifying epilepsy, seizures, and sleep disorders.

Picture of an EEG recording cap.

Figure 6. Participant wearing an EEG cap that uses electrodes to pick up voltages on the scalp.

Example of the EEG spike waves.

Figure 7. An EEG readout of voltages at 16 electrode sites. Each row is one electrode; the voltage of each electrode is mapped on the vertical axis; and time is mapped on the horizontal axis with each vertical line marking 1 second. This particular EEG readout shows the characteristic 3 Hz spike and wave discharges in a child with epilepsy (notice the 3 peaks occurring every second).

Magnetoencephalography (MEG) is similar to EEG, but instead of electrical signals, MEG picks up the weak *magnetic* fields generated by the flow of electrical charge associated with neural activity. Because the magnetic fields generated by brain activity are so small, special rooms are needed that shield out magnetic fields in the environment so that the MEG sensors pick up magnetic fields from neural activity without environmental contamination. Similar to EEG, MEG also has excellent (millisecond) temporal resolution. The spatial resolution of MEG is far better than EEG because magnetic fields pass relatively unchanged through hard and soft tissue, so are not distorted by skull and scalp. Despite MEG's excellent spatial *and* temporal resolution, it is less widely used than EEG because its much more expensive and complex to operate.

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Biswas-Diener, R. (2023). The brain and nervous system. In R. Biswas-Diener & E. Diener (Eds), Noba textbook series: Psychology. Access for free at http://noba.to/4hzf8xv6 License: CC BY-NC-SA 4.0 DEED

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definition

A neuroimaging technique that measures electrical brain activity via multiple electrodes on the scalp.

×Close definition

A term that refers to how small the elements of an image are; high spatial resolution means the device or technique can resolve very small elements; in neuroscience, it describes how small a structure in the brain can be imaged.

×Close definition

A term that refers to how small a unit of time can be measured; high temporal resolution means capable of resolving very small units of time; in neuroscience, it describes how precisely in time a process can be measured in the brain.

×Close definition

A brain science technique that measures brain activity by picking up the tiny magnetic fields generated by neural activity.

×Close definition

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4.4: Tools of Cognitive Neuroscience – Brain imaging, PET and MRI

Many imaging technologies can capture detailed inner images of the brain. In the 1970s, the development of computerized tomography (CT) scans allowed non-invasive imaging of the living brain using X-rays. CT scans are rarely used today for research purposes due to radiation exposure and relatively low image resolution.

Positron Emission Tomography (PET) scans are a powerful way to image brain *activation* (as opposed to brain structure). The PET scanner detects a radioactive substance that is injected into the bloodstream of the participant just before or while they perform a task (e.g., adding numbers). Because active neuron populations require metabolites, more blood flows into active regions bringing with it more radioactive substances. PET scanners detect the injected radioactive substance in specific brain regions, allowing researchers to infer that those areas were active during the task. PET scans are not common in biopsych research because they require the ability to work with radioactive materials and expose subjects to low-levels of radiation. However, PET is a powerful tool that provides the unique capability of identifying the distribution of particular molecules, like neurotransmitters or receptors, in the brain.

Figure 8. This is a transaxial slice of the brain taken with positron emission tomography (PET). Red areas show more accumulated tracer substance and blue areas show where little to no tracer has accumulated.

Magnetic Resonance Imaging

The most commonly used brain-imaging modality today is Magnetic Resonance Imaging (MRI). An MRI machine can produce different types of scans: high-resolution images of brain structure (*structural* MRI or sMRI) and brain function (*functional* MRI or fMRI). MRI scanners may be expensive, noisy, and claustrophobic to some, but they are harmless and painless and are powerful and prevalent tools for illuminating brain structure and function.

MR scanners use a strong magnetic field that is 60,000 times stronger than the Earth's magnetic field. As a person lies very still in the scanner, the magnetic field forces protons in their body to align. Pulsations of low-energy radio frequencies cause the protons to change their spin. As the radiofrequency is turned off, these protons return to their aligned state and give off energy that is detected by MRI sensors. The timing and amount of energy released as protons realign with the magnetic field vary based on tissue type. This variation allows clear differentiation between the brain's white matter, gray matter, cerebrospinal fluid, bone, blood, and other tissues.

Figure 9. MRI scanner with subject laying down in the scanner bore.

Structural magnetic resonance imaging (sMRI) creates detailed images of brain structure with millimeter resolution. The high-resolution 3D images might show the brain's gray matter and white matter in *voxels* (i.e. like 3D pixels) that are 1mm x 1mm x 1mm cubes. Researchers may use these images to compare the size of brain structures across different groups (for example, are areas associated with pleasure smaller in individuals with depression, or are areas controlling finger movements larger in string musicians compared to vocalists or trombonists?). These structural images can also enhance the spatial accuracy of functional magnetic resonance imaging (fMRI) measurements.

Diffusion Tensor Imaging (DTI) is a variant of structural Magnetic Resonance Imaging that focuses on myelinated axon pathways in the brain**.** DTI imaging is highly sensitive to the movement of water molecules in the brain. Because water moves differently along myelinated axons in the brain, DTI can map out the large white matter tracts, that, like superhighways, connect distant brain regions (e.g., the *corpus callosum*, a white matter fiber tract that connects right and left cerebral hemispheres, or the *arcuate fasciculus*, a bundle of axons that connects Broca's area and Wernicke's area, see **Figure 10**). DTI can be used to examine white matter integrity in diseases such as Multiple Sclerosis or to observe brain plasticity after learning a new skill like juggling.

DTI image showing the white matter tracts, including the arcuate fasciculus, a bundle of axons that connects Broca's area and Wernicke's area.

Figure 10. DTI image showing the white matter tracts, including the arcuate fasciculus, a bundle of axons that connects Broca's area and Wernicke's area.

Functional MRI (fMRI) uses the same MR scanners, but instead of capturing a high-resolution snapshot of brain structure, it measures brain "function" or activation while a subject performs some task. As a brain region becomes more active, it uses oxygen and causes an inflow of oxygenated blood to that region over the following few seconds. fMRI measures the change in the concentration of oxygenated hemoglobin, which is known as the blood-oxygen-level-dependent (BOLD) signal. From the BOLD signal, researchers infer neuronal activation in that brain region (note that fMRI does not *directly* measure the neuronal activity). Because cerebral blood flow is coupled with neural activation, researchers can map brain activation while people in the scanner perform tasks like reading, speaking, viewing images of faces or places, recalling memories, etc. In this way, fMRI provides evidence of localization of function and which areas are active during specific tasks. fMRI has high ***spatial* resolution** and the activation maps in a typical fMRI study consist of cubic voxels that are a few mm on each side. However, the ***temporal* resolution** of fMRI is quite poor and it typically takes a snapshot of brain activation averaged over a 2- or 3-second window.

In addition to measuring BOLD responses while subjects perform some task, fMRI can measure subjects' brain activation over many minutes while they perform no task (so-called "resting state scans" wherein they might lay in the brain scanner for 10 minutes while instructed "don't do anything in particular"). Such recordings have shown surprisingly correlated spontaneous fluctuations of brain regions that can be far apart from each other in the brain. Regions with highly correlated activation work together in the same large-scale distributed network. The brain has several large-scale networks including sensorimotor, attention, control, default mode, and limbic networks.

Picture showing a researcher checking MRI images.

Figure 11. Researcher checking MRI images. On the monitor on the right, activations are overlaid on brain structure; typically "hotter" colors (reds and oranges) denote *more* brain activation than a baseline, and "cooler" colors (blues and greens) denote *less* brain activation than baseline.

While fMRI is popular and powerful and people find the pretty images convincing, they are correlational and don't fully explain the causal role of specific brain regions in determining mental processes. This is an important example of why it is essential to rely upon converging evidence—as an example, correlational fMRI data coupled with causal experimental data from lab animals. Also to address some of the limits of correlational research, researchers are developing techniques that can directly modulate brain activity.

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definition

A neuroimaging technique that measures brain activity by detecting the presence of a radioactive substance in the brain that is initially injected into the bloodstream and then pulled in by active brain tissue.

×Close definition

A neuroimaging technique that uses the magnetic resonance scanner to create high resolution images of brain structure. The images show brain anatomy, including location, size, and integrity of white and gray matter (but does not reveal brain function or neuronal activity).

×Close definition

A variant of Magnetic Resonance Imaging that can non-invasively reveal unique information of white matter microstructures and axonal pathways within the central nervous system.

×Close definition

Functional magnetic resonance imaging (fMRI): A neuroimaging technique that infers brain activation by measuring changes in oxygen levels in the blood.

×Close definition

A term that refers to how small the elements of an image are; high spatial resolution means the device or technique can resolve very small elements; in neuroscience, it describes how small a structure in the brain can be imaged.

×Close definition

A term that refers to how small a unit of time can be measured; high temporal resolution means capable of resolving very small units of time; in neuroscience, it describes how precisely in time a process can be measured in the brain.

×Close definition

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4.5: Techniques that Modulate Brain Activity

Neuroimaging studies focus on correlations between brain activity and behavior and can't establish a causal role of a brain region in determining behavior. To establish a causal rather than correlational relationship, we need to alter brain function and observe resulting changes in behavior. Lesions are one way to modify brain structure and can reveal a causal relationship (e.g., when losing a brain region leads to loss of function, that brain area is necessary or involved in the function). However, invasive lesions can only be introduced in animals, which differ from humans in key ways. Lesions in human brains can only be studied in patient populations; that is, after a patient experiences brain damage from a stroke or other injury. New technologies allow researchers to temporarily and non-invasively modify human brain function.

Transcranial magnetic stimulation (TMS) is a form of brain stimulation that uses magnets to alter brain activity. Researchers place a magnetic coil over the scalp and apply a magnetic current that stimulates the neurons below the magnetic coil (**Figure 12**). Depending on the type and rate of magnetic pulses, TMS can temporarily "turn off" or "turn on" the brain area under the coil. In research domains, researchers might temporarily "turn off" or "turn on" parts of the frontal lobe and look at subsequent feelings of craving or emotion processing. TMS is also used in clinical settings and has effectively treated some individuals with depression (Perera et al., 2016).

Photo showing a transcranial magnetic stimulation (TMS) coil positioned over a person's scalp.

Figure 12. A transcranial magnetic stimulation (TMS) coil placed over a person's scalp.

Transcranial direct current stimulation (tDCS) is similar to TMS except that it uses electrical current directly (rather than inducing it with magnetic pulses) via small electrodes on the skull (Beck & Tapia, 2023). A brain area is stimulated by a low current (equivalent to an AA battery) for an extended time. When combined with cognitive training, tDCS has been shown to improve many cognitive functions such as mathematical ability, memory, attention, and coordination (e.g., Brasil-Neto, 2012; Feng et al., 2013; Kuo & Nitsche, 2012).

Gene Knockout is a genetic technique used in animals, wherein researchers remove or inactivate a specific gene. This allows researchers to study the function of that gene in a living organism and its effects on the phenotype. Gene knockout is considered a "loss-of-function mutation" (what function is lost after knocking out a specific gene?). Gene knockouts are used in many organisms including fruit flies, zebrafish, and mice. Studies using "knockout mice" have been extremely valuable in understanding the role of genes in brain development, neurological disease, cancer, immune disorders, and even the genes involved in bad breath (Pol et al., 2018). **Gene Knock-in** is a related technique, but instead of removing a gene, knock-in inserts a gene. Gene knock-in is considered a "gain-of-function mutation" (what function is gained after inserting this gene?).

Brainbow is another innovative transgenic technique (transgenic means transferring genes from one organism to another) that inserts genetic material to label individual neurons with distinct colors and produces detailed neural maps. In Brainbow, green fluorescent protein, a protein found in jellyfish and corals that exhibits bright green fluorescence, is genetically modified to produce different colors. These various fluorescent proteins are then inserted into individual neurons in different ratios, flagging each neuron with a unique color (see **Figure 13**). Brainbow has enabled the *simultaneous* mapping of hundreds of neurons and allows scientists to trace the intricate connections between neurons. Thus, Brainbow has been groundbreaking for the field of neural connectomics, which studies the organization of neural networks. This technique provides striking images of neurons and highlights biopsych research at the molecular and cellular level.

Images of the three brainbows of mouse neurons from Lichtman.

Figure 13. Three brainbows of mouse neurons from Lichtman et al. (2008). a) a motor nerve innervating ear muscle. b) An axon tract in the brainstem. c) The hippocampal dentate gyrus.

Optogenetics is an especially exciting technique for manipulating brain activity in non-human animals (Deisseroth, 2011). Optogenetics uses light to control specific populations of neurons in living animals. For the neurons to be sensitive to light, researchers genetically insert light-sensitive proteins (taken from algae) into a specific type of neuron. After inserting tiny optical fibers into the animal's brain, researchers can turn on the light to excite or inhibit these specific cells. Scientists have used the ability to control the activity of specific neuronal populations to investigate their role in learning, memory, decision-making, addiction, movement, and many other areas of active research.

In sum, the various research techniques used in biological psychology each have their strengths and weaknesses in terms of spatial resolution, temporal resolution, ease-of-use, invasiveness, cost, precision, etc. Using the different tools in a

complementary manner provides converging evidence for understanding how the brain works.

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definition

A neuroscience technique whereby a brief magnetic pulse is applied to the head that temporarily activates or inhibits ongoing neuronal activity.

×Close definition

A neuroscience technique whereby a weak current is applied to the head that temporarily activates or inhibits ongoing neuronal activity.

×Close definition

A research technique that involves removing or inactivating a specific gene in an organism (often a fruit fly, zebrafish, or mouse), which allows researchers to study the effect of that gene on the phenotype.

×Close definition

A research technique that involves inserting a specific gene in an organism, which allows researchers to study the effect of that gene on the phenotype.

×Close definition

A genetic technique in which individual neurons can be labeled and mapped using fluorescent proteins.

×Close definition

A biological technique to control the activity of neurons or other cell types with light.

×Close definition

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5: PSYCHOPHARMACOLOGY

5.1: Psychopharmacology and Neurotransmitter Action
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5.3: Basic Principles of Pharmacology
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5.1: Psychopharmacology and Neurotransmitter Action

Psychopharmacology, the scientific study of how drugs affect the brain and behavior, is a relatively new science. However, people have been taking drugs to change how they feel and think since early human history (e.g., consuming fermented fruit, early forms of beer, coca leaves as stimulants, and mind-altering mushrooms in rituals). The term *psychopharmacology* tells us that this field bridges brain, behavior, and pharmacology, encompassing a broad range of topics.

Figure 1. Drugs that alter our feelings and behavior do so by modulating neurotransmission in the brain.

Virtually any drug that changes the way you feel does so by altering how neurons communicate with each other. Neurons communicate with each other by releasing a chemical (**neurotransmitter**) across a tiny space between two neurons (the **synapse**). When the neurotransmitter crosses the synapse, it binds to a postsynaptic receptor on the receiving neuron, and the message may then be transmitted onward. Neurotransmission is far more complicated than this—but the first step is understanding that virtually all **psychoactive drugs** modulate how neurons communicate with each other.

Several neurotransmitters play crucial roles in psychopharmacological treatments and drugs of abuse (examples in **Table 1**). The neurons that release these neurotransmitters, for the most part, are localized within specific circuits of the brain that mediate these behaviors. Psychoactive drugs can either increase activity at the synapse (these are called **agonists**) or reduce activity at the synapse (**antagonists**). Different drugs do this by various mechanisms, and examples of agonists and antagonists are presented in **Table 2**. Each example includes the drug's trade name from the drug company and it generic name in parentheses.

Table 1. How neurotransmitters affect behaviors or diseases

Neurotransmitter	Abbreviation	Behaviors of Diseases Related to These Neurotransmitter
Acetylcholine	ACh	Learning and memory; Alzheimer's disease' muscle movement in the peripheral nervous system
Dopamine	DA	Reward circuits; Motor circuits involved in Parkinson's disease; Schizophrenia
Norepinephrine	NE	Arousal; Depression
Serotonin	5HT	Depression; Aggression; Schizophrenia
Glutamate	GLU	Learning; Major excitatory neurotransmitter in the brain
GABA	GABA	Anxiety disorders; Epilepsy; Major inhibitory neurotransmitter in the brain
Endogenous Opioids	Endorphins, Enkephalins	Pain; Analgesia; Reward

Table 2 provides examples of drugs and their primary mechanism of action, but it is important to realize that drugs also affect other neurotransmitters. This contributes to a drug's side effects. Current drugs lack precise targeting to specific brain regions or individual neurotransmitter systems. In many cases, individuals are sometimes prescribed one **psychotropic drug** but then may also have to take additional drugs to reduce the side effects caused by the initial drug. Some side effects can be so severe that individuals stop taking their medication.

Table 2. Examples of drugs, their primary mechanism of action, use, and whether agonists (increase activity at the synapse) or antagonists (reduce activity at the synapse).

Drug	Mechanism	Use	Agonist/ Antagonist
L-dopa	Increase Synthesis of DA	Parkinson's disease	Agonist for DA
Adderall (mixed salts amphetamine)	Increase Synthesis of DA, NE	ADHD	Agonist for DA, NE

Drug	Mechanism	Use	Agonist/ Antagonist
Ritalin (methylphenidate)	Blocks removal of DA, NE and lesser (5HT) from synapse	ADHD	Agonist for DA, NE mostly
Aricept (donepezil)	Blocks removal of ACh from synapse	Alzheimer's disease	Agonist for ACh
Prozac (fluoxetine)	Blocks removal of 5HT from synapse	Depression, obsessive-compulsive disorder	Agonist 5HT
Seroquel (quetiapine)	Blocks DA and 5HT receptors	Schizophrenia, bipolar disorder	Antagonist for DA, 5HT
Revia (naltrexone)	Blocks opioid post-synaptic receptors	Alcoholism, opioid addiction	Antagonist (for opioids)

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definition

A chemical substance produced by a neuron that is used for communication between neurons

×Close definition

The tiny space separating neurons

×Close definition

A drug that changes mood or the way someone feels

×Close definition

A drug that increases or enhances a neurotransmitter's effect

×Close definition

A drug that blocks a neurotransmitter's effect

×Close definition

A drug that changes mood or emotion, usually used when talking about drugs prescribed for various mental conditions (depression, anxiety, schizophrenia, etc.)

×Close definition

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5.2: Pharmacokinetics- What Is It and Why Is It Important?

Pharmacokinetics refers to how the body handles a drug that we take. As mentioned earlier, psychoactive drugs exert their effects on behavior by altering neuronal communication in the brain, and the majority of drugs reach the brain by traveling in the blood. The acronym ADME is often used in pharmacology and stands for Absorption (how the drug gets into the blood), Distribution (how the drug gets to the organ of interest – in this chapter, that is the brain), Metabolism (how the drug is broken down so it no longer exerts its psychoactive effects), and Excretion (how the drug leaves the body). Let's examine these processes for psychoactive drugs.

Drug Administration

Drugs can be administered through various routes, each affecting the speed at which they reach the brain. The most common route of administration is oral administration, which is relatively slow and often the most variable route. Drugs enter the stomach and then get absorbed by the blood supply and capillaries that line the small intestine. The absorption rate can be affected by many factors, including the quantity and the type of food in the stomach (e.g., fats vs. proteins). This is why the medicine labels for some drugs (like antibiotics) may specifically state foods that you should or should NOT consume within an hour of taking the drug because they can affect the absorption rate. Two of the most rapid routes of administration include inhalation (i.e., smoking or gaseous anesthesia) and intravenous (IV) in which the drug is injected directly into the vein and hence the blood supply. Both of these routes of administration can get the drug to the brain in less than 10 seconds. IV administration also has the distinction of being the most dangerous because if an adverse reaction occurs, there is little time to administer an antidote, as in the case of an IV heroin overdose.

Image showing the delivery of drug by IV into arm.

Figure 2. A drug delivered by IV reaches the brain more quickly than if the drug is taken orally. While rapid delivery has advantages, there are also risks involved with IV administration.

Why might how quickly a drug gets to the brain be important? If a drug activates the reward circuits in the brain AND it reaches the brain very quickly, the drug has a high risk for abuse and addiction. Psychostimulants like amphetamine or cocaine are examples of drugs that have a high risk for abuse because they are agonists at dopamine (DA) neurons involved in reward AND because these drugs exist in forms that can be either smoked or injected intravenously. Some argue that cigarette smoking is one of the most difficult addictions to overcome; this might partially stem from the rapid nicotine delivery to the brain (indirectly activating dopaminergic neurons), but the full story is more complicated. For drugs that reach the brain very quickly, not only is the drug very addictive, but so are the cues associated with the drug (see Rohsenow et al., 1990). For a crack user, this could be the pipe that they use to smoke the drug. For a cigarette smoker, however, the cue could be something as normal as finishing dinner or waking up in the morning (if that's when the smoker typically has a cigarette). For both the crack user and the cigarette smoker, the cues associated with the drug may cause craving and lead to relapse. This is one of the reasons individuals who enroll in drug treatment programs, especially out-of-town programs, are at significant risk of relapse if they later find themselves in proximity to old haunts, friends, etc. But this is much *more* difficult for a cigarette smoker. How can someone avoid common smoking cues like eating or avoid waking up in the morning, etc.? These examples help you begin to understand how important the route of administration can be for psychoactive drugs.

Drug Metabolism

Metabolism involves the breakdown of psychoactive drugs, and this occurs primarily in the liver. The liver produces **enzymes** (proteins that speed up a chemical reaction), and these enzymes help catalyze a chemical reaction that breaks down psychoactive drugs. Enzymes exist in "families," and many psychoactive drugs are broken down by the same family of enzymes, the cytochrome P450 superfamily. There is not a unique enzyme for each drug; rather, certain enzymes can break down a wide variety of drugs. Tolerance to the effects of many drugs can occur with repeated exposure; that is, the drug produces less effect over time, so more of the drug is needed to get the same effect. This is particularly true for sedative drugs like alcohol or opiate-based painkillers. *Metabolic tolerance* is one kind of tolerance, and it takes place in the liver. Some drugs (like alcohol) cause **enzyme induction**—an increase in the enzymes produced by the liver. For example, chronic drinking results in alcohol being broken down more quickly, so an alcoholic needs to drink more to get the same effect—of course, until so much alcohol is consumed that it damages the liver (alcohol can cause fatty liver or cirrhosis).

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definition

The action of a drug through the body, including absorption, distribution, metabolism, and excretion

×Close definition

Breakdown of substances

×Close definition

A protein produced by a living organism that allows or helps a chemical reaction to occur

×Close definition

The process by which a drug can enhance the production of an enzyme

×Close definition

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5.3: Basic Principles of Pharmacology

Learning Objectives

By the end of this section, you should be able to

- List the factors that contribute to bioavailability and describe how they can influence an individual's response to a drug.
- Describe how drugs impact neuronal signaling via their interaction with receptors and the neurotransmitter life cycle.

The physiological and behavioral effects of drugs, also known as pharmacodynamics, are a result of their molecular interactions with receptors located throughout the body. To reach these receptors, the drug must enter the body and cross into the blood circulatory system. However, the amount of drug consumed or administered does not always equal the amount of drug that is available to bind and produce an effect. The proportion of the drug that ultimately reaches the circulation system, referred to as bioavailability, is a key variable in predicting an individual's response to the drug. The range of doses in which a drug is effective without causing adverse effects is known as the therapeutic window. Lower plasma concentrations of a drug are more likely to be ineffective, whereas higher concentrations run the risk of being toxic or even lethal. The ideal drug has a large therapeutic window, meaning there is a large range of concentrations in which the drug is both safe and effective.

Factors affecting drug availability

The bioavailability of a particular drug is influenced by pharmacokinetics or the movement of the drug throughout the body. Factors such as route of administration, and the rate of absorption, distribution, metabolism, and excretion all have the potential to impact drug bioavailability.

Route of administration

The route of administration refers to how a drug is introduced to the body. Although there are several different methods for drug administration, they fall broadly into two categories: enteral administration, which involves the gastrointestinal system, and parenteral administration, which does not. The route of administration plays an important role in determining the onset of action, or the amount of time it takes to experience a drug's effect. In general, enteral administration is associated with slower onset compared to parenteral administration. Furthermore, the route of administration is often dependent on the chemical structure of the drug since certain formulations may only be effective when delivered a specific way. A few of the more common routes of administration are discussed below and diagrammed in Figure 14.2.

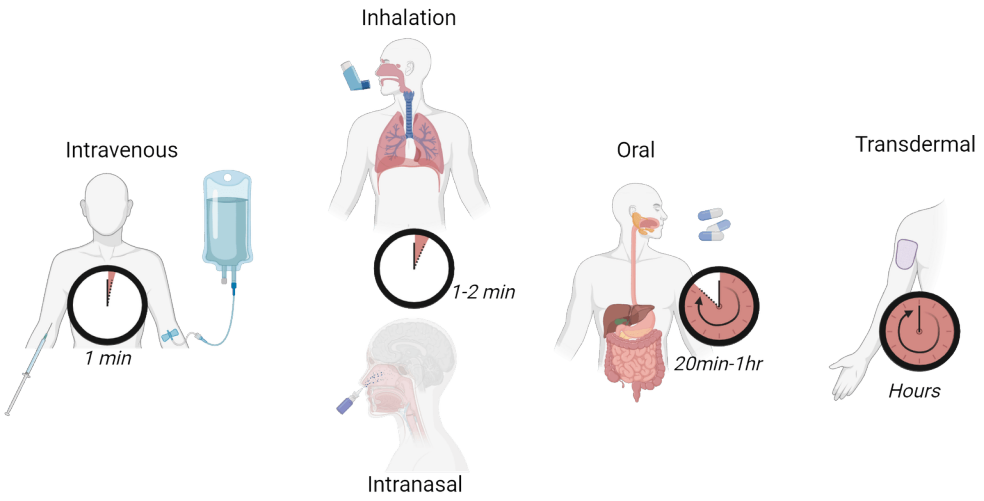


Figure 14.2 Routes of drug administration and time of action onset

Oral administration is one of the most frequently used forms of drug administration because it is generally safe, simple, and convenient to self-administer. Drugs designed for oral administration are often formulated as capsules, pills, or tablets, but can also be delivered through a liquid solution. Once ingested, the drug moves through the stomach into the small intestines where it is absorbed into the portal vein and passed through the liver before entering the main circulatory system. This process is known as first-pass metabolism. Enzymes in the liver can chemically alter the drug, resulting in less of it reaching the binding site. Certain protein-based drugs, such as insulin, are destroyed by gastric acids in the stomach before even being absorbed into the portal vein. This is why insulin is typically administered via a subcutaneous (under the skin) injection. The onset of action for orally administered drugs typically ranges from 20 minutes to an hour.

Intravenous (IV) administration is the delivery of a drug directly into the bloodstream via a hypodermic needle. In contrast to oral administration, IV administration has a very rapid onset of action (within 1 minute). Furthermore, bioavailability is essentially 100% seeing as this route of administration bypasses the gastrointestinal system and first-pass metabolism. While this is certainly advantageous when fast effects are needed, this form of administration can also lead to overdoses or other adverse effects if the drug is impure or if the dose is not calculated correctly. IV drug use can also pose additional health hazards when done without sterile equipment.

Inhalation is a route of administration that allows the drug to be absorbed into the circulatory system via the lungs. For this method of delivery, the drug must be burned to create smoke (such as with a cigarette) or volatilized into a vapor. The inhaled smoke or vapor passes through the lungs and is absorbed by the surrounding pulmonary capillaries, which quickly carry the drug into the circulatory system. For this reason, drug delivery by inhalation also produces a fairly rapid onset of action. However, inhalation of non-gaseous particles can cause damage to the airways and lungs.

Intranasal drug delivery is achieved by inhaling a substance through the nostrils or directly applying the drug to the mucous membranes of the nasal passage. The drug is then absorbed into the blood vessels that line the nasal cavity and carried into the circulatory system. Oxytocin, a peptide hormone involved in social bonding and reproduction, is sometimes delivered intranasally through a spray to facilitate breastfeeding after childbirth. Although this route of administration also results in a rapid onset of action, contaminants present in the drug may irritate the nasal passage and lead to tissue damage.

Transdermal administration delivers drugs through the skin's surface into the underlying blood vessels via a skin patch or ointment. This route is unique from topical administration, in which the drug is intended to remain on the skin surface. Hormonal contraceptives that contain estrogen and progesterone can be administered transdermally through a skin patch. This route of administration allows for a sustained diffusion of drugs over an extended time, which eliminates the need to remember to take a daily pill or injection. Although transdermal administration has a slow onset of action, it can provide extended periods of drug delivery (up to a week in some cases). The utility of this route of administration is limited by the fact that only certain types of drugs can penetrate the skin.

Absorption and distribution

As discussed earlier, a drug must be absorbed into the bloodstream and distributed throughout the body to reach its target binding site. The speed at which this occurs depends on the route of administration. Drugs delivered directly into the bloodstream will be absorbed and distributed much faster than drugs that must travel through the gastrointestinal system. For enteral methods of administration, most drug absorption occurs in the small intestines. Therefore, the time it takes the drug to reach the bloodstream is heavily dependent on how long it takes for the stomach to empty into the small intestines. The absorption process can also be affected by food being digested in the stomach. For example, calcium molecules found in dairy products, such as milk, yogurt, and cheese, can bind to certain antibiotics and prevent them from being absorbed. Similarly, medications used to treat hypothyroidism, such as levothyroxine, need to be taken on an empty stomach to enhance absorption.

One factor that can impact absorption and distribution in the brain is the blood-brain barrier (BBB), a lining of cells that acts as a border between blood vessels and extracellular fluid in the brain (Figure 14.3).

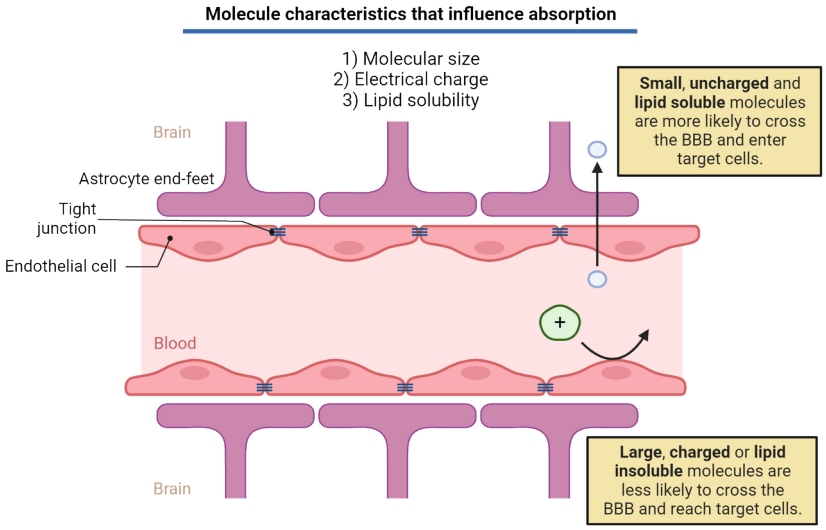


Figure 14.3 Molecule characteristics that influence absorption across the blood-brain barrier

The relatively impermeable nature of the BBB prevents the vast majority of molecules from diffusing into the brain since most compounds found in the blood are large, electrically charged or lipid insoluble. The BBB tightly regulates the entry of select nutrients and molecules into the brain via passive and active transport channels. This selectivity helps to protect the central nervous system (CNS) from pathogens that could cause systemic infection but can also prevent certain drugs from reaching the brain. Drugs with high lipid-solubility, or the ability to dissolve through the cell membrane, are more likely to cross the BBB. Many psychoactive drugs (e.g. cocaine, nicotine, fentanyl) are highly lipid-soluble molecules, a property which allows them to penetrate the BBB and interact with their targets in the brain. The BBB continues to present a challenge for developing pharmaceutical treatments for central nervous system (CNS) disorders since pharmaceutical drugs cannot always be designed as small or lipid-soluble molecules.

Metabolism

Drugs can be chemically altered by enzymes located throughout the body, although the majority of drug metabolism takes place in the liver and gastrointestinal tract. The rate of metabolism for a particular drug is influenced by how quickly these enzymes alter the drug, which differs depending on genetics, age, sex, and body weight. This process can potentially inactivate the drug, thereby reducing bioavailability. For example, alcohol is broken down in the stomach and liver by alcohol dehydrogenase enzymes which transform the drug first into acetaldehyde and then into acetic acid. In contrast, prodrugs are drugs that are inactive until they are metabolized by the body. Codeine, an opiate drug derived from the opium poppy, has very little drug effect until it is metabolized by the liver to produce morphine, a much more potent drug.

There are several ways that changes in liver enzyme function can alter drug metabolism and thereby end up changing how a drug ultimately impacts a person. Liver damage or dysfunction can lead to unpredictable changes in drug clearance and metabolism, for example. Using a drug chronically can increase the number of liver enzymes that degrade it, which over time may reduce the

amount of drug that is absorbed into the bloodstream. The administration of multiple drugs at the same time can cause drug-drug interactions, in which one drug impacts the activity of another. In addition, increased levels of one or more of the drugs may accumulate in the bloodstream if they are metabolized by the same enzyme. This phenomenon is known as competitive enzyme inhibition. Essentially, the enzyme that would be helping to break down and clear one drug is too busy breaking down the other drug. For example, cisapride, a drug used to treat gastroesophageal reflux disease, and ketoconazole, an antifungal medication, are both metabolized by cytochrome P450 (CYP) liver enzymes. When these drugs are taken together, blood levels of cisapride can reach toxic levels, which may increase the risk of adverse side effects.

Excretion

The primary way that drugs and their metabolites are removed from the body is via the kidney, which filters the blood and excretes waste materials through urine. Drugs can also be excreted from the body through feces, sweat and saliva. The amount of time it takes for the blood concentration of a drug to reach 50% of its original value is commonly referred to as the half-life. The half-life of a drug can be influenced by the route of administration. Drugs that are taken orally enter and exit the bloodstream more slowly than those injected directly into a blood vessel. A drug with a short half-life may have to be administered multiple times a day to maintain its effects, whereas the effects of a drug with a long half-life may persist for over a day with only a single administration. A long half-life may seem ideal for therapeutic purposes. However, it may also prolong unwanted or dangerous side effects of the drug. These factors, along with absorption and distribution, contribute to the drug plasma concentration over time (Figure 14.4). The length of time a drug remains at a therapeutic or effective concentration is considered the duration of action.

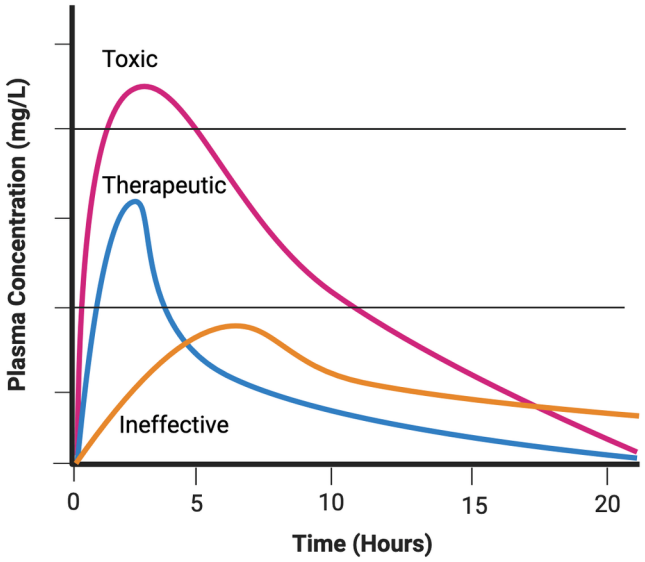


Figure 14.4 Plasma concentration over time Each curve shows the plasma concentration of a drug over time, revealing different absorption rates. Only the middle (blue) curve shows plasma concentrations within the therapeutic range without inducing toxic effects.

Drug interactions with neurotransmitter lifecycle

In addition to their interactions with receptors, drugs can also impact neuronal functioning indirectly by interfering with different stages of synaptic transmission (Figure 14.5).

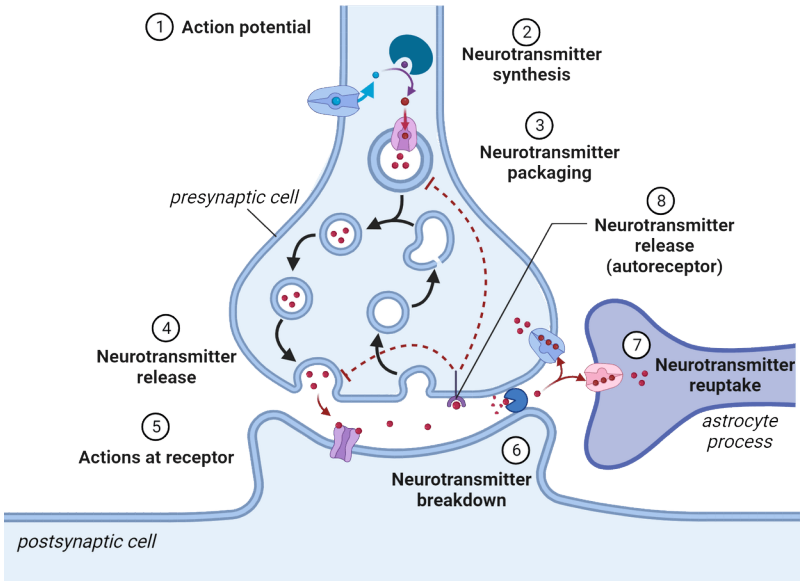


Figure 14.5 Sites of drug action

At the root of synaptic transmission is the arrival of an action potential, a step that can be altered by drugs (step 1 in Figure 14.5). For example, lidocaine, a local anesthetic, can inhibit the propagation of an action potential by blocking voltage-gated sodium channels, and ultimately prevent neurotransmitter release.

Neurotransmitters must also be synthesized to be available at the synapse. During the synthesis stage, enzymes catalyze reactions between precursor molecules to create the final neurotransmitter. Drugs that impact synthesis can either reduce or enhance the level of neurotransmitters produced in the brain (step 2 in Figure 14.5). For example, metyrosine, a drug used to treat hypertension, is known to inhibit tyrosine hydroxylase, an enzyme that is necessary for the synthesis of catecholamines like dopamine, norepinephrine, and epinephrine. Within the peripheral nervous system, elevated levels of norepinephrine and epinephrine contribute to increased heart rate and blood pressure. Thus, the depletion of these neurotransmitters can help treat high blood pressure.

After the synthesis process, neurotransmitters are then packaged into a vesicle and stored in the axon terminal. The influx of calcium from voltage-gated calcium channels following an action potential promotes vesicle docking and fusion at the axon terminal, which ultimately leads to the release of neurotransmitters. Several classes of psychoactive drugs act by altering packaging (step 3 in Figure 14.5) and/or release (step 4 in Figure 14.5) of neurotransmitters. For example, methamphetamine interferes with the functioning of dopamine transporter proteins on synaptic vesicles, which results in the escape of dopamine molecules into the cytosol. Methamphetamine also reverses dopamine transporter proteins located on the axon terminal, ultimately leading to increased dopamine release in the synaptic cleft.

To end signaling to the postsynaptic cell, neurotransmitters are either broken down in the synaptic cleft or brought back into the presynaptic cell via reuptake (steps 6 and 7 in Figure 14.5). Drugs that prevent termination may enhance postsynaptic signaling. For example, selective serotonin reuptake inhibitors (SSRIs), a class of antidepressant drugs, prevent the reuptake of serotonin into the presynaptic terminal, thereby elevating concentrations of serotonin in the synaptic cleft.

Drug-receptor interactions

Some drugs impart their neurobiological effects through interaction with receptors located on target cells in the CNS (step 5 in Figure 14.5). Most receptors are transmembrane proteins that contain an extracellular surface with a binding site where neurotransmitters, hormones, drugs, or other molecules can bind. Broadly, any molecule that can bind to a receptor's binding site is referred to as a ligand. Drug-receptor interactions can also be characterized by the binding affinity or strength of the interaction. A high-affinity ligand tends to bind to a particular receptor more than a low-affinity ligand.

Receptors

There are two main categories of ligand-binding receptors, both shown in Figure 14.6.

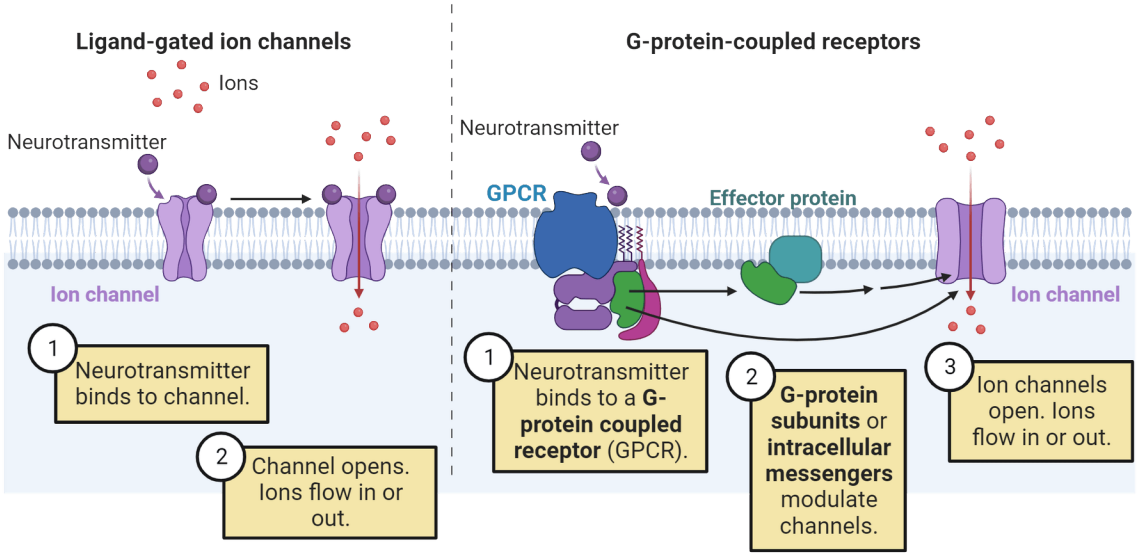


Figure 14.6 Ionotropic vs metabotropic receptors

Ligand-gated channels (also known as ionotropic receptors) are ion channels composed of proteins embedded in the cell membrane. When a ligand binds to the binding site, the membrane-spanning portions of the receptor open to form a channel that allows specific ions to cross into the cell. If the receptor is on a neuron, which is often the case for psychoactive drugs, this movement can result in either excitation or inhibition of the neuron. This response usually occurs within a millisecond of the ligand binding.

Metabotropic receptors (also known as G protein-coupled receptors) also have an extracellular active site, but these receptors do not form an ion channel. Instead, they are composed of seven transmembrane proteins that are physically linked to intracellular proteins called G proteins. When a ligand binds to the active site, the G protein disassociates from the receptor complex. Once unbound, the G protein can go on to open or close ion channels located on the cell membrane or activate or inhibit intracellular signaling cascades. Because metabotropic receptors are indirectly linked with ion channels and signaling transduction, compared to ionotropic receptors, their effects on neuronal activity occur at a slower pace and can persist for a longer period.

Receptor ligands

Ligands can be naturally produced within the body or derived from a source outside of the body. For example, endocannabinoids are neurotransmitters that are produced within the central and peripheral nervous system and bind to cannabinoid (CB) receptors. Because they are synthesized within the brain, endocannabinoids are considered the endogenous ligand for CB receptors. The primary psychoactive chemical in cannabis (THC) also binds to CB receptors. However, it is derived from a plant and is thus considered an exogenous ligand.

A dose-response curve plots the relationship between the level of receptor response and the dose of the drug (Figure 14.7).

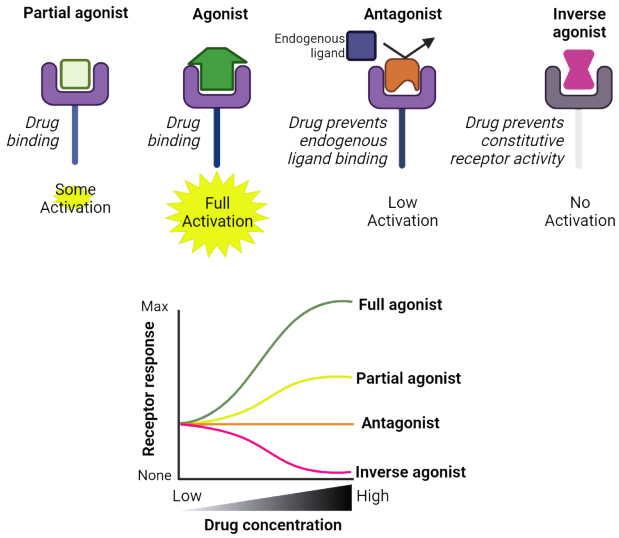


Figure 14.7 Ligand receptor interactions

A full agonist is a ligand or drug that is capable of binding to and activating a receptor with maximal efficacy. Epinephrine is an example of a full agonist at the adrenergic receptor. A partial agonist also can activate a receptor upon binding. However, it elicits a reduced receptor response compared to a full agonist, even with increasing concentration of the ligand. Buprenorphine, an opioid drug used to treat opioid use disorder, is a partial agonist at the mu-opioid receptor (MOR). Buprenorphine's reduced efficacy at the MOR decreases the risk of overdose.

In some cases, a receptor can produce a biological response in the absence of an agonist binding. This phenomenon is referred to as constitutive activity. An inverse agonist is a drug that inhibits the same binding site as a full agonist but reduces activity in a receptor that would otherwise be constitutively active. For example, certain histamine receptors exhibit agonist-independent activity, which is thought to contribute to many allergy symptoms. Antihistamines, drugs used to alleviate allergy symptoms, bind to histamine receptors and reduce their biological response instead of increasing it, thereby making them inverse agonists.

An antagonist is a ligand that blocks the activation of the receptor by preventing agonists from binding. In contrast to the inverse agonist, an antagonist does not have any intrinsic activity on the receptor itself, it simply blocks agonists from interacting with the receptor. For example, caffeine is an antagonist at adenosine receptors, which typically induce drowsiness when activated by their endogenous ligand.

Another type of agonist interaction sometimes seen with G protein-coupled receptors is biased agonism or functional selectivity. This occurs when the unique structure of a ligand allows it to preferentially activate certain intracellular signaling cascades over others. A major goal in drug development research is to design ligands that induce signaling cascades that promote the therapeutic effects of drugs while minimizing the activation of cascades associated with adverse side effects. In 2020, the Food and Drug Administration (FDA) approved the first biased mu-opioid receptor agonist for the treatment of severe pain. When tested in clinical studies, this drug produced a similar degree of analgesia (pain relief) but less nausea and respiratory depression compared to morphine (DeWire et al., 2013).

Certain ligands, called allosteric modulators, can regulate receptor activity without interacting with a receptor's orthosteric site, the location where an agonist would typically bind. Instead, allosteric modulators bind to a different part of the receptor (referred to as the allosteric site), which can ultimately alter the effects of ligands that bind to the orthosteric site. Positive allosteric modulators increase the efficacy of agonists that bind to the receptor, whereas negative allosteric modulators reduce the ability of agonists to activate the receptor. Benzodiazepines, drugs used to treat anxiety disorders, are an example of positive allosteric modulators of the $GABA_A$ receptor (Figure 14.8). When both GABA and benzodiazepines are bound to the $GABA_A$ receptor, the ion channel opens more frequently or for a longer period, allowing more chloride ions to enter the cell. This results in a greater inhibitory effect compared to when only GABA is present. In contrast to an agonist, benzodiazepines have no effect on $GABA_A$ receptor activation on their own.

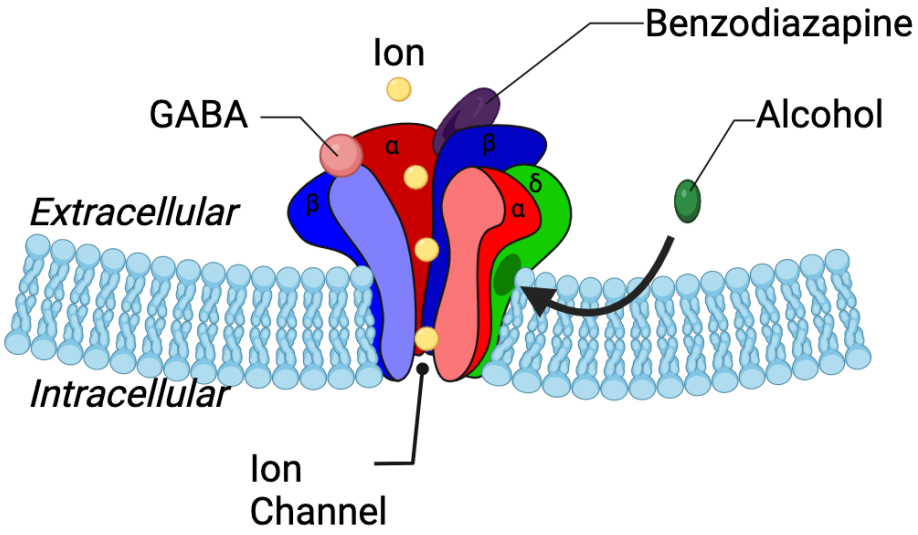


Figure 14.8 $GABA_A$ receptor agonists Many sedatives work by binding to and activating $GABA_A$ receptors.

Drug Approval Process in the United States

The U.S. Food and Drug Administration (FDA) is a federal agency within the Department of Health and Human Services that is tasked with ensuring the safety and efficacy of food, drugs, and biomedical products among other things in the U.S. The FDA's Center for Drug Evaluation and Research is specifically responsible for reviewing new drugs before they can be sold to consumers.

Before a new drug can reach the store shelf it must pass through multiple stages of testing and evaluation. First, the drug must be tested in multiple animal models to determine its safety and pharmacological profile, and whether it is effective. Next, the pharmaceutical company must submit an Investigational New Drug (IND) application, which includes the results of the initial rounds of animal testing, information on the drug composition and manufacturing, and a detailed plan for how the drug will be tested in humans. Once the FDA reviews and approves the IND, the pharmaceutical company can begin conducting clinical trials in humans.

There are generally three stages of clinical testing: Phase 1, Phase 2, and Phase 3. The main goals of Phase 1 are to evaluate the safety of the drug, identify any adverse side effects, and determine how the drug is metabolized. These trials are made up entirely of healthy volunteers. Phase 2 trials include patients who have the disease or condition that the new drug is proposed to treat. The main goal of this phase is to determine how the drug performs compared to a placebo (a substance that has no therapeutic action) or a different drug that is already approved for treatment. Both Phase 1 and Phase 2 trials tend to have a small number of participants (100 or less). In contrast, Phase 3 trials are considered large-scale studies and typically recruit over 1000 participants. The main goal of this phase is to gather more information on the safety and efficacy of the drug across different populations.

Following the completion of clinical testing, which can take several years, the analyses of all the data collected from both animal and human studies are submitted to the FDA as a New Drug Application (NDA). An independent team made up of physicians and scientists carefully reviews the submitted data to determine if the health benefits of the drug outweigh the risks. If the drug meets these criteria, the FDA will grant approval for marketing the drug in the U.S. The review process for approving an NDA can take up to 6-10 months to complete. However, in the case of public health emergencies, such as the Covid-19 epidemic, the FDA can enact its Emergency Use Authorization to allow non-FDA-approved medications to be used in certain conditions.

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5.4: Recent Issues Related to Psychotropic Drugs and Metabolism

Grapefruit Juice and Metabolism

Image of slices of grapefruit

Figure 3. Grapefruit can interfere with enzymes in the liver that help the body to process certain drugs.

Certain types of food in the stomach can alter the rate of drug absorption, and other foods can alter the rate of drug metabolism. The most well-known is grapefruit juice. Grapefruit juice suppresses cytochrome P450 enzymes in the liver, and these liver enzymes normally break down a large variety of drugs (including some psychotropic drugs). If the enzymes are suppressed, drug levels can build up to potentially toxic levels. In this case, the effects can persist long after consuming grapefruit juice. As of 2013, at least 85 drugs have been shown to interact adversely with grapefruit juice (Bailey et al., 2013). Some psychotropic drugs that likely interact with grapefruit juice include carbamazepine (Tegretol), prescribed for bipolar disorder; diazepam (Valium), used to treat anxiety, alcohol withdrawal, and muscle spasms; and fluvoxamine (Luvox), used to treat obsessive-compulsive disorder and depression. A link at the end of this chapter gives the latest list of drugs reported to have this unusual interaction.

Individualized Therapy, Metabolic Differences, and Potential Prescribing Approaches for the Future

Mental illnesses contribute to more disability in Western countries than all other illnesses, including cancer and heart disease. Globally, depression and anxiety disorders are among the highest causes of health burden, and the mental health system in most countries is under-resourced (Santomauro et al., 2021). The numbers of people affected by mental health issues are astonishing, with estimates that 25% of adults experience a mental health issue in any given year, and this affects not only the individual but also their friends and family. One in 17 adults experience a serious mental illness (Kessler et al., 2005). Newer antidepressants are probably the most frequently prescribed drugs for treating mental health issues, although there is no “magic bullet” for treating depression or other conditions. Pharmacotherapy with psychological therapy may be the most beneficial treatment approach for many psychiatric conditions, but many questions remain unanswered. For example, why does one antidepressant help one individual yet has no effect on another? Antidepressants can take 4 to 6 weeks to start improving depressive symptoms, and we don’t understand why. Many individuals do not respond to the first prescribed antidepressant and may need to try various medications before finding an effective treatment. Some individuals show no improvement with any antidepressants (Ioannidis, 2008). As our understanding of individual differences improves, we can more quickly and effectively assist those in distress.

Recent interest has focused on personalized treatment approaches. Genetic variations in cytochrome P450 enzymes affect drug-metabolism rates. The general population falls into the following 4 categories: 1) ***ultra-extensive metabolizers*** break down certain drugs (like some antidepressants) very, very quickly, 2) ***extensive metabolizers*** are also able to break down drugs fairly quickly, 3) ***intermediate metabolizers*** break down drugs more slowly than the two above groups, and finally 4) ***poor metabolizers*** break down drugs much more slowly than the other groups. Now consider someone receiving a prescription for an antidepressant—what would be the consequences if they were an ultra-extensive metabolizer or a poor metabolizer? The ultra-extensive metabolizer would be told it will probably take 4 to 6 weeks for the antidepressants to begin working (this is true), but they metabolize the medication so quickly that it will never be effective for them. In contrast, the poor metabolizer given the same dose of that antidepressant may build up such high levels in their blood (because they are not breaking down the drug), that they will have a wide range of side effects–also not a positive outcome. What if instead, prior to prescribing an antidepressant, the doctor could take a blood sample and determine which type of metabolizer a patient actually was? They could make an informed decision about the best dose to prescribe. New genetic tests are available to individualize treatment. A blood sample can determine (at least for some drugs) which category an individual fits into, but we need data to determine if this actually is effective for treating depression or other mental illnesses (Zhou, 2009). While currently costly and often not covered by insurance, such genetic testing may become crucial in psychopharmacology’s future. This research, along with studies on cell membranes, neuronal DNA, and receptor-site alterations, aims to explain the delayed onset of antidepressant effects.

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5.5: Other Controversial Issues

Juveniles and Psychopharmacology

A recent Centers for Disease Control (CDC) report suggested that as many as 1 in 5 children between the ages of 5 and 17 may have some mental disorder (e.g., ADHD, autism, anxiety, depression) (CDC, 2013). The incidence of bipolar disorder in children and adolescents has also increased 40 times recently (Moreno et al., 2007), and it is now estimated that 1 in 36 children have been diagnosed with an autism spectrum disorder (CDC, 2023). Why has there been such an increase in these numbers? This important question has no single answer. Some believe that greater public awareness has increased teacher and parent referrals. Some attribute the rise to changes in diagnostic criteria. Still others suggest environmental factors, prenatally or postnatally, have contributed to this upsurge.

Figure 4. There are concerns about both the safety and efficacy of drugs like Prozac for children and teens.

This question raises further controversy regarding the treatment of young individuals. Many psychotropic drugs used for treating psychiatric disorders have been tested in adults, but few have been tested for safety or efficacy with children or adolescents. The most well-established psychotropics prescribed for children and adolescents are the psychostimulant drugs for treating attention deficit hyperactivity disorder (ADHD), and there are clinical data on these drugs' effectiveness. However, we know far less about the safety and efficacy in young populations of the drugs typically prescribed for treating anxiety, depression, or other psychiatric disorders. The young brain continues to mature until well after age 20, so some scientists are concerned that drugs that alter neuronal activity in the developing brain could have significant consequences. Clinical trials in minors are needed to test the safety and effectiveness of these drugs, raising ethical concerns about consent, participation, and compensation.

The Elderly and Psychopharmacology

Elderly populations are often excluded from psychotropic drug safety and efficacy trials. Currently, little high-quality evidence is available to guide prescribing for older adults—clinical trials often exclude people with multiple comorbidities (other diseases, conditions, etc.), which are typical for elderly populations (see Hilmer & Gnjidict, 2008; Pollock et al., 2008). This is a serious issue because the elderly consume a disproportionate number of the prescription meds prescribed. The term **polypharmacy** refers to the use of multiple drugs, which is very common in elderly populations in the United States. Demographic projections suggest that by 2030, individuals aged 65 or older will constitute approximately 20% of the U.S. population, potentially accounting for 40% of prescribed medication consumption. Table 3 illustrates why standard clinical trials poorly capture the reality of elderly populations.

Table 3. Characteristics of clinical trial subjects vs. actual patients (Schwartz & Abernethy, 2008)
** OTC = Over the counter*

Clinical Trial Subjects	Aged Patients Who Receive Drug Therapies
One drug	Drug of interest and medications
Single dose	Chronic administration
No disease	Multiple diseases
No alcohol, tobacco, OTC* drugs, nutraceuticals	OTC* drugs, nutraceuticals, alcohol, tobacco, and other
20-40 years (vs 60-75 years)	65-100+ years
Caucasians	Caucasians and minorities
Selection bias	All corners/socioeconomic basis

Drug metabolism often slows considerably for elderly populations, so less of a drug can produce the same effect (or all too often, too much of a drug can result in a variety of side effects). One of the greatest risk factors for elderly populations is falling and breaking bones, which can happen if the elderly person gets dizzy from too much of a drug. Psychotropic medications can

also reduce bone density, thus worsening the consequences of falls (Brown & Mezuk, 2012). Despite growing awareness, geriatric pharmacotherapy presents complex medical and ethical challenges.

This chapter provided an introduction to some of the important areas in the field of psychopharmacology. Understanding psychopharmacology is crucial for understanding behavior, and has significant societal implications.

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definition

The use of many medications

×Close definition

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5.6: How Drugs Affect Neurotransmitters

The chapter concludes with some examples and animations of how drugs like alcohol, caffeine, cannabis, and opiates work at the level of neurotransmitters and synapses (The Brain from Top to Bottom, n.d.). These examples are adapted from the website The Brain from Top to Bottom. (https://thebrain.mcgill.ca/). Animations and descriptions of other drugs, including nicotine, amphetamines, ecstasy, and benzodiazepine, can be found there.

Alcohol

Alcohol passes directly from the digestive tract into the blood vessels. In minutes, the blood transports the alcohol to all parts of the body, including the brain.

Alcohol affects the brain's neurons in several ways. It alters their membranes as well as their ion channels, enzymes, and receptors. Alcohol also binds directly to the receptors for acetylcholine, serotonin, GABA, and the NMDA receptors for glutamate.

Watch the animation to learn about how a GABA synapse functions without alcohol and with alcohol. GABA's effect is to reduce neural activity by allowing chloride ions to enter the post-synaptic neuron. These ions have a negative electrical charge, which helps to make the neuron less excitable. This physiological effect is amplified when alcohol binds to the GABA receptor, probably because it enables the ion channel to stay open longer and thus let more Cl- ions into the cell.

The neuron's activity would thus be further diminished, thus explaining the sedative effect of alcohol. This effect is accentuated because alcohol also reduces glutamate's excitatory effect on NMDA receptors.

However, chronic consumption of alcohol gradually makes the NMDA receptors hypersensitive to glutamate while desensitizing the GABAergic receptors. It is this sort of adaptation that would cause the state of excitation characteristic of alcohol withdrawal.

Alcohol also helps to increase the release of dopamine by a process that is still poorly understood but that appears to involve curtailing the activity of the enzyme that breaks down dopamine.

Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this Video online

Alcohol Animation illustrating GABA synapse function without and with alcohol (click bottom right of video player to make full screen). Source: https://thebrain.mcgill.ca/flash/i/i_03/i_03_m/i_03_m_par/i_03_m_par_alcool.html#drogue

Caffeine

The stimulant effect of coffee comes largely from the way it acts on the adenosine receptors in the neural membrane. Adenosine is a neuromodulator that has specific receptors. When adenosine binds to its receptors, neural activity slows down, and you feel sleepy. Adenosine thus facilitates sleep and dilates the blood vessels, probably to ensure good oxygenation during sleep.

Caffeine acts as an adenosine-receptor antagonist. This means that caffeine binds to these same receptors, leaving fewer receptors available for adenosine and its natural "braking" effect; therefore neural activity speeds up (see animation).

The activation of numerous neural circuits by caffeine also causes the pituitary gland to secrete hormones that cause the adrenal glands to produce more adrenaline. Adrenaline is the "fight or flight" hormone, so it increases your attention level and gives your entire system an extra burst of energy. This is exactly the effect that many coffee drinkers are looking for.

In general, you get some stimulating effect from every cup of coffee, and any tolerance you build up is minimal. On the other hand, caffeine can create a physical dependency. The symptoms of withdrawal from caffeine begin within one or two days after you stop consuming it. They consist mainly of headaches, nausea, and sleepiness and affect about one out of every two individuals.

Lastly, like most drugs, caffeine increases the production of dopamine in the brain's pleasure circuits, thus helping to maintain the dependency on this drug, which is consumed daily by 90% of all adults in the U.S.

Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this Video online

Caffeine Animation showing the effects of caffeine on a GABA synapse (click bottom right of video player to make full screen). Caffeine binds to receptors, leaving fewer available for adenosine and its natural braking effect, and consequently accelerating neural activity. Source: https://thebrain.mcgill.ca/flash/i/i_03/i_03_m/i_03_m_par/i_03_m_par_cafeine.html#drogues

Cannabis

The sensations of slight euphoria, relaxation, and amplified auditory and visual perceptions produced by marijuana are due almost entirely to its effect on the cannabinoid receptors in the brain. These receptors are present almost everywhere in the brain, and an endogenous molecule that binds to them naturally has been identified: anandamide (Devane et al., 1992). This mechanism parallels opiates, which bind directly to the receptors for endorphins, the body's natural morphines.

Anandamide is involved in regulating mood, memory, appetite, pain, cognition, and emotions. When cannabis is introduced into the body, its active ingredient, Delta-9-tetrahydrocannabinol (THC), can therefore interfere with all of these functions.

THC begins this process by binding to the CB1 receptors for anandamide. These receptors then modify the activity of several intracellular enzymes, including cAMP, whose activity they reduce. Less cAMP means less protein kinase A. The reduced activity of this enzyme affects the potassium and calcium channels so as to reduce the amount of neurotransmitters released. The general excitability of the brain's neural networks is thus reduced as well.

However, in the reward circuit, just as in the case of other drugs, more dopamine is released. As with opiates, this paradoxical increase is explained by the fact that the dopaminergic neurons in this circuit do not have CB1 receptors but are normally inhibited by GABAergic neurons that do have them. Cannabis removes this inhibition by the GABA neurons and hence activates the dopamine neurons.

In chronic consumers of cannabis, the loss of CB1 receptors in the brain's arteries reduces the flow of blood, and hence of glucose and oxygen, to the brain. The main results are attention deficits, memory loss, and impaired learning ability.

Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this Video online

Cannabis animation. Video illustrating the effects of cannabis on GABA and dopamine neurons (click bottom right of video player to make full screen). Source: https://thebrain.mcgill.ca/flash/i/i_03/i_03_m/i_03_m_par/i_03_m_par_cannabis.html#drogues

Opiates (Heroin, Morphine, Etc.)

The human body naturally produces its own opiate-like substances and uses them as neurotransmitters. These substances include endorphins, enkephalins, and dynorphins, often collectively known as endogenous opioids. Endogenous opioids are produced within the body and modulate our reactions to painful stimuli. They also regulate vital functions such as hunger and thirst and are involved in mood control, immune response, and other processes.

The reason that opiates such as heroin and morphine affect us so powerfully is that these exogenous substances (originating from outside the body) bind to the same receptors as our endogenous opioids. There are three kinds of receptors widely distributed throughout the brain: mu, delta, and kappa receptors.

These receptors, through second messengers, influence the likelihood that ion channels will open, which in certain cases reduces the excitability of neurons. This reduced excitability is the likely source of the euphoric effect of opiates and appears to be mediated by the mu and delta receptors.

This euphoric effect also appears to involve another mechanism in which the GABA-inhibitory interneurons of the ventral tegmental area come into play. By attaching to their mu receptors, exogenous opioids reduce the amount of GABA released (see animation). Normally, GABA reduces the amount of dopamine released in the nucleus accumbens. By inhibiting this inhibitor, the opiates ultimately increase the amount of dopamine produced and the amount of pleasure felt.

Chronic consumption of opiates inhibits the production of cAMP, but this inhibition is offset in the long run by other cAMP production mechanisms. When no opiates are available, this increased cAMP production capacity comes to the fore and results in neural hyperactivity and the sensation of craving the drug.

Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this Video online

Opiates animation showing the effects of exogenous opioids on GABA and dopaminergic neurons (click bottom right of video player to make full screen). Source: https://thebrain.mcgill.ca/flash/i/i_03/i_03_m/i_03_m_par/i_03_m_par_heroine.html#drogues

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5.7: Neural Circuitry of Drug Reward

Learning Objectives

By the end of this section, you should be able to

- Identify the major brain regions involved in the dopamine reward pathway.
- Describe three different mechanisms for how a drug can enhance dopamine release within the reward pathway.

There are certain basic physiological needs, such as food, water, and procreation, that are essential for the survival of the individual and the species. From an evolutionary perspective, it stands to reason that behaviors that promote survival would be perceived as enjoyable to encourage the continued expression of the behavior. The dopamine reward pathway is critical in mediating motivated behavior for rewarding stimuli.

Dopamine reward pathway

The most well-characterized reward circuit in the brain originates in the ventral tegmental area (VTA), which is located in the midbrain. Within the VTA are the cell bodies of dopaminergic neurons, which are cells that synthesize the neurotransmitter dopamine. VTA dopamine neurons have two major projections: the mesolimbic pathway and the mesocortical pathway. Together, these two pathways are collectively referred to as the mesocorticolimbic dopamine pathway. Figure 14.14 shows these connections for a human brain on the left. The right image shows the parallel circuitry in a mouse brain, revealing how highly conserved these connections are between species.

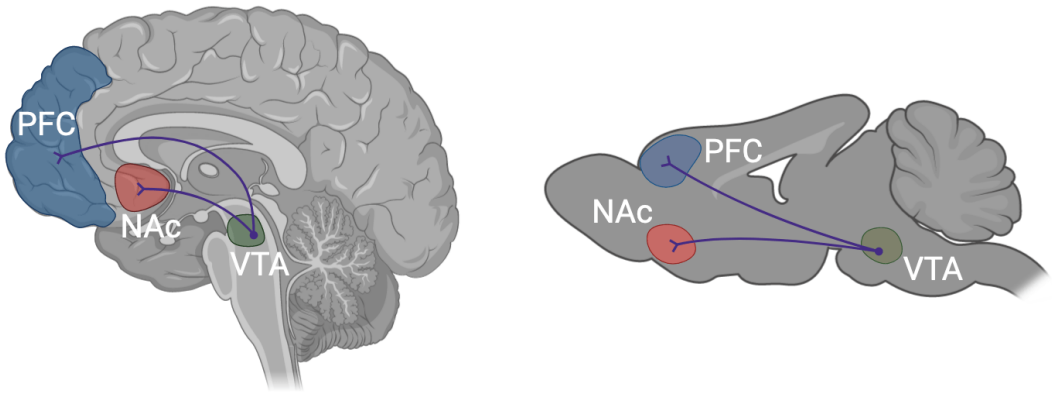


Figure 14.14 Dopaminergic pathways Dopaminergic pathways from the VTA project to PFC and NAc in both humans and rodents.

The mesolimbic pathway is composed of dopaminergic neurons that innervate cells in the nucleus accumbens (NAc), a region of the brain highly implicated in motivation and goal-directed behavior. The impact of rewarding stimuli on dopamine signaling in the NAc was first established using microdialysis, a sampling technique in which extracellular fluid is continuously collected from a probe inserted into brain tissue. The collected fluid, also known as dialysate, can then be analyzed to determine the concentration of specific neurotransmitters at different time intervals. Early microdialysis studies in rats demonstrated increased dopamine release in the NAc in response to several different types of psychoactive drugs (Di Chiara & Imperato, 1988). Similarly, positron emission tomography (PET) studies in humans show that rapid increases in dopamine concentration in the NAc are associated with the reinforcing effects of psychoactive drugs (Volkow et al., 1999).

The mesocortical pathway is made up of VTA dopamine neurons that synapse with cells in the prefrontal cortex (PFC). These dopaminergic projections play an important role in self-control, decision-making and emotional regulation. Dysregulation of this pathway is thought to contribute to the impaired self-control and compulsive behavior seen in addiction.

Although the NAc and PFC are important targets of the brain reward pathway, there are several other brain regions and neurotransmitters that mediate the cognitive processes that encode pleasurable experiences and reinforce reward-seeking

behaviors. The hippocampus and amygdala, for example, are also innervated by dopaminergic neurons that originate in the VTA and play an important role in forming memories and contextual cues associated with rewarding stimuli. To prevent the constant firing of dopaminergic neurons, GABAergic interneurons in the VTA maintain a basal tone by inhibiting dopamine release in the absence of a reward. Brain regions involved with mood regulation and stress reactivity, such as the hypothalamus and lateral habenula, can also modulate the dopamine pathway through both glutamatergic and GABAergic inputs.

Neuroscience in the Lab

Role of dopamine signaling in reward

Dopamine activity within the mesocorticolimbic pathway is a vital component of reward processing. However, the hypothesized functional role of the neurotransmitter in the brain reward system has varied throughout history. The hedonia hypothesis, first coined by Roy Wise in 1980, proposed that dopamine release directly correlates with the hedonic value, or "liking" of a pleasurable stimulus (Wise, 1980). This hypothesis was later challenged by taste reactivity studies in rodents. Similar to humans, rodents exhibit distinct facial expressions in response to appetitive versus aversive tastes. Interestingly, animals who had reduced dopamine levels in the brain reward pathway showed similar appetitive responses to a sweet taste compared to animals who had an intact dopamine system but exhibited less motivation to seek out food rewards (Berridge, Venier, & Robinson, 1989). These findings suggested that while dopamine activity is not necessary for hedonic "liking", it is important for motivational drive.

A separate series of electrophysiological experiments conducted in monkeys provided support for dopamine's involvement in reward-based associative learning as opposed to "liking". Monkeys who were presented with an unexpected appetitive stimulus exhibited increased firing of dopaminergic neurons in the VTA (Schultz, 1986). This effect was not seen when animals were presented with an aversive stimulus. After repeated pairings of an environmental cue with the appetitive stimulus, the VTA dopamine neurons began firing in response to the cue rather than the reward itself (Schultz et al., 1992). If animals were presented with the cue but did not receive the reward, VTA dopamine activity was significantly decreased compared to baseline (Schultz, Apicella, & Ljungberg, 1993).

Together, these observations gave rise to the reward prediction error hypothesis, which argues that dopamine activity encodes the error, or deviation, between predicted and experienced rewards. As illustrated in Figure 14.15, before learning, an unexpected reward elicits a strong dopamine response, which reflects a greater reward than anticipated. Once reward-based associations have been formed with the environmental cue, the cue serves as a predictor of an upcoming reward. Thus, dopamine neurons will fire in response to the cue but not the reward itself, seeing as if the reward is received there is no error between the prediction and outcome. In contrast, the presentation of a cue without the reward results in the suppression of dopamine activity, which indicates that the outcome was less than expected. These signals ultimately serve as an adaptive learning mechanism for seeking out and obtaining rewards.

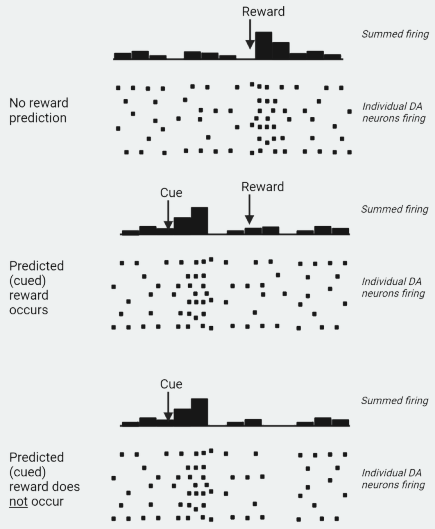


Figure 14.15 Dopamine neurons report prediction error

While the reward prediction error hypothesis helped to establish a role for dopamine in learning, more recent theories also consider the role of dopamine in modulating motivational drive in response to changing physiological and emotional states. For example, an advertisement featuring food may induce a stronger urge to seek out food in a person who is hungry compared to a person who recently consumed a meal. The magnitude of desire or "wanting" for a rewarding stimulus is referred to as incentive salience. The incentive salience theory posits that increased dopamine activity in the mesocorticolimbic pathway enhances motivational "wanting" for previously learned reward-associated cues, thereby increasing the likelihood that the reward will be sought out in the future. Building off of this, the incentive-sensitization theory of addiction hypothesizes that chronic use of psychoactive drugs, such as cocaine and heroin, dysregulates the dopamine reward pathway and enhances the incentive salience of drug-related cues to the point where they are compulsively "wanted", even in the absence of "liking" (Berridge, 2012).

Commonly used psychoactive drugs

In the United States, certain psychoactive drugs are regulated by the FDA and the Drug Enforcement Agency (DEA). These drugs are categorized into one of five schedules based on accepted medical use and potential for addiction (Table 14.2). Schedule I drugs are characterized as having the highest risk for physical and psychological dependence and no accepted medical use, whereas Schedule V drugs have the lowest potential for dependence, although these assessments do not always coincide with current scientific knowledge.

Schedule	Description	Example
Schedule 1	No currently accepted medical use in the US, lack of accepted safety, high potential for psychological and physical dependence	Heroin, LSD, marijuana, ecstasy
Schedule 2	High potential for psychological and physical dependence	Cocaine, oxycodone, fentanyl, methamphetamine
Schedule 3	Moderate to low potential for psychological and physical dependence	Buprenorphine, ketamine, anabolic steroids
Schedule 4	Low potential for psychological and physical dependence	Alprazolam (Xanax), zolpidem (Ambien), diazepam (Valium)
Schedule 5	Lower potential for psychological and physical dependence than Schedule 4	cough medicines with low doses of codeine (Robitussin AC)

Table 14.2

The most commonly used psychoactive drugs fall into four main categories, as shown in Table 14.3.

Category	Effect	Examples
Stimulant	Increases CNS activity	Amphetamine, cocaine, nicotine
Depressant	Decreases CNS activity	Alcohol, Benzodiazepines
Opioid	Pain relief, sedation, euphoria	Fentanyl, heroin, morphine
Hallucinogen	Altered sensory perception	Ketamine, LSD, psilocybin

Table 14.3

Stimulants increase levels of physiological or central nervous system activity in the body, whereas depressants reduce CNS activity. Hallucinogens are drugs that can alter your perceptions or produce changes in cognition, emotion, and consciousness to a degree that is not typically experienced with other drug categories. The term narcotics, which comes from the Greek word for "stupor", was originally used to describe any psychoactive compound with sleep-inducing properties. Nowadays, the term refers specifically to opium derivatives and synthetics. Virtually all psychoactive drugs either stimulate dopamine release or enhance dopamine receptor activity in the NAc, resulting in increased dopamine signaling within the reward pathway. Figure 14.16 shows the actions of several common classes of psychoactive drugs on the mesolimbic dopaminergic system, many of which we will describe further in the sections that follow.

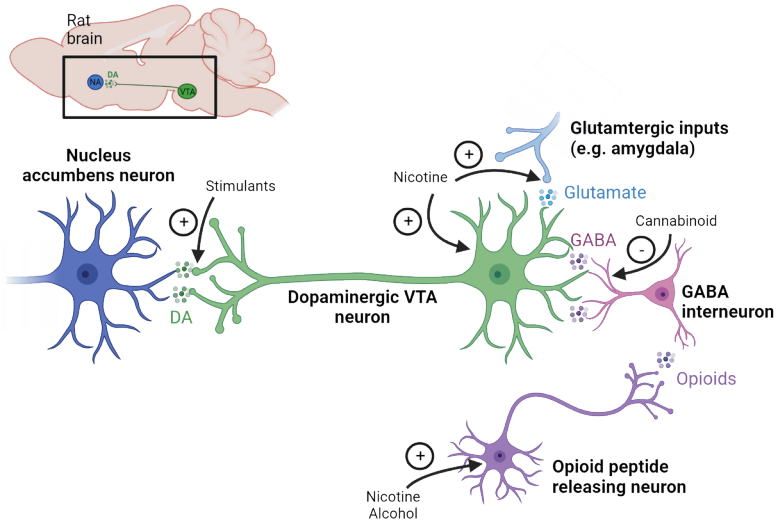


Figure 14.16 Drugs of abuse site of action summary

Opioids

The powerful analgesic and euphoric properties of opioids were recognized as early as 3400 BC. The term opiate refers to substances derived from the opium poppy plant, including morphine, codeine, and heroin. Semi-synthetic opioids, such as oxycodone and hydrocodone, are drugs that are created from natural opiates. Synthetic opioids, such as fentanyl, are manufactured entirely in a laboratory but have similar cellular and physiological effects to opiates. Opioids are most commonly administered orally via pills or injected intravenously.

Opioid receptors are inhibitory G-protein coupled receptors. Within the dopamine reward pathway, opioid receptors are primarily located on GABAergic interneurons that synapse onto dopaminergic VTA neurons. Activation of these opioid receptors hyperpolarizes the GABAergic interneurons, leading to reduced GABA release. In the absence of inhibitory input, VTA dopamine neurons become more active, resulting in increased dopamine release in the NAc. Another way to describe this mechanism is that opioids disinhibit dopamine neurons in the VTA via their inhibition of GABAergic interneurons.

Opioid receptors are also highly expressed on neurons in the brainstem that control breathing. High doses of opioids (or co-administration of opioids with other depressants) can hyperpolarize these cells, resulting in slowed or stopped breathing, also known as respiratory depression. If not treated, respiratory depression may lead to loss of consciousness, coma, or even death. Naloxone (Narcan) is an opioid receptor antagonist that rapidly blocks the effects of opioid drugs already in the body and can restore normal breathing in a person who is experiencing an overdose.

Alcohol

Alcohol, a depressant, is one of the oldest and most widely used psychoactive drugs in the world. It is produced as a byproduct of the fermentation of sugars by yeast. In 2021, 84% of Americans aged 18 or older reported drinking alcohol at some point in their lifetime (SAMHSA, 2021).

Several different receptor types and neurotransmitters in the brain are affected by alcohol. The reinforcing properties of alcohol are thought to be mediated in part by its modulation of the endogenous opioid system. Alcohol administration increases the synthesis of opioid peptides (i.e. beta-endorphin) in the brain. Similar to exogenous opioid drugs, these peptides also bind to mu-opioid receptors on GABAergic interneurons in the VTA and disinhibit dopamine release in the NAc.

As a positive allosteric modulator of the $GABA_A$ receptor, alcohol also enhances inhibitory signaling in the brain, leading to an overall reduction in arousal.Many of the sedative effects of alcohol, such as slurred speech, incoordination, and slowed reaction time, are mediated by its activity at the $GABA_A$ receptor. Alcohol also suppresses glutamate release and inhibits NMDA receptor signaling, which further reduces CNS activity and also contributes to memory loss and impaired cognitive functioning. As with all drugs, the acute behavioral and physiological effects of alcohol are heavily dependent on the amount that is absorbed

into the bloodstream. Whereas lower concentrations of alcohol may only produce mild symptoms, rapid and excessive alcohol consumption, also known as binge drinking, increases the risk of adverse effects, such as loss of consciousness, coma, or death.

Nicotine

Nicotine, a stimulant substance naturally found in tobacco leaves, is the primary psychoactive chemical in tobacco products such as cigarettes and cigars. Although inhalation is a common route of administration for nicotine, it can also be chewed, snorted, or absorbed through the skin via a patch. In 2021, 22% of Americans aged 12 or older reported using tobacco products or nicotine vaping devices (such as electronic cigarettes) in the past month (SAMHSA, 2021).

Nicotine is an exogenous ligand for the nicotinic acetylcholine receptor (nAChR), an excitatory ligand-gated ion channel expressed widely throughout the brain and peripheral nervous system, although nicotine has a higher affinity for nAChRs in the brain than those in the neuromuscular junction. The reinforcing effects of nicotine are mediated by the activation of nAChRs located within the mesolimbic dopamine pathway. Stimulation of nAChRs expressed on glutamatergic inputs to dopaminergic VTA neurons, and the VTA neurons themselves, elevates dopamine release in the NAc. Similar to alcohol, nicotine also increases the synthesis of endogenous opioid peptides. Nicotine's stimulant effects, including increased heart rate and blood pressure, are due to the activation of nAChRs on the adrenal glands which stimulate the release of epinephrine and norepinephrine. These mechanisms have also been associated with enhanced attention and cognitive performance.

Cocaine

Cocaine is a stimulant chemical derived from the coca plant, which is indigenous to South America. It first became popularized in Western medicine in the 1800s as a cure-all and continues to be used today in medical contexts as a topical analgesic. Small concentrations of cocaine can be ingested by chewing the leaves of the coca plant. However, in modern recreational usage, it is more commonly snorted, smoked, or solubilized and injected intravenously.

Rather than binding to a receptor directly, cocaine exerts its molecular effects by inhibiting reuptake transporter proteins. These proteins are located in the cell membrane and are responsible for removing neurotransmitters from the synaptic cleft by drawing the molecules back into the presynaptic axon terminal. Thus, in the presence of cocaine, dopamine can stay in the synapse longer and continue binding to its receptor on the postsynaptic neuron (Figure 14.17). Similar to nicotine, cocaine also increases physiological arousal by enhancing epinephrine and norepinephrine release in the periphery.

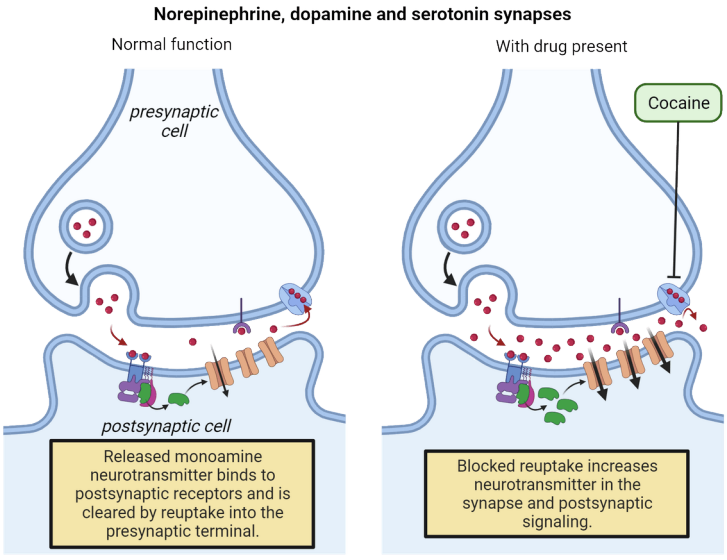


Figure 14.17 Cocaine effects at the synapse

Tetrahydrocannabinol (THC)

The primary psychoactive substance in cannabis (also known as marijuana) is the cannabinoid tetrahydrocannabinol (THC). Cannabis, which is derived from the cannabis plant, is commonly administered via inhalation, although edible formulations have

become popular. THC is the exogenous ligand for the cannabinoid (CB) receptor, a G-protein coupled receptor located throughout the body. There are two subtypes of CB receptors. The CB_1 receptor is expressed primarily in the brain, whereas CB2 receptors are found mainly within the immune system.

The reinforcing effects of THC are mediated by its activity at presynaptic CB_1 receptors located on GABAergic interneurons that innervate dopamine cells. CB_1 receptors are primarily inhibitory G-protein coupled receptors. Therefore, the binding of THC to the receptor hyperpolarizes the GABAergic interneuron and disinhibits dopamine release in the NAc. At low doses, THC can enhance mood and increase relaxation. Higher doses of THC may distort sensory perceptions and induce paranoia, though these effects appear to be rare and may be dependent on the strain, or genotype, of the plant. Cannabidiol (CBD) is another type of cannabinoid found in cannabis that also binds to CB_1 receptors. However, in contrast to THC, CBD does not have any intoxicating effects. This may be because CBD is a negative allosteric modulator of the CB_1 receptor and thus suppresses receptor activation.

At the federal level, cannabis and its derivatives are currently classified as a Schedule 1 drug, although there is strong evidence that cannabinoids are effective in treating certain medical conditions (Whiting et al., 2015). As of 2023, 38 states have legalized the use of cannabis for medical purposes and 23 states and Washington D.C. have legalized cannabis for recreational use by people 21 or older.

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5.8: Neurobiology of Addiction

Learning Objectives

By the end of this section, you should be able to

- List and describe the three stages of the addiction cycle.
- Discuss the advantages and disadvantages of the brain disease model of addiction.

In 2021, over 46 million people met the criteria for having a substance use disorder (SUD) (SAMHSA, 2021). The Diagnostic and Statistical Manual of Mental Disorders (DSM) classifies a SUD as uncontrolled or hazardous substance use despite negative outcomes, such as medical and legal issues, loss of employment, or estrangement from family and friends. While "SUD" and "addiction" are often used interchangeably, SUD severity ranges from mild to severe, with the most severe forms being classified as addiction.

Neurobiological model of addiction

A well-cited neurobiological framework for studying addiction conceptualizes the condition as a repeating cycle composed of three stages that feed into each other (Wise & Koob, 2014) (Figure 14.18).

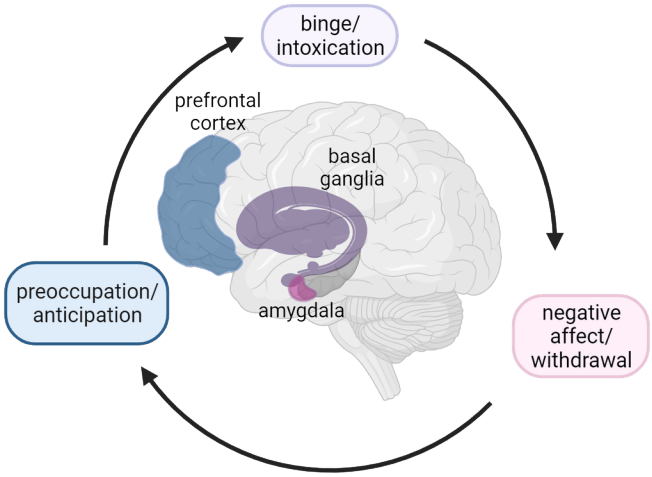


Figure 14.18 Koob model of addiction cycle

The binge/intoxication stage is associated with the initial euphoric effects elicited by many psychoactive drugs, which serve as a powerful reinforcer for continued drug use. In contrast, the withdrawal/negative affect stage is characterized by reduced positive associations with the drug. Prolonged drug use can lead to tolerance, or decreased drug effectiveness over time, in addition to diminished interest or motivation for non-drug-related rewards. Drug cessation may result in withdrawal, a constellation of highly aversive physical (i.e. sweating, vomiting, diarrhea, seizures), and psychological (i.e. anxiety, depression) symptoms. Whereas physical symptoms typically subside within a week or so, the psychological aspects of withdrawal can continue for months or longer. At this stage, drug use is typically motivated by a desire to avoid withdrawal symptoms as opposed to seeking euphoric effects. The preoccupation/anticipation stage occurs during periods of abstinence when individuals experience strong cravings for the drug and become engrossed with seeking out and obtaining the drug. Thus, one of the most challenging aspects of treating SUDs is the risk of chronic relapse or a repeated pattern of returning to drug use after a period of abstinence. The proposed neurobiological mechanisms that contribute to these distinct stages are described below.

Binge/Intoxication

As discussed earlier in the chapter, almost all psychoactive drugs enhance activity in the mesocorticolimbic dopamine system. Importantly, these drug-induced increases in dopamine signaling often occur faster and to a larger and more prolonged extent compared to natural stimuli (Figure 14.19). This extra strong stimulation of the mesolimbic dopamine system is thought to induce neuroplastic changes, such as increased dendritic spines or insertion of receptors into the synapse, within the larger basal ganglia system which regulates complex processes including motivation, decision-making, and emotions. The activation of brain circuits that mediate reward-based learning ultimately increases the incentive salience, or motivational drive, for the drug and drug-associated environmental cues (i.e. specific people, places, or items that have previously been paired with drug use).

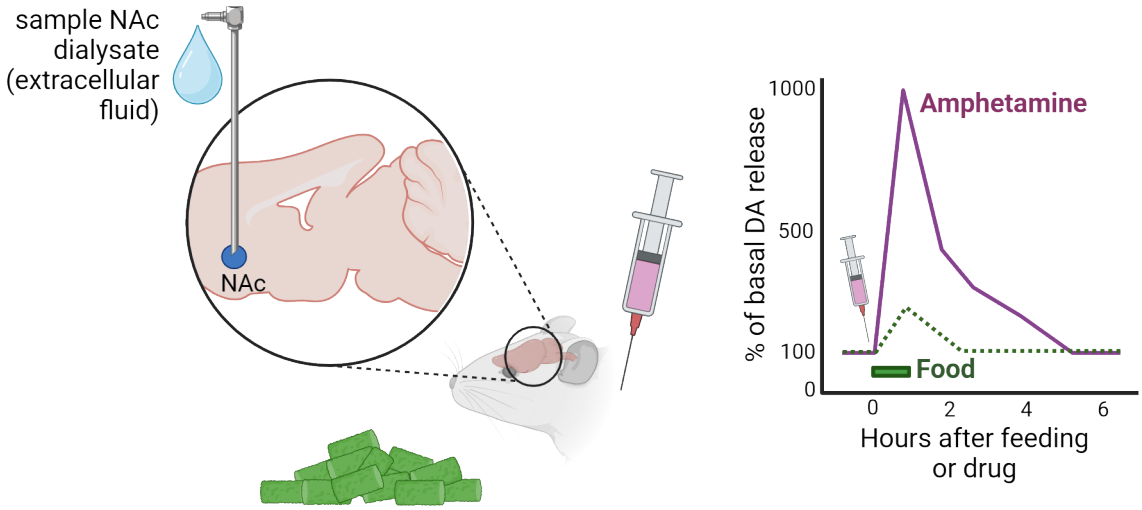


Figure 14.19 NAc dopamine release with food vs amphetamine

Negative Affect/Withdrawal

Drug dependence refers to a physical and/or psychological state in which drug use is necessary to avoid withdrawal. It is typically preceded by the development of tolerance, in which increasingly higher doses of the drug are required to achieve the original effect (Figure 14.20).

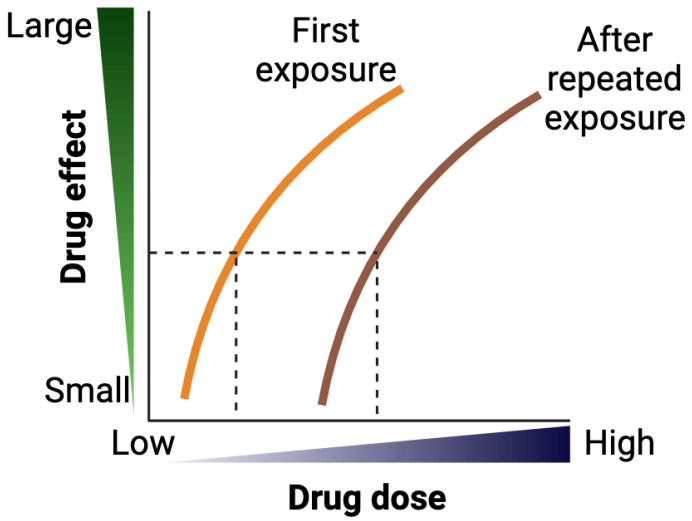


Figure 14.20 Tolerance Repeated use of a drug can lead to a shift in response, such that more drug is needed to achieve the same effect.

Tolerance can arise through several different mechanisms. Drug-induced changes in metabolism, such as elevated liver enzyme activity, can lead to faster degradation and clearance of the drug, resulting in reduced bioavailability. Alternatively, tolerance may be caused by changes in cellular responses to the drug following repeated exposure. For example, whereas initial drug use enhances dopamine release, chronic drug exposure reduces dopamine release and downregulates the expression of dopamine receptors within the dopamine reward pathway (Volkow et al., 1997; Martinez et al., 2004) (Figure 14.21). With less neurotransmitter and receptor availability comes less receptor binding and signaling, ultimately leading to reduced drug effects.

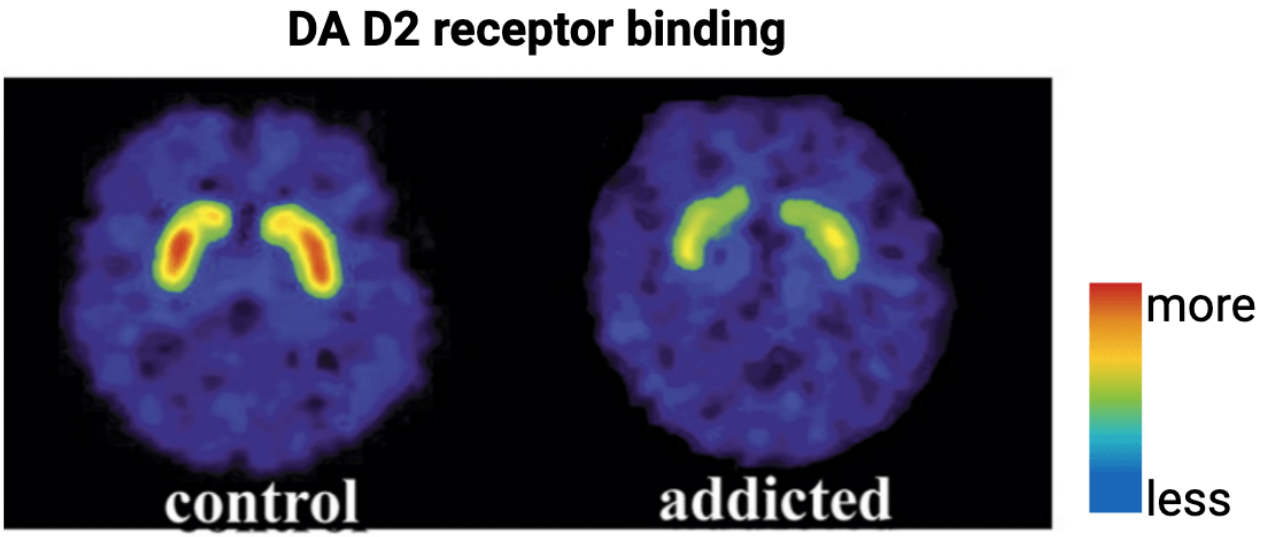


Figure 14.21 Dopamine (DA) D2 receptor binding Position emission topography (PET) scan studies demonstrate reduced expression of D2 dopamine receptors within the basal ganglia of participants with cocaine use disorder compared to controls. Image credit: 1993 Wiley-Liss, Inc. Image reused with permission: Volkow, N.D., Fowler, J.S., Wang, G.-J., Hitzemann, R., Logan, J., Schlyer, D.J., Dewey, S.L. and Wolf, A.P. (1993), Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse, 14: 169-177. doi.org/10.1002/syn.890140210.

Tolerance can also manifest from conditioned behavioral responses to environmental cues associated with drug use (Siegel, 1999). Drug users who were presented with drug preparation materials and asked to self-inject experienced significantly fewer physiological responses to the drug compared to drug users who received a passive infusion of the drug (Ehran et al., 1992). This finding suggests that the mere anticipation of drug administration may be sufficient to induce compensatory physiological mechanisms that weaken the drug's effects. While drug dependence is highly associated with SUDs, it does not necessarily equate to addiction. For instance, a person who drinks caffeinated beverages daily may become dependent on caffeine and experience withdrawal symptoms (e.g. headache, fatigue, irritability) if they skip a day, but it is highly unlikely that they would develop the pathological behaviors that characterize SUDs.

The negative psychological symptoms associated with chronic drug use and withdrawal are mediated by increased activation of brain stress systems and impaired functioning of reward circuits. While the mechanisms underlying these effects are not well understood, they are thought to be caused by drug-induced neuroadaptations that sensitize circuits involved in stress response. Several rodent studies have demonstrated that withdrawal from chronic drug exposure increases stress hormone activity in the extended amygdala, an anatomical region including the amygdala and bed nucleus of the stria terminalis (BNST) that is highly implicated in both stress response and emotional processing (Koob, 2008). On the other hand, the blockade of stress hormone signaling prevents the manifestation of anxiety-like behavior following drug cessation. Collectively, these mechanisms are believed to contribute to the aversive psychological components of drug withdrawal that act as a negative reinforcement for continued drug use.

Preoccupation/Anticipation

Increased preoccupation, or fixation on seeking out and obtaining drugs, may be caused by drug-induced alterations in neuronal processes within the hippocampus and prefrontal cortex (PFC). Neuroimaging studies in humans have demonstrated increased hippocampal activation during cue-elicited craving (Volkow, Fowler, & Wang, 2004). Furthermore, individuals diagnosed with a SUD exhibit abnormal activity in the PFC and impaired performance in cognitive tasks that are dependent on the PFC (Bolla et al., 2003). As proposed by the incentive-sensitization theory of addiction, drug-induced dysregulation of reward-based learning

pathways may cause drugs and drug-associated cues to become hyper-salient, leading to intense cravings during abstinence. This, coupled with impaired impulse control and self-regulation mechanisms, may explain why factors such as environmental cues or stress can reinstate uncontrollable drug-seeking behavior in individuals who are in recovery.

Neuroscience across species: Intravenous self-administration

The brain reward system is remarkably conserved across species. Rodents, in particular, share many of the same brain regions, neurotransmitters, receptors, and genes found in humans. Furthermore, rodents exhibit similar behavioral and neurobiological responses to psychoactive drugs, making them an excellent translational model for investigating the neural mechanisms underlying the different stages of addiction.

Intravenous self-administration (IVSA) is considered the gold standard for studying drug-seeking behavior in an animal model (Figure 14.22). Using IVSA, researchers can examine the variables that contribute to different levels of responding to a drug reward. In this procedure, a catheter is surgically implanted into the jugular vein of a mouse or rat. The catheter is connected to a syringe containing the drug of interest. The rodent is then trained in an operant chamber to press a lever to receive an intravenous delivery of the drug. Often drug delivery is paired with an auditory or visual cue, such as a tone or light.

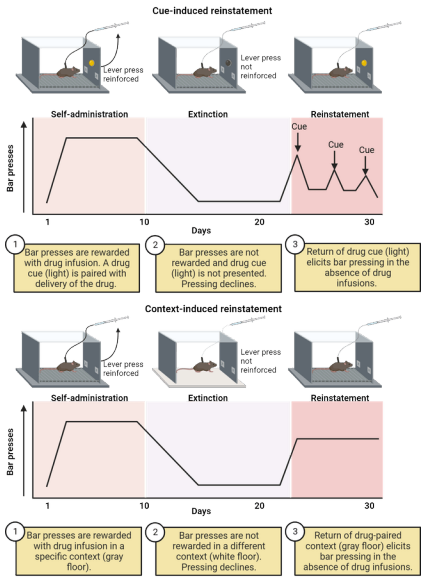


Figure 14.22 Self-administration paradigm

To investigate how much effort an animal will exert to receive the drug, the experimenter can manipulate the ratio schedule, which is the number of lever presses required to receive the drug reward. In a fixed ratio schedule, the animal must perform a predetermined number of lever presses to receive a single delivery of the drug. For example, in a fixed ratio 1 schedule (FR1), the animal receives one delivery for each lever press within a session, whereas a fixed ratio 5 schedule (FR5) requires the animal to perform at least 5 lever presses to receive a single dose. In contrast, a progressive ratio schedule requires escalating responses for a single delivery within a session. In this scenario, the animal may initially only need to lever press a few times to receive one delivery, but over time may need to lever press over a hundred times to receive the same reward. The highest ratio schedule achieved within a certain time period before the animal stops responding is referred to as the breakpoint. A high breakpoint is indicative of increased motivational desire or “wanting” of the drug.

During extinction, the drug and drug-associated cues are removed, or the chamber context is changed (different wall pattern, floor texture, odor, etc.). Over time, the lack of reinforcement leads to a reduction in lever pressing. However, drug-seeking behavior (i.e. lever pressing) can be quickly restored by either exposing the animal to a drug-associated context or cue, a stressor (i.e. footshock), or an injection of the drug itself before testing. This phenomenon is referred to as reinstatement and closely mimics relapse behavior in humans. The top of Figure 14.22 shows this experimental paradigm coupled with cue-induced reinstatement while the bottom shows context-induced reinstatement. Note in both cases that bar pressing increases during self-administration when lever pressing is reinforced by drug infusions, decreases during extinction when the drug and associated cue or context is removed, and increases again when either the drug-associated cue or context is returned in the absence of reinforcement from drug infusions.

History of neuroscience: Opioid crisis

In 2017, the opioid crisis was declared a public health emergency in the United States. The history of this epidemic is often characterized by three distinct waves of opioid-related overdose deaths, with the first wave beginning in the 1990s. This first wave can be traced to a change in how pain was treated medically. In 1996, the American Pain Society instituted pain as the fifth vital sign (in addition to body temperature, heart rate, respiration rate, and blood pressure). Consequently, healthcare institutions revised their guidelines to prioritize pain assessment and management. Around the same time, the pharmaceutical company Purdue Pharmaceutical released OxyContin, a sustained-release opioid painkiller. OxyContin was aggressively marketed to physicians and pain management professionals as a non-addictive opioid, even though these claims were never substantiated with clinical evidence. This marketing campaign led to the overprescription of opioids and the subsequent rise in prescription opioid overdoses between the late 1990s to 2010.

In response to these deaths, state and federal agencies began monitoring the distribution of prescription opioids, and physicians were issued guidelines on more conservative prescribing of opioids. The second wave of the opioid epidemic coincided with the increased availability of heroin in the United States. Many individuals who had become dependent on prescription opioids switched to heroin because it was cheaper and easier to obtain. Consequently, heroin-related overdoses increased fivefold between 2010 and 2016.

The third wave of the opioid epidemic began in 2013 and was driven by the import of synthetic opioids, such as fentanyl, into the drug market. Fentanyl is significantly more potent than heroin, which makes it more addictive, but also increases the risk of overdose. The emergence of the Covid-19 pandemic in 2020 and subsequent disruptions in health care combined with social and economic stressors further exacerbated the opioid crisis. Synthetic opioids are currently the leading cause of drug overdose deaths. In 2018, the National Institutes of Health launched the HEAL (Helping to End Addiction Long-term) Initiative to address the opioid crisis. The initiative seeks to develop more effective and evidence-based approaches to treating opioid use disorder and enhancing pain management.

Risk/protective factors

Many people use drugs with high addictive potential without ever developing an addiction. However, several genetic and environmental factors have been associated with an increased risk of developing a substance use disorder (SUD). At the individual level, biological or genetic predispositions can contribute to an increased likelihood of drug misuse. Genome-wide association studies (GWAS) have helped to identify genetic variants that are associated with certain SUDs. For example, a mutation in the gene that codes for the mu-opioid receptor (OPRM1 A118G) is associated with higher susceptibility to developing opioid dependence in certain populations (Bond et al., 1998). In addition to potential heritable factors, a family history of drug use can compound risk by increasing access to or availability of the drug. Early-life drug use (during childhood or adolescence) can alter brain development, which may contribute to long-term behavioral and cognitive issues in addition to an increased risk of developing a SUD later in life (Moustafa et al., 2021). Certain personality traits, such as impulsivity, have been linked to an increased risk of addiction (Ersche et al., 2010). Furthermore, mental health disorders, including anxiety, depression, attention deficit hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD), are often comorbid with SUDs.

Many psychosocial and environmental variables can serve as protective factors by either reducing the likelihood that the individual develops an addiction in the first place or enhancing access to treatment in the case they are diagnosed with a SUD.Protective factors include supportive social structures, participation in community-based initiatives, treatment availability, and access, educational campaigns, beneficial economic conditions, and insurance coverage to name a few.

People behind the science: Dr. Yasmin Hurd

The past few decades have witnessed a significant shift in policies surrounding the medical and recreational use of cannabis at the state level. With the increased prevalence of cannabis products across the country, concerns have been raised about the potentially harmful long-term effects of cannabis use. Dr. Yasmin Hurd, a neuroscientist at the Icahn School of Medicine at Mount Sinai (Figure 14.23), is well known for her contributions to enhancing our understanding of the neurodevelopmental effects of early-life THC (the active ingredient in cannabis) exposure. Her laboratory uses both preclinical (involving animal models) and clinical studies to better understand the neurobiological mechanisms that underlie addiction and other neuropsychiatric disorders. This approach to science is known as translational research since the goal is to convert basic science findings into information that can ultimately benefit humans.



Figure 14.23 Dr. Yasmin Hurd Image from: By Droldn, CC BY-SA 4.0, https://commons.wikimedia.org/w/inde...curid=64216948

In an innovative study combining both animal and human research, Dr. Hurd and her colleagues investigated postmortem fetal brain samples that had either been exposed to cannabis during gestation or had no prenatal exposure (DiNieri et al., 2011). They found that gestational exposure to cannabis was associated with decreased dopamine receptor expression in the nucleus accumbens (NAc), a brain region highly implicated in reward processing.

To further examine the effects of cannabis on the developing brain, Dr. Hurd's research team developed a rodent model in which pregnant rats were treated with daily intravenous injections of either THC or an inactive solution throughout gestation. To control for the potential effects of drug exposure on maternal behavior, offspring of THC-exposed rats were fostered by rats that had no drug exposure. Brain samples were collected on postnatal day 2 (a developmental period comparable to the second trimester of a human pregnancy) and at 8 weeks, which is considered young adulthood in rodents. Similar to the human fetal brain samples, rats prenatally exposed to THC exhibited reduced dopamine receptor expression in the NAc compared to non-exposed controls shortly after birth. Strikingly, this effect was still observed at the 8-week time point. Furthermore, adult rats who had previously been exposed to THC demonstrated increased sensitivity to opioid rewards. Taken together, these findings suggest that early-life THC exposure has long-lasting effects on dopamine receptor function within the mesocorticolimbic pathway, which may increase vulnerability to the reinforcing effects of psychoactive drugs later in life.

Science as a process: Is addiction a brain disease?

The brain disease model of addiction characterizes addiction as a chronic and relapsing condition that arises from drug-induced neuroplastic changes in the reward and mood circuits of the brain. Sensitization of brain reward systems causes drugs and drug-associated stimuli to become compulsively "wanted", leading to a persistent craving. Over time, the development of tolerance and recruitment of "anti-reward" brain systems reduces the amount of pleasure gained from the drug and increases negative affect in the absence of the drug. Collectively, these neuroadaptations are thought to underlie behavioral shifts from constrained to compulsive drug use which can overcome the will to abstain from drug use.

The brain disease model has been influential in the development of evidence-based treatments for addiction, such as medication for reducing craving and withdrawal, and cognitive behavioral therapies for improving self-regulation. Classifying addiction as a disease has helped inform public health policy, such as the Mental Health Parity and Addiction Equity Act of 2008, which required that health insurance plans provide the same level of benefits for SUD treatment as other medical illnesses. Additionally, proponents argue that the brain disease model helps to reduce the stigmatization of addiction as a moral failing, which in turn reduces barriers to seeking out treatment.

Although the brain disease model has grown in popularity over the last few decades, several issues have been raised regarding this theory. Opponents of the brain disease model argue that it overemphasizes biological processes while downplaying the influence of societal, psychosocial and environmental factors. There are concerns that this may lead to an over-reliance on biomedical approaches at the expense of more holistic public health strategies. Furthermore, some argue that labeling addiction as a disease diminishes personal agency and motivation to change behaviors. Alternative theories propose that rather than a

pathological state, addiction is a natural learned response to rewarding environmental stimuli that can be overcome by behavioral and cognitive modifications.

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6: SENSATION AND PERCEPTION

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6.1.2: The Retina

6.1.3: Visual Processing Begins in Bipolar, Horizontal, Amacrine and Ganglion Cells

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6.1: THE VISUAL SYSTEM

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6.1.4: The Thalamus and Primary Visual Cortex

6.1.5: Extrastriate Cortex

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6.1.1: An Overview of the Visual System

Learning Objectives

By the end of this section, you should be able to

- Describe the region of the electromagnetic spectrum that is perceived by our visual system, and the relative energy of photons at long and short wavelengths.
- Describe the major parts of the eye and their role in focusing light to create a clear image.

In this section, we will meet the range of the electromagnetic energy spectrum that we call "light," and see how the structure of the eye provides an optical system that creates a sharply focused image of the visible world on the sensory structure at the back of the eye, the retina.

We Capture Photons of Light Reflected from Objects Around Us

Light is a form of electromagnetic radiation, energy packaged in particles called photons. Physicists understand that light is both a particle and an electromagnetic wave, and although light can be described by the energy in each photon, light is more typically described by its wavelength on the electromagnetic spectrum. Electromagnetic wavelengths stretch from long wavelength, low energy radio waves to short wavelength, high energy gamma rays. (Figure 6.2)

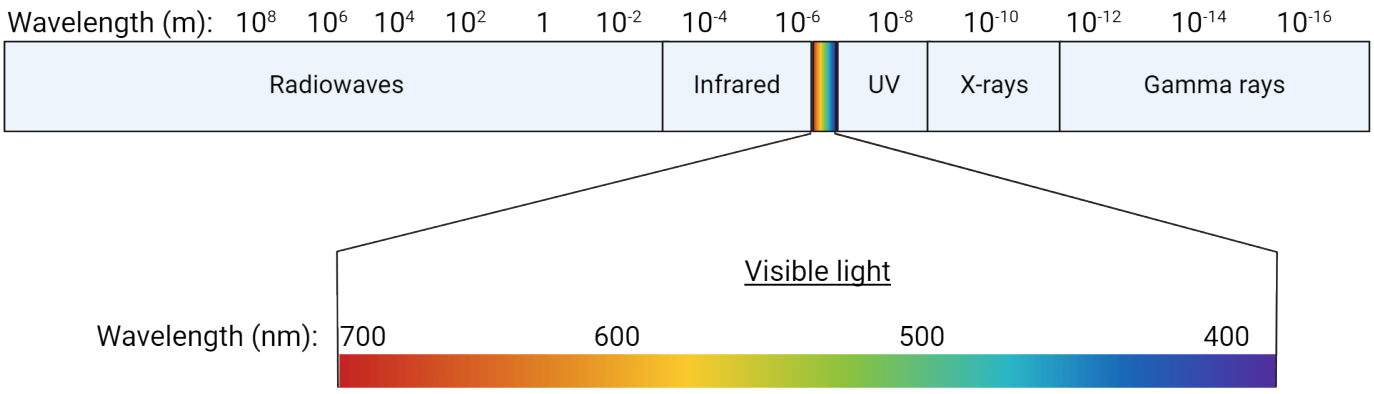


Figure 6.2 Light is a component of the electromagnetic spectrum

Sunlight includes wavelengths from infrared to ultraviolet (UV) that penetrate the atmosphere, but only the middle of that range penetrates water, which is where vertebrate vision first evolved. This is the visible spectrum that our eyes can detect. Different components (wavelengths) of the visible spectrum are absorbed or reflected by the surfaces of objects and our visual system interprets the reflected wavelengths as an object's color and shape. Shorter wavelengths within the visible spectrum we call blue while longer ones look red. White light combines wavelengths from the entire visible spectrum. Bright lights produce many photons per second, while dim lights emit few photons per second.

Anatomy of the Eye

The eye is the primary sensory structure that intercepts electromagnetic waves in the visible spectrum, eventually allowing us to perceive light. Figure 6.3 shows the major parts of the eye.

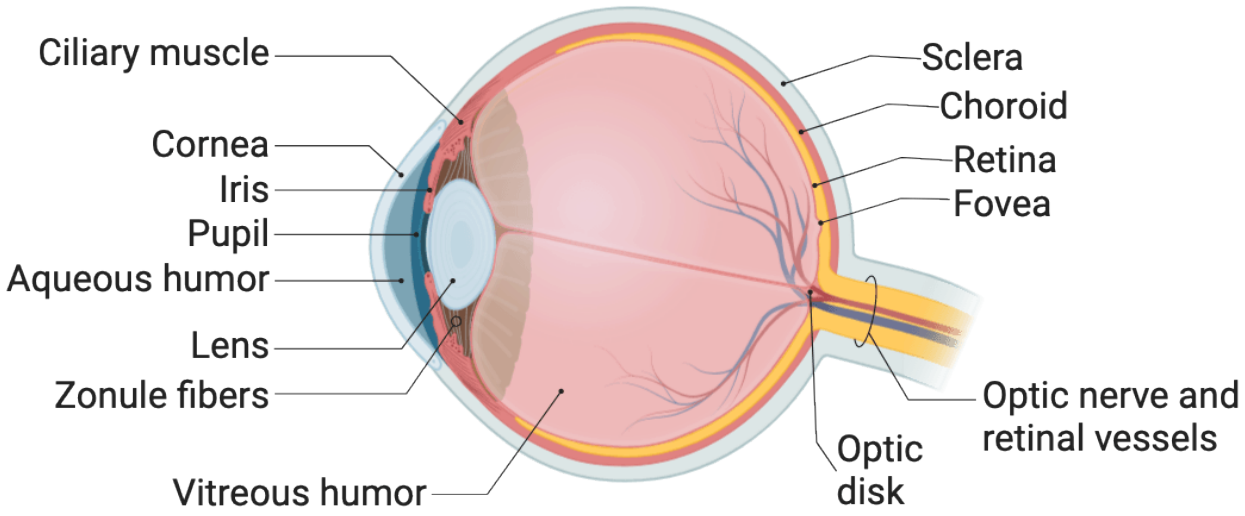


Figure 6.3 Anatomy of the human eye

At the front of the eye, the eye's optics are like the lens of a camera. The rays of light reflected from objects spread out in space. The cornea and crystalline lens intercept the arriving rays of light and bend them to form a focused image on the retina at the rear of the eye. Interestingly, because lenses invert images, the projection of the world on the retina is upside-down and left-right reversed. Figure 6.4 shows how light reflected from objects diverges in space but is refocused and flipped around for its projection on the retina.

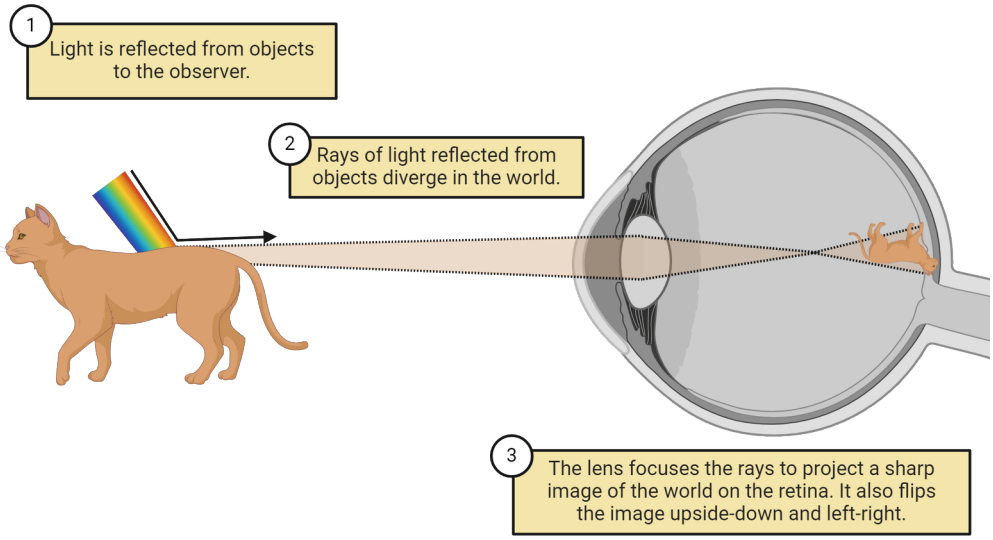


Figure 6.4 Objects reflect rays of light that reach the eye

The ciliary muscle and zonule fibers pull on the lens to flatten it and shift the focus to distant objects; when relaxed, the lens rounds up to focus on nearby objects. A clear liquid, the aqueous humor, fills the space between the cornea and the lens, and a clear, jelly-like vitreous humor fills the globe of the eye. Blood vessels spread over the inner surface of the eye next to the vitreous humor.

At the back of the eye, photoreceptors (rods and cones) embedded in the retina respond to the light hitting them, and several layers of nerve cells process the image, responding to borders between light and dark. The final retinal neurons, called retinal ganglion cells, send their axons out of the eye, bundling together to form the optic nerve, which transmits visual information to the brain. The optic disk is the region where the ganglion cell axons leave the eye and blood vessels enter. There are no photoreceptors in the optic disk, which creates a "blind spot" in our vision, although we are normally unaware of it. The fovea at the center of the retina is a region of tightly packed photoreceptors that provide our highest visual acuity. When we look at an

object, we turn our head and eyes to project the object's image onto the fovea, where we perceive details most clearly.

The remaining structural features include the choroid, a layer behind the retina with blood vessels that nourish the retina and a screening pigment to absorb stray light and prevent internal reflections. Behind that is the tough white of the eye, the sclera.

Correcting Optical Flaws: Myopia, Hyperopia and Presbyopia

Sharp vision requires the image projected on the retina to be in good focus, but for many people, the focus is in front of the retina (myopia) or behind the retina (hyperopia) (Figure 6.5). Corrective lenses restore sharp focus on the retina. Although in some cases people are born with an eye that is too short or too long for good focus, and thus need to wear corrective lenses from an early age, there is also some indication that constant close-up work can affect the continued development of the eye's shape and lead to myopia.

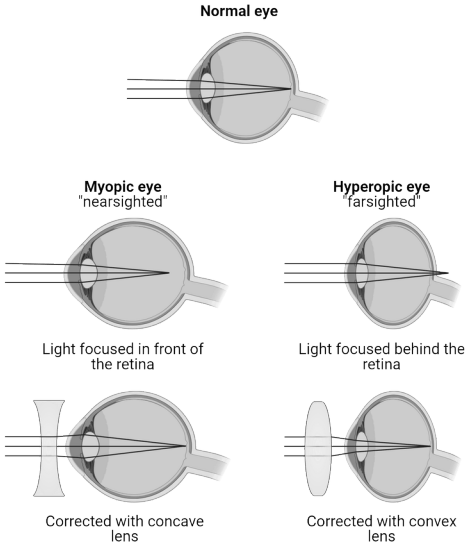


Figure 6.5 Correcting optical flaws

Even people who do not need corrective lenses when they are young eventually require reading glasses as they age. This condition is called "presbyopia," literally "old eyes," and it results from the lens of the eye becoming less flexible as people age. The lens normally becomes rounder to focus on nearby objects, but as people age, the lens becomes more rigid and is unable to change its shape to focus on nearby objects such as pages of text. At that point, corrective lenses are needed to supplement the lens's ability to focus.

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6.1.2: The Retina

Learning Objectives

By the end of this section, you should be able to

- Describe the layers of the retina and the five major cell types
- Describe the functional differences and anatomical distributions of the two kinds of photoreceptors: rods and cones
- Describe the steps in phototransduction
- Explain how cones transduce color information by using different visual pigments with maximal sensitivity to different wavelengths of light

In this section, we will explore the retina, and meet its five major types of neurons. We will see that vision begins with specialized sensory receptors, the rods and cones, which capture light energy and create a neural signal, a process called phototransduction. We will learn that rods function best in dim light while cones are responsible for our vision in bright light, our high-acuity detailed vision, and color vision. We will encounter the surprising steps in phototransduction between capture of a photon and closing of membrane channels that produce the subsequent change in the electrical potential of a rod or cone. Finally, we will discover that our color vision depends on three types of cones that differ in the absorption spectrum of the molecules that capture photons.

The Retina Is Composed of Several Neural Cell Types

The retina (Figure 6.6) arranges five types of nerve cells in distinct layers. The retinal processing chain for conscious vision begins with the receptors (rods and cones) that absorb light. The rods and cones make synapses with bipolar cells, which connect in turn to ganglion cells. Horizontal cells support visual processing with lateral synaptic connections to receptors and bipolar cells. Amacrine cells provide lateral connections in the synaptic layer between bipolar and ganglion cells. Ganglion cell axons spread across the inner retinal surface, gathering as a bundle to leave the eye as the optic nerve. The figure does not show the pigment epithelium above the receptors, or the extensive array of blood vessels that spread over the retina next to the ganglion cells.

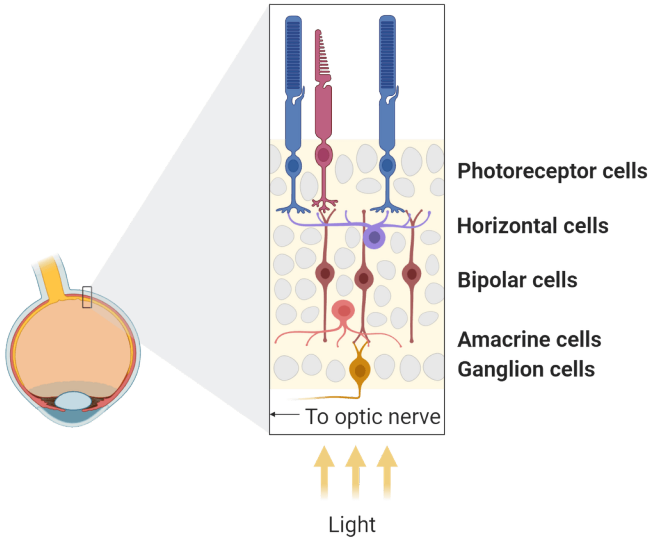


Figure 6.6 Retina structure

Embryologically, the retina is an outpocketing of the brain, and because it is more accessible than the developed brain and arranged in clear layers of defined neuronal cell types, it has been the subject of many experimental studies. This began in the 1890s when Cajal published images of retinas stained by the Golgi method, and identified many of the cell types. Since all vertebrate retinas have the same general structure, retinas with relatively large cells have been the most intensively studied, such as the retina of the mudpuppy, a large amphibian related to frogs and salamanders.

The human retina shown in Figure 6.7 has relatively small cells, but it is clear they are arranged in distinct layers. Although the eye is sometimes cited as evidence for “intelligent design,” the retina is actually a poor optical design because light must pass through several layers of neurons to reach the photoreceptors. These layers scatter the light and blur the image. It is never possible to know exactly why evolution produced a particular structural outcome, but two theories have suggested why the receptors are placed in an optically poor position, facing away from the light. One possibility is that because the receptors are metabolically very active, they require a dense blood supply, which they receive by facing the blood vessels in the choroid layer. A second possibility is that receptors evolved from ciliated cells that lined the embryonic neural tube (the “connecting cilium” is a group of microtubules arranged like a cilium that are still present in photoreceptors). As additional retinal layers are added during development, the receptors remain in an optically poor position. The fovea compensates for this “unintelligent” optical design by pushing aside the neural layers at our center of gaze, where tightly packed cones provide our sharpest visual acuity.

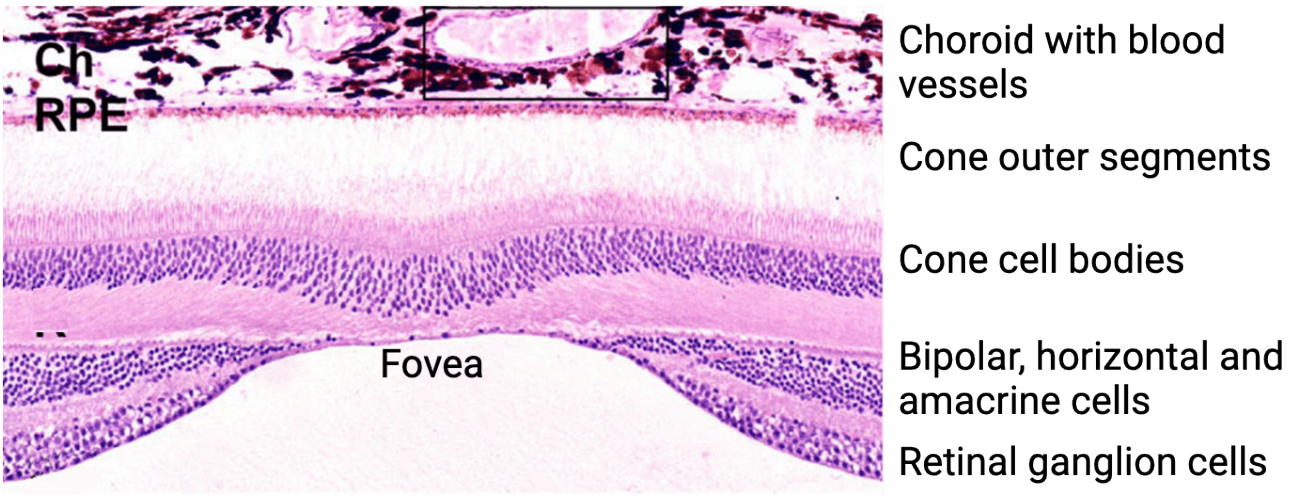


Figure 6.7 Fovea structure In the fovea, inner layers are pushed aside so light can hit photoreceptors directly.Image credit: Gregory S. Hageman, Karen Gaehrs, Lincoln V. Johnson and Don Anderson. AGE-RELATED MACULAR DEGENERATION (AMD) BY GREGORY S. HAGEMAN, KAREN GAEHRS, LINCOLN V. JOHNSON AND DON ANDERSON. In: Webvision, http://webvision.med.utah.edu/ CC BY-NC 4.0

Rods and Cones Capture Photons of Light

In an earlier section, we introduced photoreceptors, the specialized neurons that respond to light. Photoreceptors (Figure 6.8) have an outer segment of discs, or infolded membrane in which millions of visual pigment molecules are embedded. These pigment molecules give photoreceptors the ability to capture light and will be discussed more below. Photoreceptors also have an inner segment with mitochondria, the nucleus, and other structures typical of all cells. The synaptic terminal is the photoreceptor’s output region, where it connects to bipolar and horizontal cells.

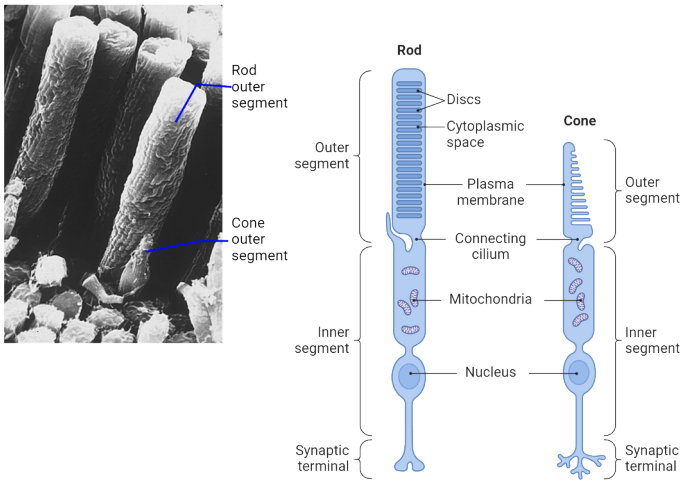


Figure 6.8 Morphology of photoreceptors "Image credit: Deric Bownds, U Wisconsin, personal communication to R. Olivo.

Our photoreceptors come in two types, each with a unique function in vision: cones and rods. The human eye has about 6 million cones, concentrated in the fovea and central retina but also distributed sparsely in the retinal periphery. Cones are responsible for high-acuity color vision in daylight. The human retina also has about 120 million rods, which are absent from the fovea but distributed across the rest of the retina. Rods serve low-acuity vision in dim light (such as moonlight), and under optimal dark-adapted conditions a rod can respond to as little as a single photon of light. In daylight and typical artificial light, the rods no longer respond because the bright light saturates their response, and only the cones signal differences in brightness.

Rods and Cones Depolarize in the Dark and Hyperpolarize in the Light

When neurobiologists first succeeded in recording from rods and cones with intracellular electrodes, they were puzzled by what they found. Most sensory receptors, including invertebrate photoreceptors, depolarize in response to a stimulus, but vertebrate photoreceptors hyperpolarize (become more negative) in response to light. Figure 6.9 shows an example of the kind of data one of these experiments generated, where a photoreceptor's intracellular electrical response was recorded while light was flashed on it. Dim flashes elicited a small hyperpolarization, and bright flashes evoked a large hyperpolarization. The receptors in the dark also had a surprisingly depolarized resting potential, about -40 mV instead of the -60 mV more typical of nerve cells. Everything seemed backward!

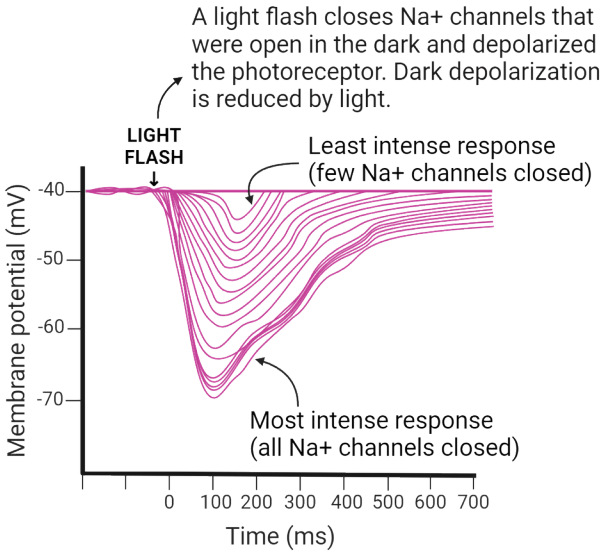


Figure 6.9 Rod and cone membrane potential changes

Later work unraveled the mystery. In the dark, channels in the outer segment are open and admit positive Na+ ions, creating a depolarized resting potential. Capturing photons of light leads to closing some of these sodium channels, which diminishes the resting depolarization, an apparent hyperpolarization. With brighter lights and more photons captured, more of the channels close, leading to greater degrees of hyperpolarization. In a way, we can think of the response to light as allowing the photoreceptors to return to their “real” resting potential (the potential when the sodium channels are closed, about -60 mV like other neurons). Light interrupts the depolarization that occurs in the dark. Like all other neurons, photoreceptors release their transmitter (glutamate) when they are depolarized, so photoreceptors continually release transmitter in the dark, and light interrupts transmitter release. In the next section, we will discuss how photoreceptors keep Na+ channels open to become depolarized in the dark and how light exposure cancels that.

Phototransduction

Eventually, researchers worked out how the capture of photons by visual pigment molecules in the disk membranes of photoreceptors led to closing sodium ion channels in the cell membrane. We call this process of turning photons into an electrical signal "phototransduction" (Figure 6.10). Here, we will describe this process in rods. Cones use similar processes but differ in the wavelengths of light that they absorb, which will be discussed in the next section.

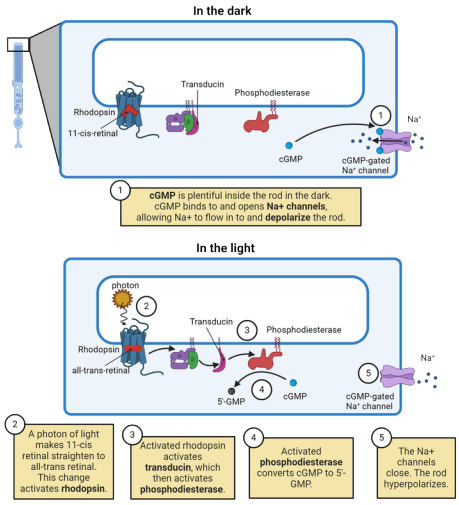


Figure 6.10 Phototransduction

In rods, rhodopsin molecules are the visual pigment packed into the disk membranes. Rhodopsin molecules consist of two components: opsin, a large protein, and 11-cis retinal, a small subunit that is derived from Vitamin A. In the dark, the 11-cis retinal has a bent side chain. Capturing a single photon provides the energy to straighten the side chain to its straight, “all-trans” shape. This in turn activates the opsin protein, which leads to a series of steps that reduce the level of cGMP, a messenger molecule in the cytoplasm. While the intermediate steps may seem detailed, the important point is that light leads to closure of sodium channels that are open in the dark.

As Figure 6.10 shows, cGMP is normally abundant in the dark and attaches to Na+ channels in the cell membrane, keeping them open. In the dark, Na+ ions enter the cell and create a depolarized resting potential. The action of light reduces the level of cGMP, which leads to closure of Na+ channels and less depolarization (which appears as hyperpolarization). The more photons that each photoreceptor catches, the lower its level of cGMP and the more Na+ channels that close. In bright light, when most or all of the Na+ channels are closed, the cell is essentially at its “real” resting potential: strongly hyperpolarized from its resting state in the dark.

Color Vision in the Retina: Three Kinds of Cones

Rhodopsin, the visual pigment that catches photons and begins the process of phototransduction, is found in rods (“rod opsin”), but our retinas have three other visual pigments found in three types of cones. These pigments differ slightly in their opsin protein but work in similar ways. The different opsins give the pigments different absorption spectra, making them effective in catching

photons at different peak wavelengths. Figure 6.11 shows the peak absorbance for the 4 major visual pigments found in human photoreceptors. For example, rhodopsin in rods has its absorption peak at 498 nm, in the middle of the spectrum, while the three cone pigments have peaks in the short wavelengths (S or "blue cones," peak at 420 nm), middle wavelengths (M or green cones, 534 nm), or long wavelengths (L or red cones, 564 nm). The middle and long wavelength pigments differ only slightly because they diverged only recently in evolution, giving humans and old-world monkeys three cone types. Most mammals such as dogs, cats and new-world monkeys have only two types of cones, one for short wavelengths (blue) and one for long wavelengths (yellow). Thus, the color vision of most mammals is different from ours, and your pet dog or cat does not see colors the same way you do.

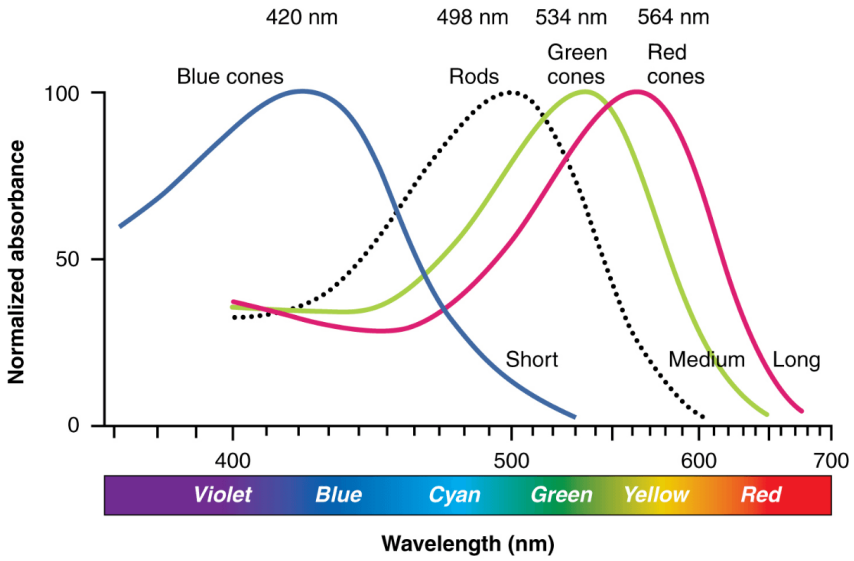


Figure 6.11 Absorption spectra of the four visual pigments in the human eye Three visual pigments in three kinds of cones underpin our trivariant color vision. Image credit: Image by OpenStax - Anatomy & Physiology, https://openstax.org/books/anatomy-a...ory-perception, CC BY 4.0

Although each absorption spectrum indicates that a single pigment can catch photons in a range of wavelengths, one pigment cannot distinguish between a small number of photons at the pigment's best wavelength and many photons at a wavelength that the pigment does not absorb well. Both stimuli could result in the same total number of photons being caught, and any photon that is caught initiates phototransduction in the same way. (Figure 6.12)

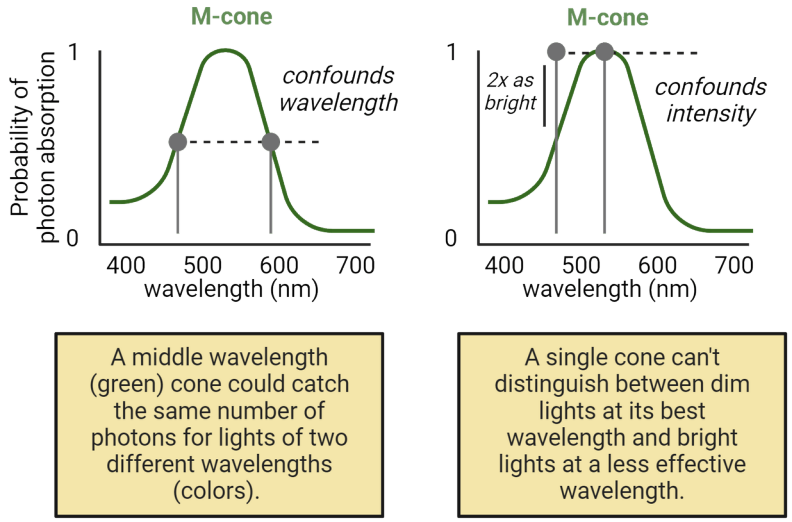


Figure 6.12 One visual pigment cannot discriminate colors Image credit: Image redrawn from: Patterson SS, Neitz M and Neitz J (2019) Reconciling Color Vision Models With Midget Ganglion Cell Receptive Fields. Front. Neurosci. 13:865. doi: 10.3389/fnins.2019.00865. CC BY 4.0

To distinguish light of two wavelengths, it is necessary to compare the responses of nearby cones with different pigments. For example, if the blue-absorbing cones in a patch of the retina catch many photons but nearby green or red cones catch only a few, then the light is at the blue end of the spectrum.

Since we have three types of cones, our color vision has three primary colors. Together, they can generate the appearance of any possible color. Looking at a TV or computer screen with a magnifying glass will reveal blue, green and red pixels (Figure 6.13). By controlling the brightness of each pixel, the screen simulates any real-world color. Red and green pixels together give us the sensation of yellow, and all three types together appear white. It's as if each pixel type is activating one of the three cone types. In combination, the RGB pixels evoke responses in the cones that are equivalent to their response to any real-world color.

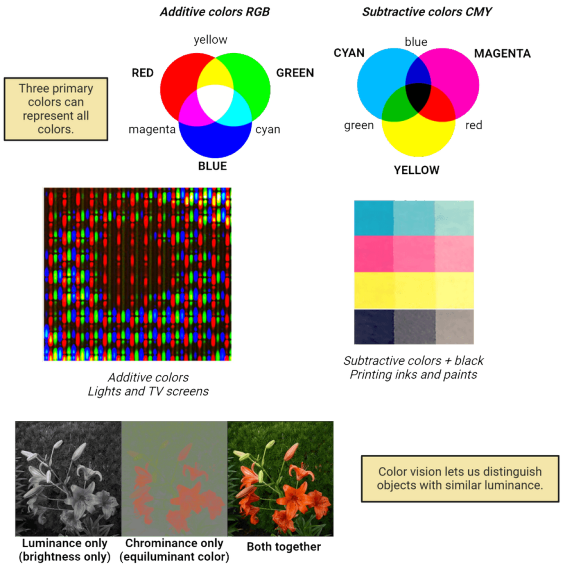


Figure 6.13 Primary colors image credit: "Luminance-hrominance image: By Algr, CC BY-SA 3.0, https://commons.wikimedia.org/w/inde...curid=31044071; RGB color model: By pd4u, CC0, https://commons.wikimedia.org/w/inde...curid=65835679; CMY color model: By Jipre, CC0, https://commons.wikimedia.org/w/inde...curid=14670042"

For lights and TV screens, where photons are added together to make the final mixture, red, green and blue are the primary colors. But surfaces covered in paints and inks subtract photons from the illuminating light, reflecting the non-absorbed photons. For example, a yellow paint patch in white light absorbs blue photons and reflects red and green, which appear to us as yellow. The three primary colors for subtractive surface colors are cyan, magenta and yellow (CMY). As explained in our example, yellow absorbs blue, reflecting green and red, while magenta absorbs green and reflects red and blue, and cyan absorbs red and reflects blue and green. For printing inks (Figure 6.13), the three primary inks together should appear black, but in practice the mixture often looks muddy, and a fourth ink, a true black, is usually added. Test strips of the four primary printing inks in different densities can often be found on printed materials, including the hidden flaps of cookie packages.

As shown in the bottom of Figure 6.13, color allows us to distinguish objects that have equiluminant surfaces (surfaces that would appear equally bright in a grayscale image) but reflect different wavelengths. The relatively recent evolution of separate red and green cones in primates (including humans) from a single yellow-absorbing cone further improves discrimination. Detecting red apples in the midst of green leaves would be difficult without our trichromatic color vision.

Color Blindness

Some people carry a genetic variation that gives them only two cone types instead of three, or they produce an anomalous version of one of the cone pigments. As a result, they make color matches that differ from those made by typical trichromats, who have three types of cones. They are not actually "blind" to a color, but rather can't distinguish some colors that trichromats see as different. Color blindness affecting the red or green genes is the most common, occurring in about 8% of males and only 0.4% of females (Neitz & Neitz, 2011). The red and green genes are both on the X chromosome (further evidence that they were duplicated recently in evolution). Since XY biological males have only one X chromosome, they cannot compensate for a defective gene, unlike XX females who have two different X chromosomes, one from each parent. Blue blindness is very rare, since the blue gene is on a chromosome for which everyone has two copies.

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6.1.3: Visual Processing Begins in Bipolar, Horizontal, Amacrine and Ganglion Cells

Learning Objectives

By the end of this section, you should be able to

- Describe the direct pathway for transmitting information from photoreceptors to the brain
- Define the difference between on-center and off-center bipolar cells and how they help detect edges
- Explain how horizontal cells facilitate the center-surround nature of bipolar cell receptive fields
- Describe the difference in how on-center and off-center retinal ganglion cells respond to light in their receptive fields
- Define the major types of retinal ganglion cells and their contribution to visual perception
- Describe how retinal ganglion cells contribute to detecting color edges through the use of opponent color responses

In many ways, the millions of rods and cones spread across the retina are like the pixels of a digital camera. Each photoreceptor reports on the number of photons it is catching from the image projected on the retina. It is tempting to imagine that this is the information that the optic nerve transmits to the brain for further processing, but that is not what happens. The retina's layers of nerve cells between the photoreceptors and the ganglion cells transform the information from a report on color and brightness to a report of color and brightness borders in the region served by each ganglion cell. In this section, we will learn about how the cells of the retina provide the first step in visual processing, detecting the edges of objects.

Bipolar Cells

Take a moment to remind yourself of the cellular architecture in the retina, from Figure 6.6 in the previous section. From the photoreceptors, the next synaptic partners in the pathway out of the eye are bipolar cells. This is where detecting borders begins. Bipolar cells gather information from the photoreceptors that synapse directly onto them and also from additional photoreceptors in a surrounding region, creating a circular region with a center and a surround that together are the bipolar cell's receptive field (see Feature Box on the concept of receptive fields). This arrangement is diagrammed on the left side of Figure 6.14. As mentioned, photoreceptors in the center of the receptive field synapse directly onto the underlying bipolar cell, while receptors that contribute to the surround connect to horizontal cells that modulate the synapses from central photoreceptors, thereby canceling the bipolar cell's response to the center. (Photoreceptors make multiple synapses, so one receptor can contribute to the center of one bipolar cell's receptive field but also help form the surround for other bipolar cells.) Contrast between the light falling on the center and the surround is required for a bipolar cell to respond. Uniform illumination is not effective.

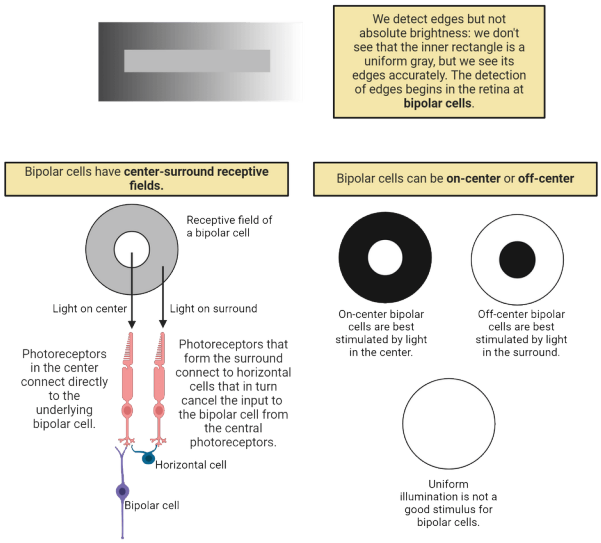


Figure 6.14 Bipolar cell types

We are actually not very good at perceiving brightness. In the gray rectangle in the top of Figure 6.14, we don't see that the inner rectangle is a uniform gray, but we see its edges accurately. Similarly, we make poor judgments of absolute brightness (if you are now in a room lit by artificial light, is the room brighter than the light outdoors on a cloudy day? it's hard to know the answer.). On the other hand, we are very good at detecting and remembering edges. A cartoon drawn with just a few lines can easily represent a face or an object for us.

The center-surround receptive fields of bipolar cells provide the first processing step that ignores absolute brightness in favor of detecting contrasting borders between light and dark. This arrangement is sensitive to contrast because bipolar cells respond in opposite ways to input from photoreceptors in the center of their receptive field compared to photoreceptors in the receptive field surround. To better understand how this works, we need to consider the two types of bipolar cells, on-center and off-center bipolar cells.

About half of bipolar cells are on-center, where the bipolar cell depolarizes to light covering the center of the receptive field if a darker region surrounds the center, or off-center, which is the reverse. In an on-center cell, the bipolar cell is directly affected by responses of the photoreceptors that synapse on it directly. The photoreceptors in the surround do not synapse directly on the bipolar cell. Instead, they synapse on horizontal cells, a type of interneuron that serves as a bridge between photoreceptors and bipolar cells. Activating horizontal cells cancels the bipolar cell's response to the center stimulus.

Although the complete neural circuit is more than we will explore here, it still may surprise you that light in the center of the receptive field depolarizes on-center bipolar cells but has the opposite effect on off-center bipolar cells. How can there be two types of bipolar cells, both of which receive direct synapses from photoreceptors in the center of their receptive fields? The cells differ because they have different molecular receptors for the neurotransmitter glutamate that is released by rods and cones. Recall that neurons release transmitter only when they are depolarized, and also that rods and cones are depolarized in the dark. This means that in the dark, the depolarized rods and cones release glutamate continually onto the bipolar cells they connect to. For an off-center bipolar cell, a dark patch of a visual scene falling in the center of the receptive field will depolarize the receptors and lead to the release of glutamate. The receptor for glutamate in off-center bipolar cells depolarizes the cell, so if the photoreceptors in the center are in the dark, the off-center bipolar cell receives transmitter and is depolarized: an off response.

On-center bipolar cells have a different receptor for glutamate, one that leads to activation of a second messenger that closes depolarizing channels. Light on the center of the receptive field interrupts the release of transmitter from photoreceptors, which stops activation of the messenger that closes depolarizing channels in the bipolar cells. Those channels then open, and the bipolar cell depolarizes, producing an on-response. Thus, because they have different receptors for the neurotransmitter glutamate, on-center and off-center bipolar cells have different responses to light in the center of their receptive field.

While it's helpful to understand the mechanisms for on and off responses, let's return to the important task that bipolar cells accomplish: responding to contrast between light and dark regions of the image while ignoring uniform illumination. If we imagine the image background as a medium gray, the two types of bipolar cells would depolarize in response to either dark spots or bright spots covering the center of their receptive fields. Although uniform illumination is not a good stimulus, a border between light

and dark falling on the receptive field works well if it puts light or dark on the center and the opposite illumination on at least part of the surround. The bipolar cells' response to contrast is conveyed to the next stage of retinal processing, the ganglion cells. Since the distances are very short, action potentials are not necessary to transmit signals, and bipolar cells are "non-spiking," making only graded changes in potential. The bipolar cells release varying amounts of their transmitter, which is also glutamate, depending on how depolarized they are.

The Concept of Receptive Fields

We referred above to the center-surround receptive field of a bipolar cell, but the concept of receptive fields actually began more than a century ago to describe areas of the skin that activate individual touch receptors. A single touch receptor axon typically branches to innervate a small patch of skin, and touching anywhere in that patch of skin will generate action potentials in that sensory axon. The patch of skin was called the sensory axon's "receptive field." Later, the concept was expanded to include sensory systems (like vision) where some regions of the receptive field might excite the neuron while other regions inhibit responses. The concept was further expanded to apply to neurons in the brain linked by a synaptic network to receptors that might be many synapses away. In the visual system, as we will see in later sections, a cortical neuron's receptive field describes the pattern on the retina (or a screen in front of the animal) that optimally excites or inhibits the neuron, even if the neuron is deep in the brain and far removed from the initial sensory receptors that contribute to its response. A neuron's receptive field is a succinct description or diagram of the pattern of stimuli that determine the neuron's response.

Retinal Ganglion Cells

Like the bipolar cells that drive them, retinal ganglion cells have center-surround receptive fields and are either on-center or off-center, characteristics they inherit from the bipolar cells that excite them. On-center ganglion cells are driven by on-center bipolar cells, and off-center bipolar cells drive off-center ganglion cells. Because the ganglion cell axons transmit signals a significant distance to the brain, retinal ganglion cells do make action potentials, and they are the first cells in the retinal processing chain that do so. In Figure 6.15, an on-center ganglion cell on the left responds with a burst of action potentials to a bright spot on its receptive field center, and also to a dark ring on the surround. Both patterns represent contrast between the center and the surround. The ganglion cell also responds to reverse patterns, but they inhibit the cell's spontaneous firing instead of exciting firing. A dark spot on the center or a bright ring on the surround inhibits an on-center ganglion cell. Since uniform light does not activate bipolar cells, it also does not activate ganglion cells.

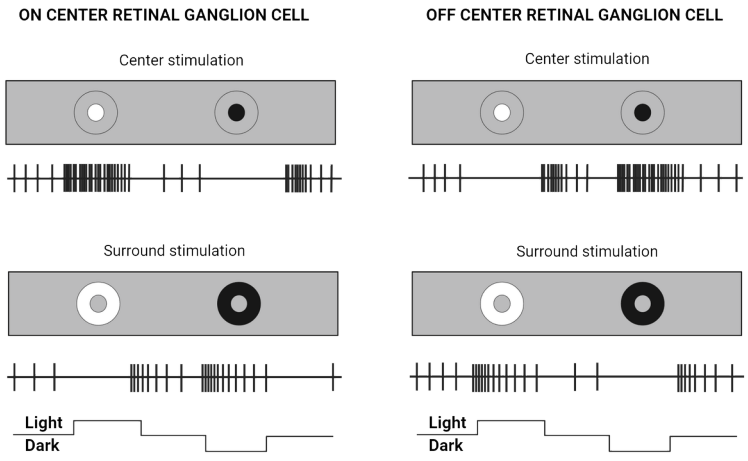


Figure 6.15 Retinal ganglion cell receptive fields

The off-center ganglion cell on the right in Figure 6.15 has the opposite responses. A dark spot on the center or a bright surround excites the cell, while the opposite patterns inhibit it. In all cases, a boundary between light and dark is necessary to generate a response in ganglion cells. It is that information about borders and edges, not brightness, that is carried to the brain in the optic

nerve.

The optic nerve projects to several different destinations in the brain because it carries axons from several types of ganglion cells. The on- and off-center ganglion cells that are responsible for conscious visual perception provide more than 80% of the axons in the optic nerve. Those important ganglion cells can be further divided into two groups, relatively few large ganglion cells with large receptive fields and large axons that conduct signals rapidly (the “magnocellular” cells), and very abundant smaller cells with small receptive fields and medium diameter axons that conduct more slowly (the “parvocellular” ganglion cells). Magnocellular and parvocellular axons connect to neurons in different layers of the lateral geniculate nucleus of the thalamus, which we will discuss in 6.4 The Thalamus and Primary Visual Cortex.

The difference in receptive field sizes of magnocellular and parvocellular ganglion cells gives them different roles in conscious visual perception. The abundant parvocellular cells with small receptive fields provide detailed, high-acuity vision, including details of the image that falls on the fovea. If you look straight ahead at a scene, the center will appear sharp, but if without moving your eyes you pay attention to objects near the edge of your visual field, you will discover that peripheral vision is quite blurry. If you wish to inspect peripheral details, you move your eyes to project those details on the fovea, where vision is sharp. Our brains create the illusion that the entire scene is sharply focused, but in fact, peripheral regions served by ganglion cells with large receptive fields are not sharp at all. However, magnocellular cells are very sensitive to motion. If you wiggle your fingers near the edge of your peripheral vision, you will easily detect their motion even though they are blurry. The large diameter axons and rapid conduction velocity of magnocellular ganglion cells helps convey information about motion quickly to the brain.

Two other types of retinal ganglion cells convey responses to light but do not contribute to conscious visual perception. One evolutionarily older class of ganglion cells, less than 10% of all ganglion cells, has wide receptive fields and narrow axons, and projects to the superior colliculus. These ganglion cells contribute to generating eye movements as we watch a scene. The highest visual area in the brains of fish and amphibians, the optic tectum, is the precursor of the superior colliculus in mammals, but it has been superseded by the evolutionarily new visual pathway for visual perception that leads to the thalamus and the visual cortex. Another category of specialized ganglion cells, about 1% of the total, are the intrinsically photosensitive ganglion cells (ipRGCs). These cells contain the pigment melanopsin, which makes them directly responsive to light. They do not contribute to visual perception (and are sometimes called “non image-forming” cells, NIFs), but most of them project to the suprachiasmatic nucleus and help control circadian rhythms. A few ipRGCs project instead to the brain nucleus that controls the pupillary reflex, which constricts the iris in response to bright light.

The retina is carpeted in these multiple types of ganglion cells, and the receptive fields overlap within and between types. Any visual pattern falling on the retina will activate many ganglion cells, with the specific responses depending on the portions of the image that fall within each ganglion cell’s receptive field. There are between one and two million retinal ganglion cells in each human retina. Receptive field centers can be as small as a single cone in the fovea, where the parvocellular ganglion cells are dense, or much larger in the periphery where the ganglion cells are spread out and have large receptive fields.

Color Vision in the Retina: Opponent Color RGCs

Many experiments to record electrical activity from retinal cells were first performed in fish and amphibians because their retinal cells are much larger than in mammals, making them easier to penetrate with sharp microelectrodes. The goldfish retina was also the site of the first measurements of absorption spectra for individual cones, revealing three types as in our retinas. Meanwhile, research on color vision in people mostly involved a controversy among psychologists about whether three primary colors explained color vision, or whether vision involved pairs of complementary colors. This controversy continued for many years because both sides turned out to be right. At the receptor level, three cone types account for the three primary colors, but retinal ganglion cells receive input from cones representing opposing pairs of color and thereby respond to pairs of complementary colors.

Early recordings from retinal ganglion cells in the goldfish retina showed excitation to one color but inhibition to its complementary color, establishing the concept of opponent colors. Soon after, recordings were made from lateral geniculate neurons in monkeys, which have receptive fields like ganglion cells, and this settled the debate about color vision in humans. Figure 6.16 shows responses of a goldfish retinal ganglion cell to blue-green light, which excited bursts of action potentials, and to red light, which inhibited the cell’s spontaneous firing. Other ganglion cells were the reverse, excited by red and inhibited by green. Later, other ganglion cells were found that had opponent responses to blue and yellow. This corresponded to observations about human vision, where we can’t imagine a reddish-green or a yellowish-blue because those pairs are opponent colors.

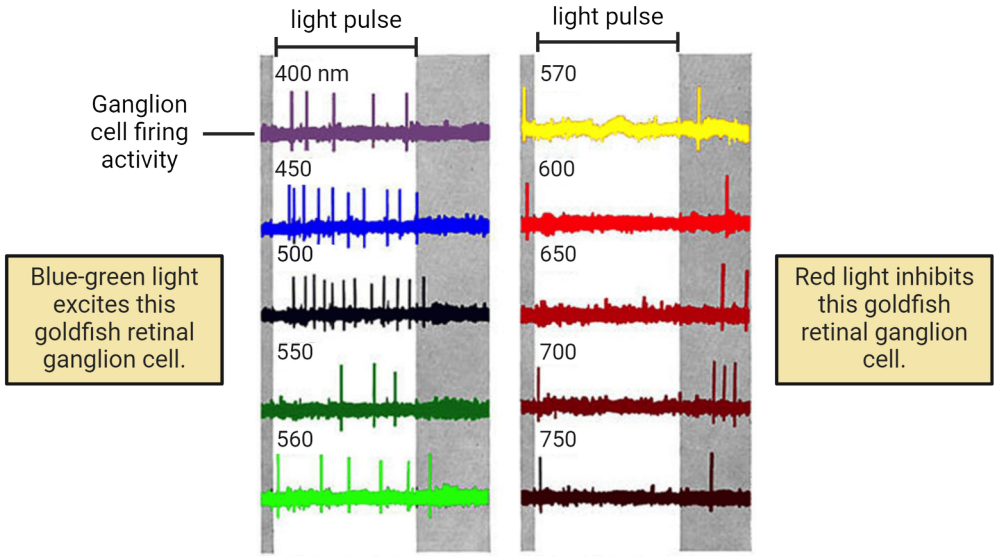


Figure 6.16 Opponent color retinal ganglion cells firing in goldfish retina Image credit: Reproduced with author permission: Kolb, Helga & Fernandez, Eduardo & Nelson, Ralph. (2007). Webvision: The Neural Organization of Retina and Visual System (From Webvision, http://webvision.med.utah.edu/). Section: Anatomy and Physiology of the Retina, Ch: Visual Responses of Ganglion cells. Ralph Nelson. Fig 17

Across many vertebrate retinas, including fish, color vision at the ganglion cell level was found to fall into the three categories shown in Figure 6.17.

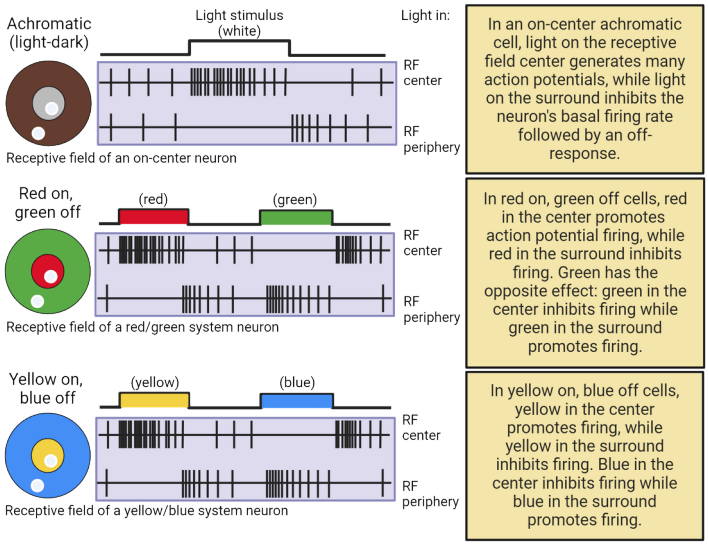


Figure 6.17 Opponent color retinal ganglion cells receptive fields

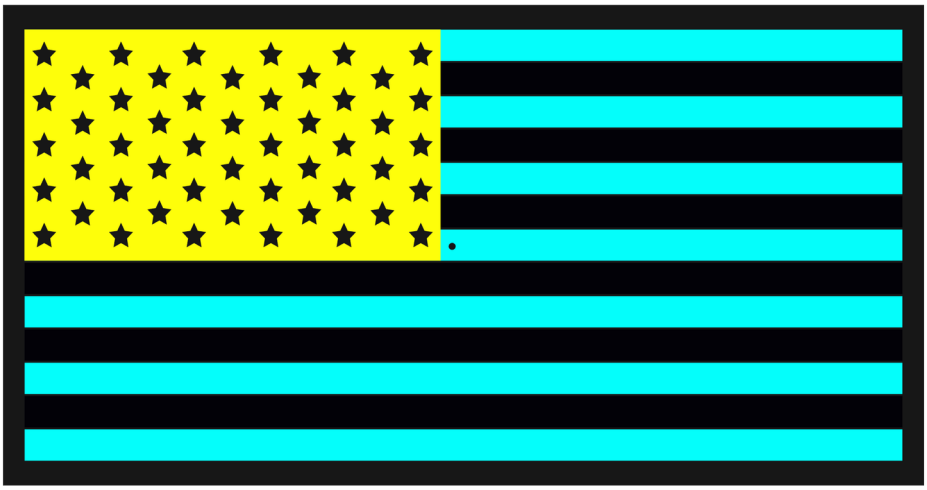
One class of ganglion cells pools the responses of different cone types, responding to light or dark on their receptive fields but not to differences in color. These are the achromatic ganglion cells where a spot of white light in the center of an on-center receptive field excites the cell, while a white spot in the surround inhibits the cell and produces a brief burst of activity when the light goes off, an “off response.” The example in Figure 6.17 is an on-center, off-surround ganglion cell like the neurons we discussed in the previous section.

Another class, red/green ganglion cells, are excited by a red spot in the receptive field center, while a green spot in the center inhibits the cell and produces an off response. The responses in the surround are reversed: red inhibits and green excites. These are opponent-color cells, and the strongest response for this example would be to a red stimulus in the center surrounded by a green ring. Other red/green cells would have the reverse organization, excited by a green spot in the receptive field center against a red surround. These cells would respond well to a border between red and green areas.

A third class, blue/yellow ganglion cells, is organized in a similar way, but now the best stimulus for the example shown would be a yellow spot against a blue background. (Recall that yellow excites both red and green cones.) The reverse type also exists, responding best to a blue spot against a yellow background. These are all examples of “double-opponent” cells, where the center and surround have opposite responses to color spots. In the human retina, the ganglion cells are red/green or blue/yellow, but the receptive fields are usually not divided into a center and surround. Instead they are “single opponent” cells, still excited by one color and inhibited by its complementary color, but across the entire receptive field.

The number of cones contributing to the response of a single retinal ganglion cell varies with the cell’s location in the retina. In the fovea, where we have the highest visual acuity, a ganglion cell’s receptive field center may be as small as a single red or green cone. In the retinal periphery, ganglion cell receptive fields are larger, driven by clusters of cones, and visual acuity is much lower.

You can experience opponent color organization in your own visual system by staring at Figure 6.18 and then looking at a blank page or a white wall. An afterimage will appear with colors that are the complements of the colors in Figure 6.18. Black will appear white, cyan will appear red, and yellow areas will be blue. This is an indication of opponent color organization, which begins at the ganglion cell level. Afterimages occur when prolonged exposure to one color causes an opponent-color ganglion cell to adapt, becoming less sensitive to the exposed color while retaining full sensitivity to the complementary color. Flooding the receptive field with white light would ordinarily activate both opponent colors, but because one color system has adapted, the balance is shifted and the ganglion cell responds as if it is being exposed to the complementary color—which is what we see in the afterimage.



Stare at the dot in the center for 30 seconds, then stare at a blank wall.

Figure 6.18 Visual after-effects of opponent color retinal ganglion cells

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6.1.4: The Thalamus and Primary Visual Cortex

Learning Objectives

By the end of this section, you should be able to

- Describe how visual pathways divide visual information from left and right visual fields for projection to right and left cortical areas, respectively
- Define the optimal stimuli for simple and complex cortical cells
- Describe how LGN receptive fields combine within the receptive field of simple cortical cells to drive simple cell activity
- Describe how simple cortical cell receptive fields combine within the receptive field of complex cortical cells to drive complex cell activity
- Describe the retinotopic map of the primary visual cortex
- Describe the functional architecture of the primary visual cortex, including ocular dominance columns, cytochrome oxidase blobs, and orientation pinwheels
- List the different types of stimuli that can excite primary visual cortical cells, including their combination with color

From the retina, the main visual pathway for conscious perception goes to the lateral geniculate nucleus of the thalamus (LGN), after which LGN neurons project to the primary visual cortex. Visual information then goes to a series of extrastriate visual areas, the inferotemporal cortex, and a number of other brain regions involved in identifying, localizing, and interacting with visually perceived objects. In this section, we will sample several of these areas to see how neurons code visual information, eventually reaching neurons that are selectively responsive to objects and faces located anywhere in the visual field.

Visual Fields and the Visual Pathway

Figure 6.19 shows the first stages of the visual pathway, going from the eye through the thalamus to the primary visual cortex.

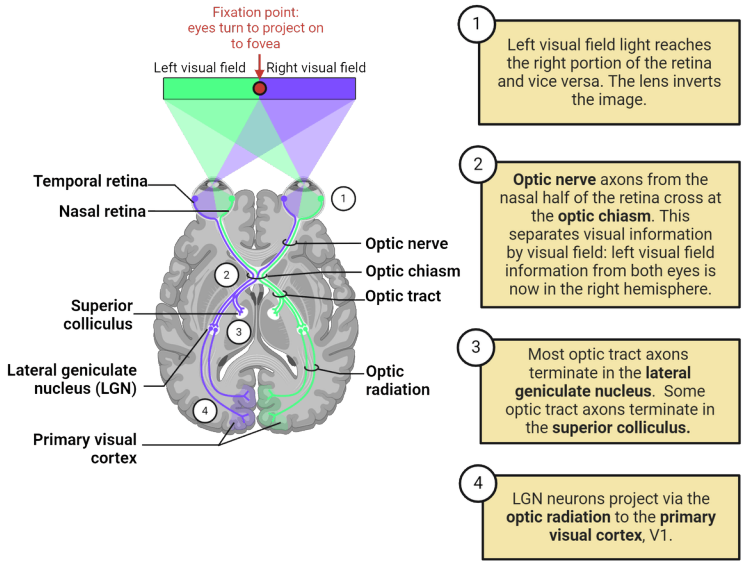


Figure 6.19 Visual pathways

Each eye is turned to project the fixation point between the left and right visual fields onto the fovea in the center of the retina. Because lenses invert images, the left visual field (shown in green) is imaged on the right side of each retina, and the right visual field (purple/blue) is imaged on the left side. Ganglion cell axons from both sides of the retina bundle together to form the optic nerve, which leads to the optic chiasm in the midline. There, the nasal (inner) half of the axons from each retina cross over, while the temporal (outer) half remains on its side of origin. Consequently, the right side of the brain (green) receives axons from the right half of each retina, and the left brain (purple) receives axons from the left retinas. Because the left retina views the right

visual field, each hemisphere of the brain receives information about the opposite side of the visual world from both eyes. Lesions in the visual pathway on one side of the brain lead to deficits in seeing the opposite side of the visual world.

Lateral Geniculate Nucleus

The main cerebral target for the retinal ganglion cell axons is the lateral geniculate nucleus (LGN), a structure in the thalamus on the path to the primary visual cortex. The LGN is a six-layered structure. The left side of Figure 6.20 shows the LGN in a post-mortem monkey brain. The dark purple dots are cell bodies and show how distinct these six layers are. Each of these layers is unique in the input it receives. Two layers are composed of large neurons, magnocellular layers 1 and 2, and four layers are composed of smaller neurons, the parvocellular layers 3-6. Magnocellular retinal ganglion cells, which convey low resolution information and respond well to motion, send their axons to the magnocellular LGN layers. Parvocellular ganglion cells with small receptive fields, red/green opponent color responses, and high resolution connect to the parvocellular layers. There are also small intermediate koniocellular LGN layers, which were overlooked in early studies. They are the target for axons from blue/yellow ganglion cells. The neurons in each LGN layer are arranged in a two-dimensional array that matches the ganglion cell locations in the retina. This preserves a map of receptive field positions, a retinotopic map.

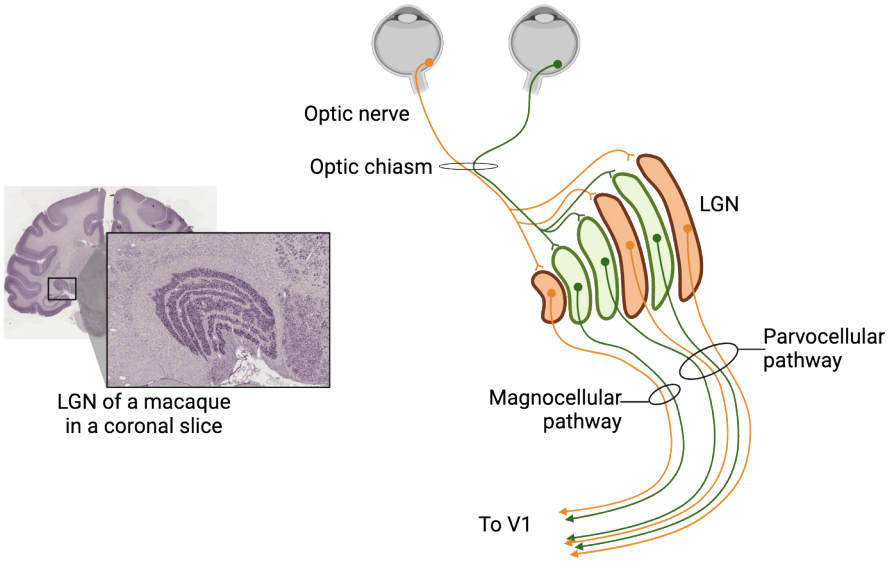


Figure 6.20 Layers of neurons in the lateral geniculate nucleus Information from the two retinas reaches separate layers of the LGN. Image credit: Primate LGN images from BrainMaps: An Interactive Multiresolution Brain Atlas; http://brainmaps.org [retrieved on 11-10-2021]

Although ganglion cells from the right half of each eye project to the LGN on the right side of the brain, the ganglion cells from each eye connect to different layers of the LGN. Thus, information from the two eyes remains separate in the LGN, and neurons driven by both eyes will not appear in the visual pathway until the next stage, the primary visual cortex.

V1 Simple, Complex and “Hypercomplex” Neurons

LGN neurons that receive input from retinal ganglion cells send their axons to the primary visual cortex (V1), a large visual area in the posterior occipital lobe and midline. This area is also called “striate” cortex because cross sections appear striated, or striped, and it is also sometimes referred to as “area 17” in reference to labels for different cortical areas based on their appearance. V1 is the first stage of visual processing in the cortex. In a collaboration that began in 1958, David Hubel and Torsten Wiesel conducted an extensive research program to discover how V1 cells respond to visual stimuli (more about them and their experiments can be found later in this section). By recording from individual cortical neurons in experiments that often lasted for more than 24 hours, they showed that the cortex could be understood at the level of individual neurons, and that the neurons had receptive fields responsive to edges. This continued earlier stages in the perception of objects and scenes. Hubel and Wiesel’s experimental method was to advance an insulated needle electrode into the visual cortex to pick up extracellular action potentials from neurons along the electrode’s path (see Methods: Electrophysiology). They projected visual stimuli on a screen facing the anesthetized animal (initially cats and later monkeys), while they searched for the most effective visual stimulus. By listening to the neuron’s action potentials as they altered the projected stimulus, they mapped the neuron’s receptive field: the visual pattern that optimally excited the cell. Once they characterized a neuron’s receptive field, they advanced the electrode until it encountered another

neuron, which they then mapped. In this way, they gathered data on the receptive fields of hundreds of V1 neurons in each experiment.

In addition to mapping receptive fields, they also kept data on the location of each neuron along the electrode's track, so they could later reconstruct the positions of the mapped neurons on slices of the post-mortem brain. In this way, they not only were able to classify V1 neurons into functional categories, but they also revealed the functional architecture of the primary visual cortex.

The earliest experiments recording from individual neurons in V1 used stimuli that had been effective in exciting or inhibiting retinal ganglion and LGN cells: small light or dark spots. Many cortical cells could be stimulated and mapped with small spots. But unlike the earlier neurons in the visual pathway, where receptive fields were circular with opposing center and surround regions, the cortical receptive fields had elongated excitatory and inhibitory areas organized along straight-line edges. Hubel and Wiesel found that bright bars, dark bars, or an edge between light and dark were even more effective than spots as stimuli. For a vigorous response, the straight-line stimulus had to be at an appropriate angle of orientation aligned with the receptive field edge, and positioned exactly within the receptive field (Figure 6.21). These first cortical cells with receptive fields that could be mapped with small spots they called "simple cells."

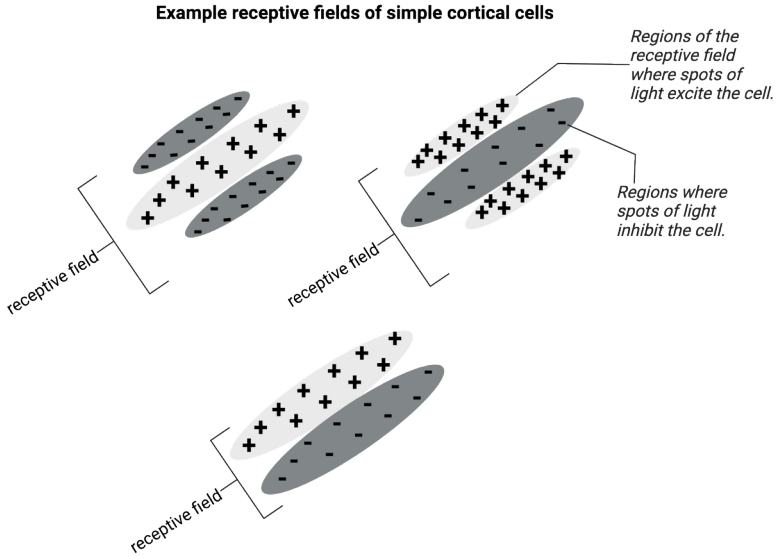


Figure 6.21 V1 simple cortical cells A simple cell responds to a small spot of light in its receptive field with excitatory "on" responses in some regions, or with inhibitory "off" responses in adjoining regions.

Hubel and Wiesel also discovered a second group of cortical cells that could not be stimulated with small spots. They named these cells complex cells. At first, they were a puzzle to the experimenters. Hubel has told the story of how they accidentally discovered what was special about complex cells. After struggling for hours without finding an effective stimulus for the neuron they were recording from, they slid a glass slide out of the projector, and as the faint dark edge of the slide moved across the screen, the neuron suddenly fired vigorously. It soon became clear that complex cells would respond to edges but not to spots. Their receptive fields could not be divided into static excitatory and inhibitory areas. Instead, complex cells responded to an appropriately oriented straight-line edge at any position in the receptive field. If the angled light or dark bar swept across the receptive field, the cell would respond continuously. (Figure 6.22) Many complex cells were also directionally selective, responding to an edge moving in one direction but not the reverse. This was different from simple cells, where an appropriately oriented edge would be effective at only one exact position; complex cells would respond to the stimulus at any position. This seemed to be a step beyond simple cells, hence the name "complex."

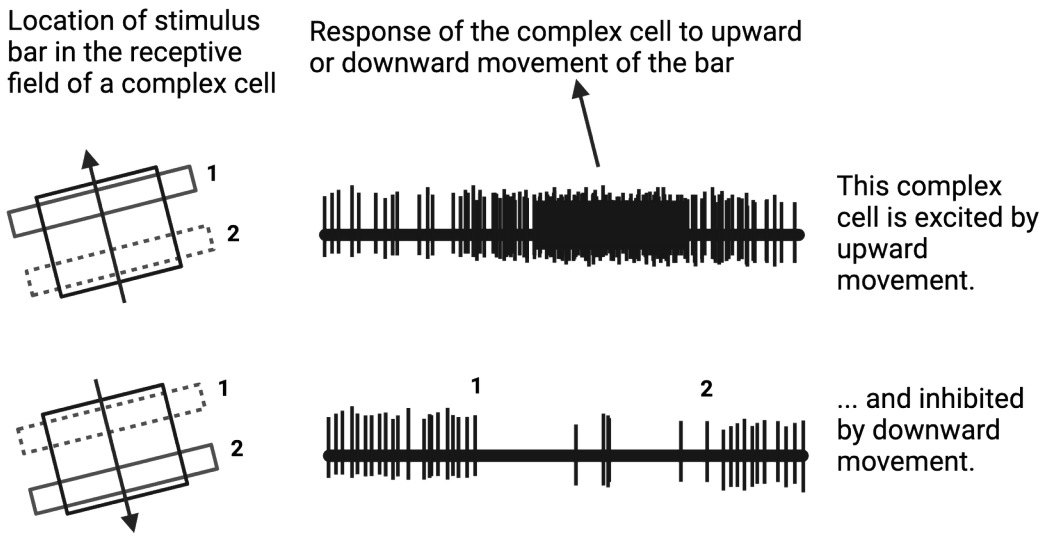


Figure 6.22 V1 complex cells respond to orientation and direction Complex cells respond to an appropriately oriented edge of light anywhere in their receptive field, not just at one exact position like simple cells. Many complex cells are directionally selective.

Hubel and Wiesel recorded videos that showed how they mapped receptive fields of simple and complex cells. The videos show the screen in front of the animal on which stimuli are projected, and we hear the action potentials (as clicks) produced by the neuron they are mapping. Although the video quality is not the best, these historically important videos show how V1 neurons respond selectively to projected visual stimuli.

Other neuroscientists explored responses of V1 neurons to other visual stimuli in addition to the projected bright or dark bars and edges that Hubel and Wiesel used. One group of stimuli, which are generated on a computer screen, are sinusoidal luminance gratings. These look like soft-edged stripes, and are discussed in the Feature Box on spatial frequency selectivity. Theoretically, any image can be broken down into its component spatial frequencies, which makes these stimuli of particular interest. V1 neurons actually respond more vigorously to appropriately oriented spatial frequency gratings than they do to simple bars or edges, and a neuron's preferred spatial frequency is now considered a significant characteristic of its receptive field.

Building Simple and Complex Receptive Fields

Hubel and Wiesel were interested in how information from LGN neurons with center-surround receptive fields could be transformed into the elongated receptive fields of cortical cells. They proposed that a simple cell in V1 receives excitatory synaptic input from a group of LGN neurons that have overlapping receptive fields located in a staggered straight line. Activating any one of the LGN cells with an appropriate light or dark spot would slightly excite the simple cell, but activating all of the LGN neurons with an oriented edge that covered all their receptive field centers would excite all of the LGN cells. This would elicit a vigorous response from the simple cell. Later experiments that recorded simultaneously from LGN and V1 neurons confirmed this scheme. Figure 6.23 shows the proposed cellular anatomy of these connections on the left, with multiple LGN neurons converging to excite a single V1 simple cell. The receptive field perspective on the right shows how a bar of light would provide the most effective stimulus for a V1 simple cell receptive field.

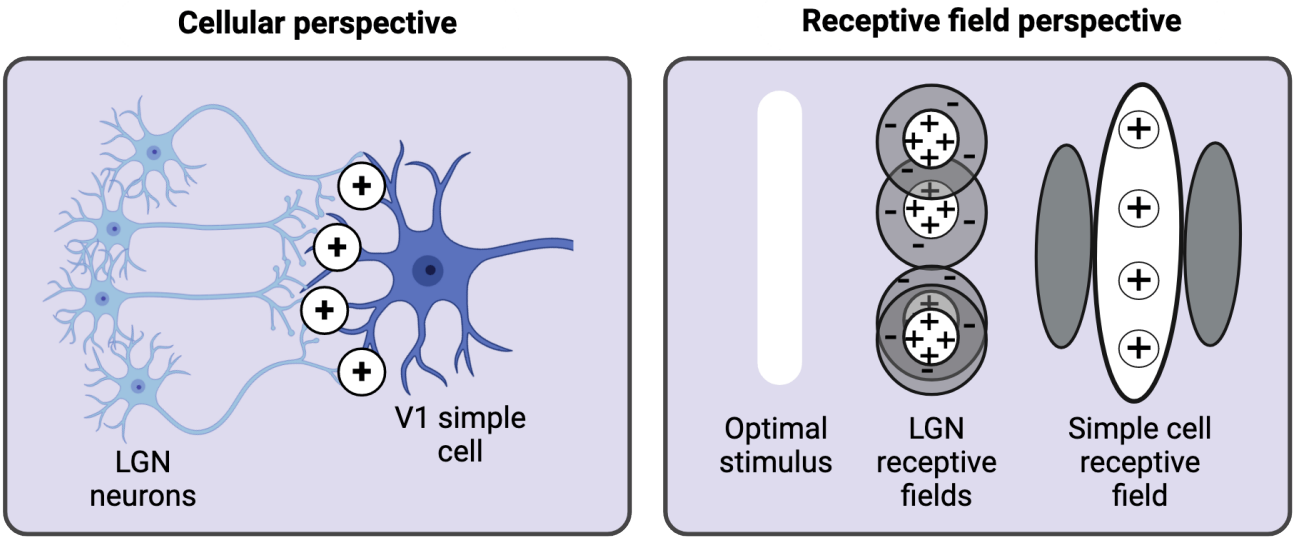


Figure 6.23 Simple cell connections to LGN neurons A bar of light maximally excites the simple cortical cell.

Hubel and Wiesel further proposed that complex cells were excited by the activity of a group of simple cells that had overlapping but similar receptive fields (Figure 6.24). An edge at an appropriate angle and position would excite one or more of the simple cells, thereby exciting the complex cell. But the stimulus could be at any position in the receptive field and still excite the complex cell. A moving edge crossing the receptive field would lead to continuous excitation. Directional selectivity could be imposed by additional circuitry that enhanced the complex cell's response to movement in one direction but suppressed the response to the opposite direction.

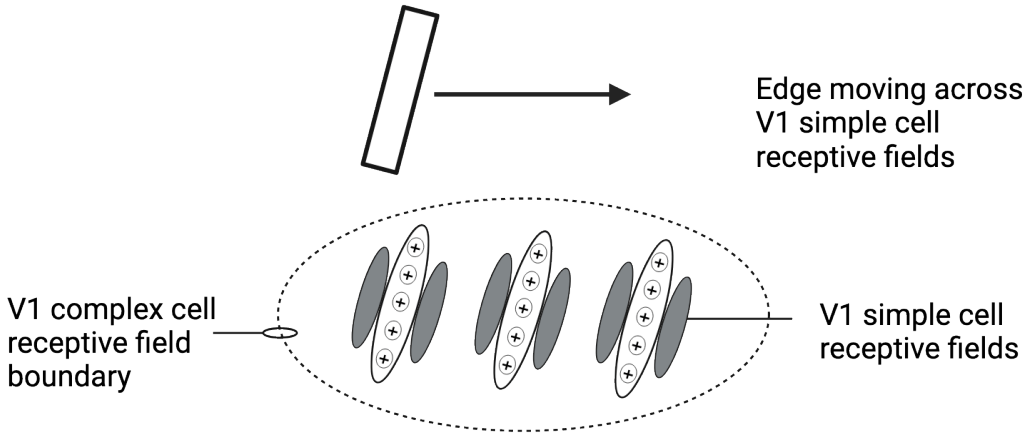


Figure 6.24 V1 complex cells respond to simple cells A vertical-edge stimulus moving across a series of simple cell receptive fields can continually activate a complex cell.

As Hubel and Wiesel continued their exploration of complex cells' responses, they found an additional characteristic. Making an appropriate stimulus bar longer so it spilled beyond the receptive field had no effect on the responses of many complex cells, but it decreased the response of other complex cells (Figure 6.25). This effect, where a stimulus bar extending beyond the receptive field actually inhibits a cortical cell's response, is referred to as endstopping. They named the new category "hypercomplex cells." Later research suggested that endstopping was a variable characteristic of every complex cell, and most neuroscientists no longer regard hypercomplex cells as a separate category. Figure 6.25 shows examples of complex cells with weak endstopping (top) and strong endstopping (bottom). Notice how both examples respond more and more to a stimulus as it elongates to fill the receptive field, but one stops responding when the stimulus extends beyond the receptive field. That complex cell shows endstopping in action.

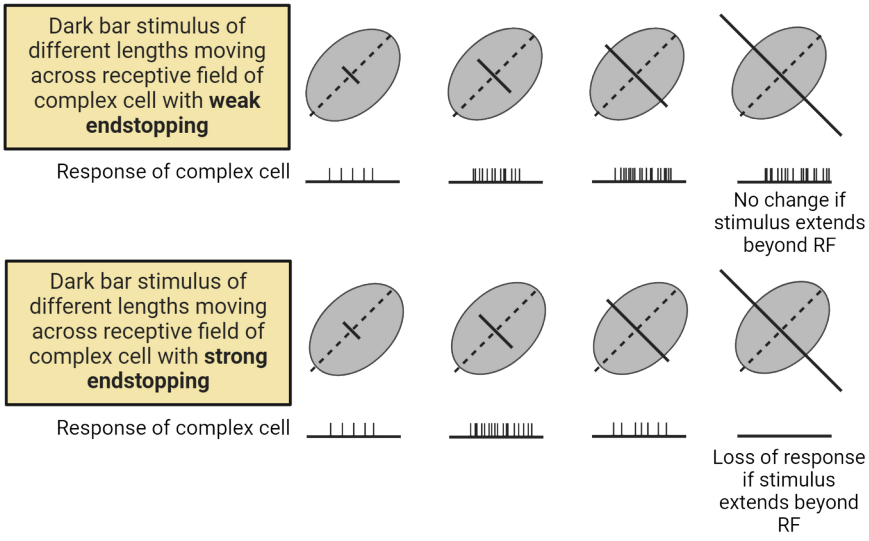


Figure 6.25 Endstopping

The functional purpose of endstopping has been puzzling, but one possible explanation is that it would make complex cells respond selectively to curved edges. A long curve falling in the receptive field would excite an end-stopped neuron if the segment within the receptive field had an appropriate orientation angle, but the part of the curve falling outside the receptive field would have a different angle that would not trigger endstopping. In contrast, long straight lines would retain the same orientation angle outside the receptive field and would activate inhibitory endstopping.

Spatial Frequency Selectivity

Neurons in V1 respond selectively to sinusoidal luminance gratings, which is yet another characteristic of a neuron's receptive field. These gratings look like evenly spaced stripes with soft edges. Three examples are shown at the top of Figure 6.26. They are called "sinusoidal" because the grating's brightness changes from light to dark and back again with a profile of intensity that resembles a sine wave. Gratings are specified by how many stripes fit in one degree of visual angle. Low spatial frequency gratings have broad stripes and appear blobby, while high spatial frequencies have narrow stripes and convey fine detail.

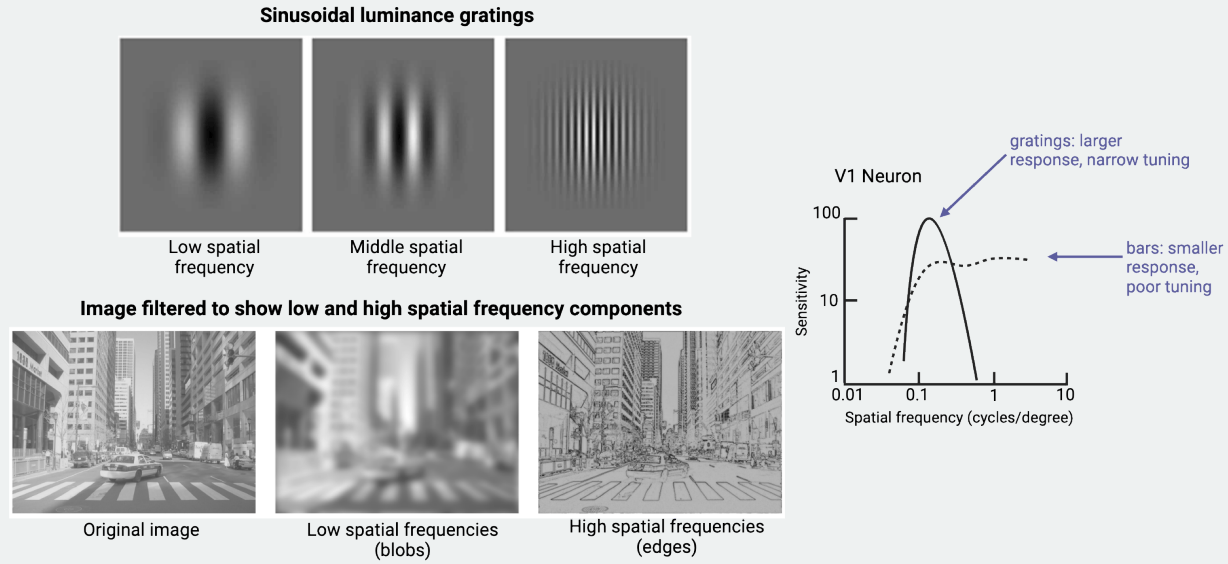


Figure 6.26 Spatial frequency selectivity Stimulating a V1 neuron with a series of spatial frequency gratings or a set of bars of different widths shows that the best SF grating is more effective than the best bar, and the neuron is more narrowly tuned for spatial frequency than for bar width. Image credit: Street scene from Berman D, Golomb JD, Walther DB (2017) Scene content is predominantly conveyed by high spatial frequencies in scene-selective visual cortex. PLoS ONE 12(12): e0189828. https://doi.org/10.1371/journal.pone.0189828 CC BY 4.0.

Selectivity for spatial frequency seems important because any real image can be computationally decomposed into its component spatial frequencies ("Fourier analysis"). The street scenes in the middle of the figure illustrate the contributions of low and high spatial frequencies to a real image. The original image (left) contains a full range of spatial frequencies, but if just the low spatial frequencies are presented (center), the scene appears blobby and out of focus. Alternatively, the high spatial frequencies show the scene's edges and reveal fine detail (right).

Interestingly, if a V1 neuron is stimulated with a series of appropriately oriented sinusoidal luminance gratings, the neuron will respond best to a particular spatial frequency and the response will fall off sharply at non-optimal frequencies. This makes the neuron narrowly tuned to its best spatial frequency. If instead the same neuron is stimulated with bars of different widths, the most effective bar does not elicit as strong a response as the best grating, and the tuning is not very sharp (narrower bars continue to excite the neuron). This is shown at the right of Figure 6.26, which plots relative sensitivity vs. spatial frequency. In their studies of V1 neurons, Hubel and Wiesel displayed rectangular bars of light from a slide projector on a screen in front of the animal, but most experimenters now use sinusoidal luminance gratings on a computer screen.

Binocular Units

We noted earlier that information from the right side of each retina ends up on the right side of the brain, but axons from the two retinas synapse in separate layers of the lateral geniculate nucleus. This means that LGN neurons projecting to the primary visual cortex will be driven by one eye or the other but not both. In V1, however, binocular neurons are found that are driven by both eyes (Figure 6.27). Covering one eye and then the other while the animal views the stimulus screen shows whether the V1 neuron responds best to the left eye, the right eye, or often to both eyes together. If one or the other eye is more effective than the other alone, this is classified as "ocular dominance," yet another characteristic of a V1 neuron's receptive field.

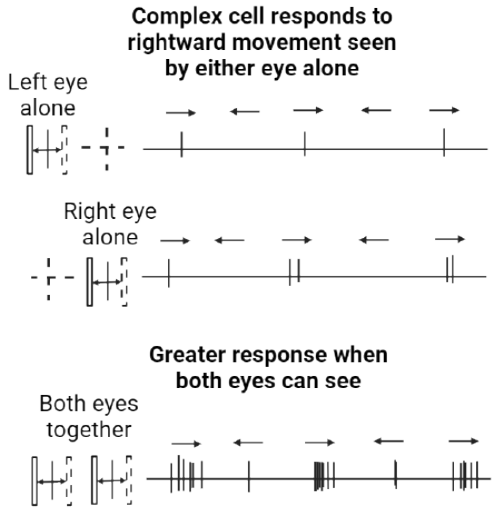


Figure 6.27 V1 biocular units

It was also possible to demonstrate that these binocular neurons contribute to stereo vision. For some neurons, moving an appropriately angled edge in space in front of the animal generated a strong response only if the stimulus was at a particular distance. Moving it nearer or farther decreased the neuron's response. Such neurons would report on the depth of edges in the visual scene. You can demonstrate stereoscopic depth perception in your own vision by moving a finger on your outstretched arm close to you and far away while closing one eye and then the other. You automatically perceive the distance of your finger as its relative position on your two retinas changes, affecting depth-sensitive neurons in your visual system. But automatic stereo vision operates only for near distances. For outdoor scenes, for example, there are other cues to depth such as occlusion (which objects are in front of others) and atmospheric haze, while relative positions of distant objects on our two retinas are no longer significant.

People Behind the Science: David Hubel and Torsten Wiesel

Hubel and Wiesel began their collaboration at Johns Hopkins University in 1958 working in the laboratory of Steven Kuffler, who had discovered receptive fields of retinal ganglion cells. Their goal was to record from neurons in the visual cortex. Both were immigrants to the US, Hubel from Montreal Canada and Wiesel from Sweden. Their experiments employed an electrode that Hubel had designed, a stiff tungsten wire sharpened to a pointed tip and insulated except for the tip. A miniature hydraulic drive bolted to the animal's skull held the electrode and allowed it to be slowly advanced into the cortical tissue, where it recorded extracellular action potentials from neurons. At first, they used the stimulus arrangement that Kuffler had used to map the receptive fields of ganglion cells, adapting it to record from the cortex by draping a bedsheet across the ceiling on which they could project spots of light. Hubel has described how awkward this was, and they soon switched to the arrangement they subsequently used for all future experiments. An anesthetized cat faced a screen on which the visual stimuli were projected, while the experimenters listened to action potentials from a neuron as they attempted to find the optimal visual stimulus to evoke a maximal response. Listening to neuronal activity provided an effective way of monitoring responses. The electrical signal was amplified and sent to a loudspeaker, where the action potentials sound like clicks. This made it easy to detect when a neuron is responding well. You can experience Hubel and Wiesel's method of mapping receptive fields in a series of videos that they made to demonstrate their work. Although the 1960s image quality is poor by modern standards, these historically important videos let you hear a V1 neuron's action potentials while you see the projection screen as the experimenters search for the best stimulus.

When Kuffler soon moved to Harvard, Hubel and Wiesel moved with him, and began experiments on cats and later monkeys that revealed cortical neurons that detect edges and boundaries. In addition to classifying different types of neurons by their responses to visual patterns, they also characterized the cortex's functional anatomy, revolutionary experiments that greatly advanced our understanding of the cerebral cortex and led to further discoveries.

An appreciative account of Hubel and Wiesel's work was published 50 years after their first paper: (Wurtz, 2009). Hubel's Nobel Prize address is also available; it is a very readable, informal account of their work. An online video of his Nobel lecture shows Hubel's casual speaking style.

Functional Anatomy of V1

The orderly layout of the retina is preserved in the layers of the lateral geniculate nucleus and in the surface of the primary visual cortex. This is the retinotopic map, shown in the left side of Figure 6.28. The right visual world is represented in the left visual cortex, with an orderly arrangement of receptive fields from the central retina to the periphery. Because there are many more retinal ganglion cells and LGN cells serving the fovea and central retina compared to the periphery, a disproportionately large area of cortex is devoted to the center of the visual field.

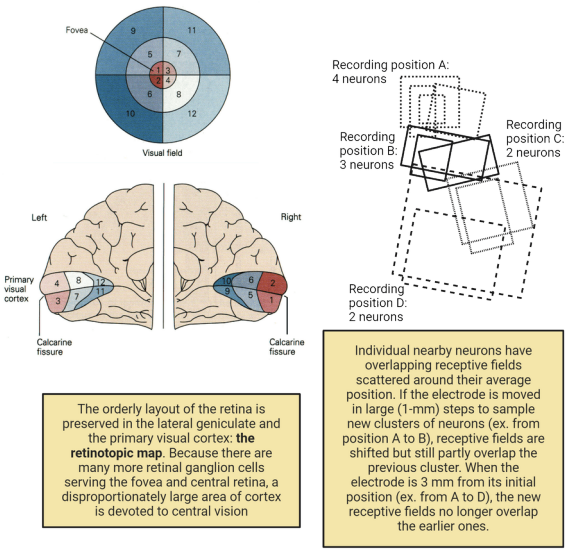


Figure 6.28 V1 visuotopic organization> Image credit: Retinotopic map by Jaygandhi786, CC BY-SA 4.0, https://commons.wikimedia.org/w/index...curid=39926315

The retinotopic map was established using several methods, including locating visual deficits (scotomas) for soldiers in World War II who had suffered head wounds that lodged shrapnel in the visual cortex. This established the overall layout of the human retinotopic map by presenting the average position in the visual world of the receptive fields of neurons from different cortical locations

Hubel and Wiesel added fine detail to the map by recording from individual neurons. A representation of their findings is shown on the right side of Figure 6.28. The receptive fields of nearby neurons overlap around their average position in visual space, but if the electrode is moved about 3 mm across the cortical surface, the receptive fields of neurons in the new location no longer overlap with receptive fields for the earlier location.

In addition to mapping hundreds of receptive fields in their experiments on V1, Hubel and Wiesel also recorded data on the location of each neuron along the electrode's track. This allowed them to later reconstruct the positions of the mapped neurons on slices of the post-mortem brain, which helped reveal the functional anatomy of the primary visual cortex. They noticed that as their electrode was advanced vertically (radially) deeper into the cortex, receptive fields of neurons along the electrode's track shared the same orientation preference. A nearby radial penetration encountered neurons that shared a different orientation preference, indicating that the cortex was organized in vertical orientation columns. They also saw broad regions that shared ocular dominance, where one eye drove a binocular neuron more strongly than the other eye. This changed from one eye to the other if the electrode was advanced horizontally (tangentially) across the cortex. They concluded that the cortex was organized in vertical columns of neurons that shared orientation and ocular dominance preferences. Later researchers used a different technique, optical recording, to reveal the two-dimensional organization of orientation and ocular dominance columns in V1. Optical recording detects differences in blood supply that reflect the level of activity of nearby neurons. In this way it resembles fMRI, but it provides finer detail and requires creating a window in the skull to permit imaging of the cortical surface. By imaging the cortex while systematically presenting a series of oriented stimuli delivered to one eye or the other, regions of maximal activity

could be identified. Using computational techniques to give each orientation preference a false color, the orientation columns were revealed to be arranged like pinwheels, while the ocular dominance columns were long stripes (Figure 6.29).

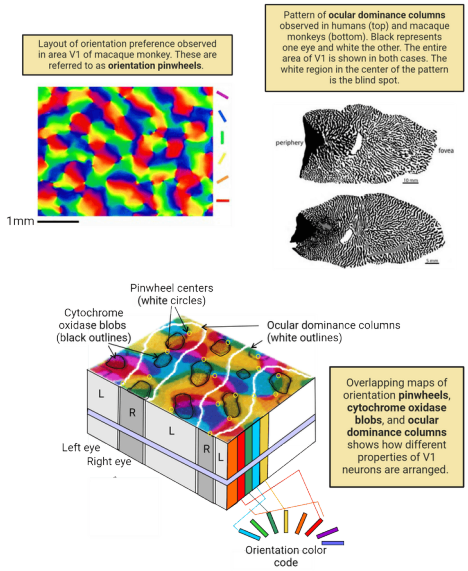


Figure 6.29 V1 orientation pinwheels and ocular dominance columns Image credit: Orientation pinwheels modified from Blasdel & Salama (1986) by Nicholas V. Swindale in 'Visual map'. http://www.scholarpedia.org/article/Visual_map CC BY-N-SA 3.0. 2D black and white ocular dominance columns image modified with permission from Adams et al. (2007) by Nicholas V. Swindale in 'Visual map'. http://www.scholarpedia.org/article/Visual_map CC BY-NC-SA 3.0. 3D ocular dominance column image by Pancrat, CC BY-SA 4.0, commons.wikimedia.org/w/inde...curid=18097523

Another structural feature in the cortex had been identified earlier: cytochrome oxidase blobs in the upper layers of the cortex. Cytochrome oxidase is an enzyme associated with metabolic activity, and by using a substrate that leaves a colored reaction product, the cortex was shown to have a regular array of “blobs," small patches of neurons with high metabolic activity. The array of blobs across V1 seen in stained microscope sections became another architectural element to add to V1’s orientation and ocular dominance columns. Optical recording using achromatic (non-colored) striped gratings at various angles or gratings with alternating red and green stripes demonstrated that the cytochrome oxidase blobs coincide with regions that respond most strongly to color stimuli.

Putting all these features together created an overlapping map of orientation pinwheels, cytochrome oxidase blobs, and ocular dominance columns (shown in the bottom of Figure 6.29). The cortex has a repeating modular structure. Within each module, the blobs and the pinwheel centers are both aligned along the center of the ocular dominance columns, but they do not have a specific relation to each other. The overall implication is that as the visual cortex is built in development, a repeating subunit structure is genetically specified to organize the cortex.

The final aspect of cortical architecture to consider is cortical layers. V1 is named “striate” (striped) cortex because of the prominent layering seen in cross sections of stained cortex. There are six anatomical layers, numbered from 1 at the cortical surface to 6 adjoining the white matter. The layers turn out to have functional differences (Figure 6.30). Axons from the LGN arrive at the cortex in layer 4 and also in layer 6. Layer 4 is where simple cells are found (red dots), supporting the theory that simple cells receive direct synapses from LGN axons. Complex cells (blue) are found in Layers 2-3 and Layers 5 and 6, where they could receive connections from simple cells in the same column, again consistent with the theory that simple cells drive complex cells. Complex cells in the upper layers project to more advanced cortical areas, leading to the next stages of visual processing. Complex cells in layer 5 project to the superior colliculus, and cells in layer 6 project back to the LGN, modifying the LGN’s responses to signals from the retina.

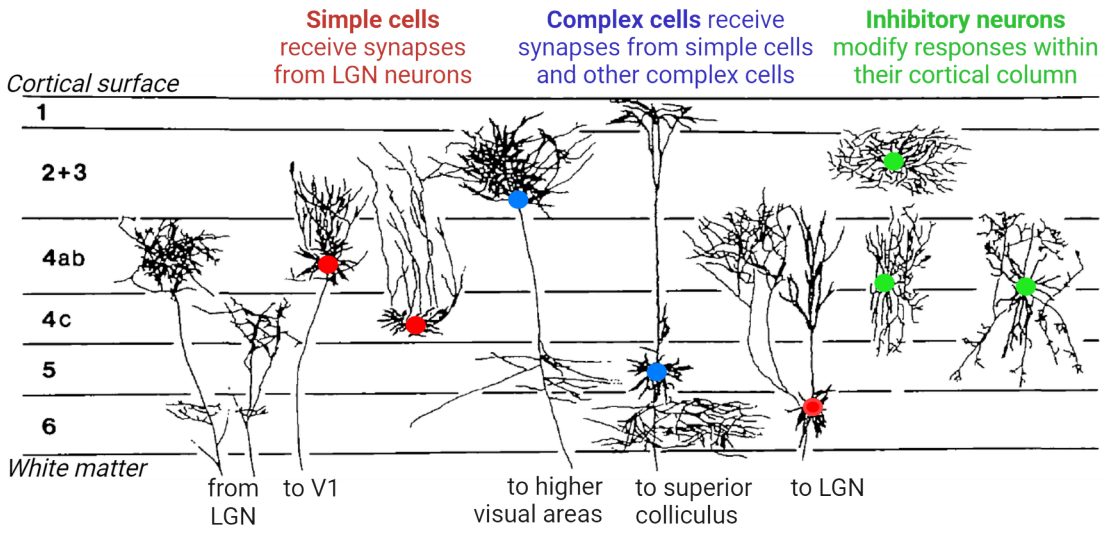


Figure 6.30 Layers of the visual cortex Image credit: reproduced with permission from Oxford University Press. All color elements added to enhance clarity. Original from: Gilbert CD. Circuitry, architecture, and functional dynamics of visual cortex. Cereb Cortex. 1993 Sep-Oct;3(5):373-86. doi: 10.1093/cercor/3.5.373. PMID: 8260807.

Color Vision in the Cortex

Most neurons in V1 receive their input from the LGN's parvocellular, color-selective layers, but surprisingly, relatively few V1 neurons respond selectively to colors. In monkey V1, one type of color-selective receptive field has a center-surround, double opponent receptive field. This is shown in the top of Figure 6.31. The example in the figure shows a neuron that is excited by red in the center and inhibited by the opponent color in the center (green). In the surround, the responses are reversed: green excites and red inhibits. A pattern where the two colors meet at an edge is the strongest stimulus.

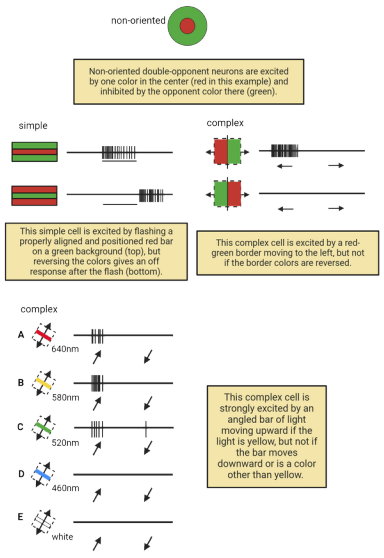


Figure 6.31 Many neurons in V1 respond selectively to colored stimuli

Other primate V1 neurons include simple and complex cells that are selective for color stimuli. The simple cell in the middle of Figure 6.31 is excited by flashing a properly aligned and positioned red bar on a green background (top), but reversing the colors elicits an off response after the stimulus ends (bottom). The complex cell in the middle of Figure 6.31 is excited by a red-green border moving to the left, but not if the border moves to the right, and not if the colors are reversed.

An interesting complex cell (bottom of Figure 6.31) is strongly excited by an angled bar of light moving upward if the light is yellow,

but not if the bar moves downward or if it is a color other than yellow. Note that white light does not excite this neuron, which means it would be overlooked in an experiment that did not test colored stimuli. These complex cells have all of the stimulus selectivities that we met earlier, such as orientation angle and movement direction, but in addition they are selective for color. Color selectivity in V1 is not well understood, and some aspects remain controversial. These and other V1 neurons provide the beginning of our visual perception of the form, color and location of objects, but V1 is just the first stage of visual processing. Processing continues in areas outside of the striate cortex: the extrastriate cortex.

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6.1.5: Extrastriate Cortex

Learning Objectives

By the end of this section, you should be able to

- Describe the broad functional role of the dorsal and ventral visual processing streams in the cortex
- Describe the stimulus-selectivity of inferotemporal neurons and how they were discovered

Visual processing continues in several cortical regions adjacent to V1 referred to as extrastriate cortex (“extra” means outside of V1). Most of the extrastriate areas have a retinotopic map like V1, but the individual receptive fields are larger and many fields cross the visual midline. Since we detect and recognize objects placed anywhere in the visual field, especially in the fovea where we see fine detail, wider receptive fields that cross the midline would be necessary to support conscious visual perception. V1 is just the beginning of cortical visual processing, and the extrastriate cortical areas are where additional stages of visual processing occur.

Extrastriate Visual Areas Overview

The extrastriate cortex beyond V1 divides into two major pathways: a dorsal pathway concerned with stimulus position and movement, and a ventral pathway leading to the perception of objects, faces, bodies, and scenes. The two pathways were first identified through experiments with monkeys trained on tasks that required distinguishing the location of an object (“where”) or the appearance of an object (“what”). Lesions in the dorsal and ventral cortex selectively interfered with one task or the other. Later studies recording from neurons confirmed the two pathways. Figure 6.32 shows many of the extrastriate visual areas that have been discovered. The relative size of each cortical area is represented by the size of the labeled boxes, and the number of axons connecting areas is represented by the thickness of the lines between them. These connections go in both directions, with axons projecting forward from a lower to a higher area, and also feedback connections from higher areas to lower ones. In fact, except for the one-way optic nerve from the retina to the LGN, all other visual areas have both ascending and descending connections, and the descending (feedback) connections have been shown to modify the activity of neurons in lower areas. For example, V1 projects strongly to V2 and V4, but those areas also project back to V1.

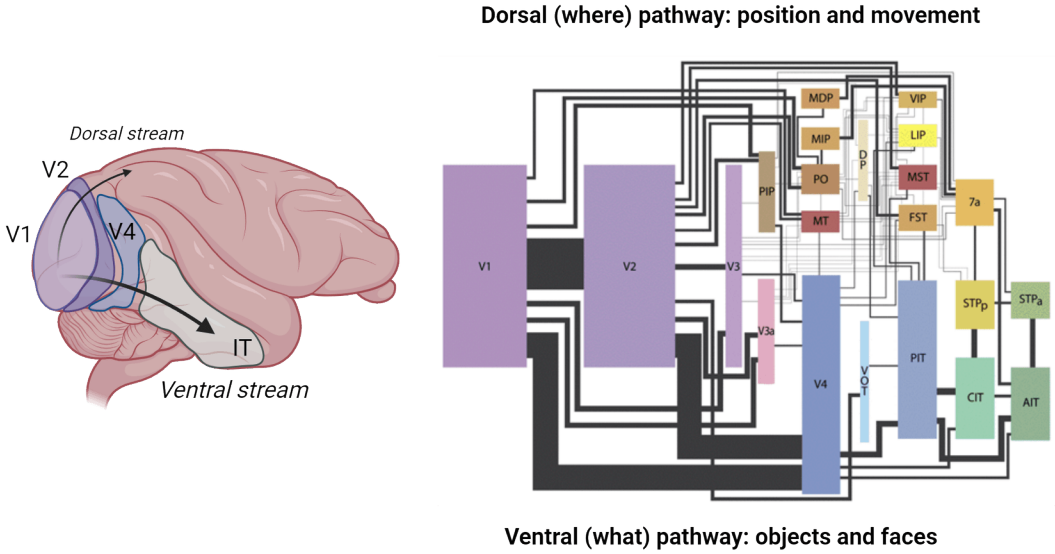


Figure 6.32 Anatomy and functional connections of extrastriate areas Image credit: Wiring diagram reprinted from Neuron, Vol. 60, Wallisch & Movshon,Structure and Function Come Unglued in the Visual Cortex, Pages No.195-197, Copyright (2008), with permission from Elsevier. www.cell.com/neuron/pdf/S089...08)00851-9.pdf

That path, V1 to V2 to V4, is the main pathway for conscious visual perception. It leads to the temporal cortex (specifically the

anterior (AIT), central (CIT) and posterior (PIT) inferotemporal cortex). These IT areas are locations for patches of neurons that respond selectively to shapes, faces, colors and places. These components of the ventral stream are discussed in the following sections.

Dorsal Stream

The dorsal stream visual pathway processing areas have received less attention than the ventral stream, but one area that has received interesting experimental attention is area MT, "middle temporal." The MT cortex is a motion-selective area organized in columns where all the neurons in a column are selective for a single direction of movement. Experiments at Stanford University showed that monkeys trained to report the direction of movement of subtle regions of random dots moving amidst stationary dots could be led to see sub-threshold movements if a column in MT was electrically stimulated (Salzman et al., 1990). The stimulation caused the neurons in that column to fire, which led the monkey to perceive movement that did not actually exist. The experiment was a direct demonstration that activity in an extrastriate area can lead to a visual perception.

Ventral Stream

The ventral "what" pathway for conscious visual perception leads from V4 to the lower ("inferior") surface of the temporal lobe, the inferotemporal cortex (IT). Receptive fields of neurons in IT are significantly different from the earlier visual areas. They are not organized in a retinotopic map, but instead are grouped by the similarity of their most effective stimuli, such as the shapes of objects or the components of faces. IT receptive fields are very large (from 25 to 70 degrees of visual angle, a substantial span of the visual field's 180 degrees), they always include the fovea, and they span the midline to include portions of both the left and right visual fields. Effective stimuli for an IT neuron can include objects, faces, or hands, independent of the size or exact position of the stimulus.

The selectivity of IT neurons represents major steps toward conscious visual perception. Neurons in the first stage of cortical processing, the simple cells of V1, have small receptive fields (about 1 degree) that require exact positioning of an oriented edge. They will detect small components of an object's outline, with thousands of V1 neurons responding to even a small object. Shifting the stimulus's position or size in the retinal image will activate a completely different population of V1 neurons. In contrast, IT neurons are flexible in their response to the position and size of the retinal image, a necessary step in perceiving objects.

Extensive experiments to record from IT neurons began in the 1980s. Among the earliest findings were that posterior IT areas, the ones closest to extrastriate cortex, had optimal stimuli that were more elaborate than V4 neuron receptive fields. Actual objects such as toy animals were effective, although a tiger's face, for example, could be reduced to a simpler image of a rectangle with attached circles. More anterior regions of the IT cortex had more complex receptive fields, with patches of neurons that responded selectively to faces, colors, and scenes.

If a visual area like IT has neurons with selective responses to complicated images, a methodological problem arises. How do the experimenters know if they have found the optimal stimulus? It is feasible to show a test array of hundreds of photos of different images, flashing each photo briefly while detecting if an IT neuron fires action potentials, but the most effective stimulus may not be in the test set. The best that can be accomplished is to identify a general category that the neurons respond to, and then narrow down the important details in the stimulus. This strategy has been employed to characterize neurons that respond to objects and faces.

Another approach, especially for intermediate extrastriate areas like V4, has been to use computer-generated patterns that are systematically and randomly varied. Variations that lead to more vigorous firing are retained, while less effective variations are discarded. Repeating the cycle and continuing to choose more effective variations eventually generates apparently optimal stimuli, but they are often complicated and do not resemble simple geometric shapes that are easily described in words. This remains a puzzling aspect of visual processing.

Face-Selective Units

In the 1980s, exploratory recordings made by Charles Gross and his colleagues at Princeton University discovered neurons in monkey IT that responded vigorously to images of faces. The faces could be of monkeys, humans, or even cartoons, but if the eyes were omitted or the image was scrambled, the response was reduced or eliminated (Figure 6.33). Faces are an important element of communication for monkeys and humans. Faces support identification of familiar individuals, and they also reveal emotional expressions from unfamiliar strangers. In recording from randomly encountered neurons in electrode penetrations of

IT, the Princeton group found neurons that were selective for a variety of images, not just faces.



Figure 6.33 Face-selective units Recordings in inferotemporal cortex of monkeys shows neurons that respond selectively to faces. Image credit: Journal of Neurophysiology, Vol. 46, Issue 2. Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque. C Bruce, R Desimone, C G Gross. (1981). With permission from The American Psychological Association.

People Behind the Science: Dr. Doris Tsao and Current Approaches to Studying Face-Selective Units

Dr. Doris Tsao and her collaborators have introduced a more targeted approach to investigating face-selective units in primates. Dr. Tsao began her work on face patch neurons as a graduate student and postdoctoral scientist at Harvard Medical School, collaborating with Winrich Freiwald and Professor Margaret Livingstone. Tsao continued this work as a professor at Caltech, where she received a MacArthur “genius” award, and continues it now at the University of California at Berkeley. Dr. Tsao and her collaborators used fMRI to locate six face patches in IT cortex that contain neurons responsive to faces. They then recorded from individual neurons in each patch. Figure 6.34 (right side) shows the responses of 182 neurons in a face patch (vertical axis) to 96 standard images (horizontal axis) of faces, bodies, fruits, gadgets, hands, and scrambled photos. The images were flashed on a screen in random order. Each horizontal row represents the responses from one of the 182 recorded neurons, with red indicating a strong response. For analysis, the responses were lined up to place all the responses to one stimulus image in a vertical line, and to group the stimuli into six categories. For almost all the neurons in a face patch, it was clear that only the 16 images of faces consistently elicited strong responses, with little or no response to the other images.



Dr. Doris Tsao

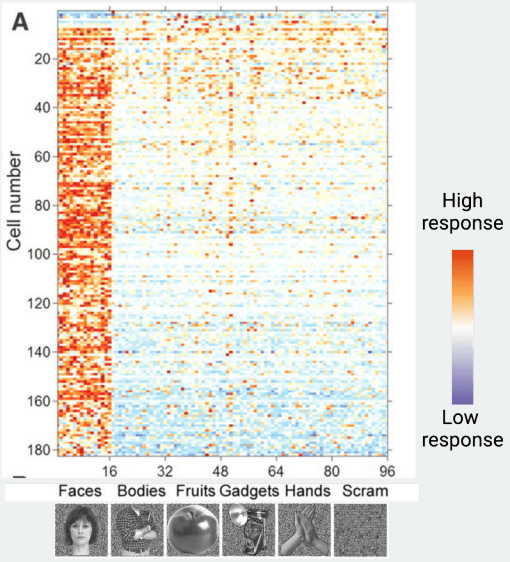


Figure 6.34 Doris Tsao and fMRI study of face-selective units Responses recorded from 182 individual neurons in one face patch show that only images of faces elicited strong responses from neurons in the face patch. Image credit: Doris Tsao by Giantnanoassembler, CC BY-SA 4.0, https://commons.wikimedia.org/w/inde...curid=71887161. Data and images of stimuli: Tsao DY, Freiwald WA, Tootell RB, Livingstone MS. A cortical region consisting entirely of face-selective cells. Science. 2006 Feb 3;311(5761):670-4. doi: 10.1126/science.1119983. PMID: 16456083; PMCID: PMC2678572. Reprinted with permission.

Other experiments used cartoon faces as stimuli, permitting systematic variation of features such as the proportions of the face, the size of the nose, the diameter of the eyes, and the height of the hair. Different neurons were tuned to extremes of some features but not affected by variations in other features. Later research found two additional face patches where the responses were affected by whether the face was familiar to the monkey being tested. One clear conclusion was that a given face would elicit responses from a large subset of neurons in multiple face patches, with different faces activating different subsets.

In online videos, Dr. Tsao explains characteristics of the first face-selective neurons she studied as well as her later work at Caltech.

Face patches have also been identified by fMRI in the human brain, a region called the fusiform face area (FFA). Research on IT face patches continues, with a goal of revealing how advanced visual processing occurs in sequential stages for a well-defined image category. These studies may help explain how a scene that activates millions of neurons in multiple cortical areas leads to our conscious perception of the components of the visual world around us.

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6.2: THE AUDITORY SYSTEM

6.2.1: Acoustic Cues and Signals
6.2.2: How Does Acoustic Information Enter the Brain?
6.2.3: How Does the Brain Process Acoustic Information?

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6.2.1: Acoustic Cues and Signals

Learning Objectives

By the end of this section, you should be able to

- Identify auditory cues and signals and explain their behavioral relevance.
- Describe what an acoustic wave is and how it propagates through air and interacts with solid objects.

The world is full of sound, and almost every species of animal possesses the ability to sense and respond to sounds. Indeed, hearing is so important that several components of the auditory system have evolved not once but many times. In this section, we will explore what causes sound, first from the standpoint of function and then from the standpoint of physics. This will prepare you for the next section, which covers how sound is detected by the ear and transmitted to the brain.

Why is the sense of hearing important?

Like every other sensory system, the auditory system has evolved because it provides useful information about the objects and events in an animal's environment. Animals that can accurately sense what is happening around them can respond in a way that increases their chances of survival and of successfully passing on their genes. Hearing is especially valuable to survival because sound can travel over long distances and around obstacles, allowing animals to make timely responses, for example by fleeing from a predator before it gets too close.

To further illustrate why hearing is such an important sense, consider the female bird pictured perching in the center of Figure 7.2. Sounds are coming from every direction. Some are not especially relevant, like the splash of a turtle falling into the water or the rippling of water flowing in the stream. Other sounds carry important information, like the rustle in the nearby bushes that could be coming from a predator, or the song of a nearby male advertising himself as a potential mate. Sounds that are produced *unintentionally* are called cues, whereas sounds produced *intentionally*, with the goal of communicating something, are called signals.

Some of the most common and important cues are the sounds animals make as they move. Predators and prey alike have evolved to move as quietly as possible to minimize the cues they give about their presence and location. It is almost impossible to avoid making any sounds, however. Sticks break, grasses rustle, and even simply moving through the air can create turbulence. As we will see, all of these events can generate acoustic waves that travel for tens of meters or even further. Just as there is selective pressure for animals to move quietly, many species have evolved extremely sophisticated and sensitive auditory systems. For example, the common house cat (*Felis domesticus*) can hear a mosquito flying in a quiet room from as far as 30 m away — no wonder my cat seems to appear from nowhere the moment I open a can of food!

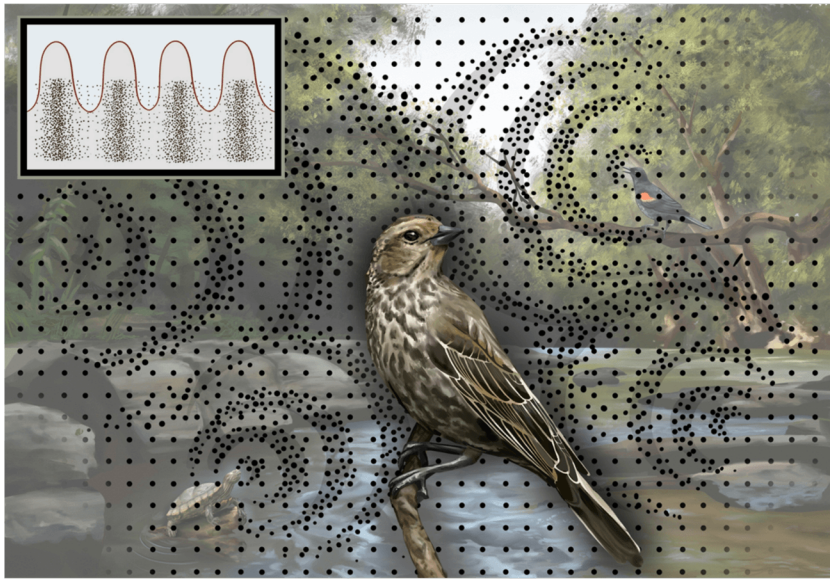


Figure 7.2 Acoustic signals Perceiving the acoustic scene: the acoustic signals converge, resulting in perception. Brush rustles: potential predator? Turtle leaves water: Interference, not a threat. Potential mate singing: Stimulus to prioritize. Water flowing: Noise, background stimulus, not important. Image credit: Created by Natalie M. Lucas. CC BY-NC-SA 4.0.

In contrast with cues, acoustic signals have evolved to allow one individual, called a sender, to influence the behavior of another individual, the receiver. Birdsong, for example, is a signal that communicates to female songbirds that a potential mate is nearby. The male sings with the intent of influencing females to approach and mate. In many species, the song also informs the female of how desirable the male is, because only healthy males can produce songs with a certain level of complexity (Nowicki and Searcy 2004). Acoustic mating displays are common throughout the animal kingdom, including many insects, fishes, amphibians, birds, and mammals.

Acoustic signals can also be used to broadcast the identity of the individual producing the signal, as long as receivers can distinguish the unique features of each individual's signal. Individual recognition is particularly important to animals that live in large social groups where visual cues are not easily distinguished, as in a flock of nesting seagulls or a herd of elephants (McComb et al., 2000) or where individuals need to find each other over long distances, as in dolphins and other marine mammals (Sayigh et al., 1999).

Animals use acoustic signals to communicate to each other about more than just themselves. When social animals are foraging in large groups, a few individuals may keep watch and signal to the group about sources of danger. Acoustic signals have a particular advantage here because they can travel long distances and around obstacles that would block sight. For example, vervet monkeys have different kinds of alarm calls that indicate the presence of specific kinds of predators (Seyfarth and Cheney 1990). When one monkey sees a leopard, it makes the "leopard" call, and the other members of its troupe will climb into trees, even without themselves seeing the leopard. In contrast, when a monkey makes the "eagle" call, the troupe will hide in nearby bushes that are too thick for an aerial predator to enter. The monkeys' auditory system must be able to discriminate between these signals for them to respond appropriately.

Humans have evolved a much more elaborate system of acoustic communication called speech, in which words are formed from combinations of distinct vocal elements called phonemes. For example, the vowels in the English words "bat" and "pat" are the same phoneme (/a/), whereas the initial consonants (/b/ and /p/) are different. One of the most important tasks of the human auditory system is to identify and discriminate between similar-sounding phonemes, and this ability is shaped by the sounds an infant hears in the first year of life.

Some species produce acoustic signals for themselves to hear, with the purpose of detecting obstacles and prey in their environment. Because sound waves reflect from solids and liquids, they can be used for echolocation. The ability to echolocate has evolved separately in bats and in some aquatic mammals. Echolocating animals produce short vocalizations that reflect off nearby objects. Specialized neural circuits use the delay between the signal and its echo to determine distances to those objects, while other circuits compute the direction of the object (see 7.3 How Does the Brain Process Acoustic Information?) and even some of its physical characteristics (Moss and Sinha 2003). A bat hunting by echolocation can easily discriminate between a solid obstacle and a delicious insect, and it can rapidly alter its course of flight to intercept the insect while avoiding the obstacles (Surlykke et al., 2009).

In summary, the sense of hearing serves many important functions for humans and other animals. Acoustic cues and signals are a critical source of information about predators, prey, obstacles, and dangers in the nearby environment, as well as the presence and intentions of conspecifics (other animals of the same species). In the next section, we will see how the physical nature of sound allows it to transmit this information in a way that complements the other senses.

How is sound produced?

What is sound? From the perspective of physics, sound consists of pressure waves moving through air or some other physical material. Waves are found throughout nature and share a common mathematical description. At the same time, acoustic waves have special properties that make them distinct from other kinds of waves.

To illustrate what a wave is, imagine throwing a rock into a still pool of water. When it hits the surface, the rock will displace some of the water, causing it to rise in a circle around the point of impact. Gravity pulls the displaced water back down, which in turn pushes up the water a little further out. This process repeats again and again to produce what we observe: a ripple *traveling* outward from the point of impact. An acoustic wave moves in much the same way, except that instead of a two-dimensional surface moving up and down, the molecules of the air move closer together and further apart, and the wave spreads in three dimensions.

Now instead of throwing a rock into a pool, imagine clapping your hands together. As your hands meet, they push air out of the space between them. Where does this air go? There is air all around your hands, but air is mostly empty space, so there is plenty of room for the displaced molecules of air to crowd in with the molecules that are already there. Now there is a region around your hands where the air is at a higher pressure, with an increased density of air molecules. The compressed molecules in the region of higher pressure push out into the surrounding space, which is less dense, or rarefied. This creates a new region of higher pressure, which in turn spreads further out from your hands. Just as the water ripple radiates out in a circle from a central point, the pressure wave created by your hands clapping radiates out in a sphere. If a microphone or some other pressure sensor is placed along the path of the wave, it will measure successive increases and decreases in the pressure at that location as the wave travels through space (Figure 7.3).

It is important to notice that the individual air molecules do not move nearly as fast or as far as the acoustic wave. The air itself is not flowing, as in a wind. Instead, neighboring molecules are bumping into each other, and an individual molecule pushed out from a region of higher pressure may only travel a few nanometers before it collides with another molecule. Sound waves move through air at around 343 m/s, but this varies depending on temperature and elevation.

Acoustic waves can be described in terms of three principal quantities: amplitude, frequency, and phase. Amplitude (also called intensity or level) is a measure of how much the air pressure changes between compression and rarefaction. Clapping your hands more forcefully causes a larger increase in pressure and a wave with a higher amplitude. Amplitude is measured in units of pressure (in the metric system, Pascals); however, because the perception of acoustic amplitude follows a logarithmic scale, it is more often reported in units of decibels of sound pressure level (dB SPL). As shown in Table 7.1, each step of 20 on the decibel scale corresponds to a proportional, ten-fold increase in the pressure.

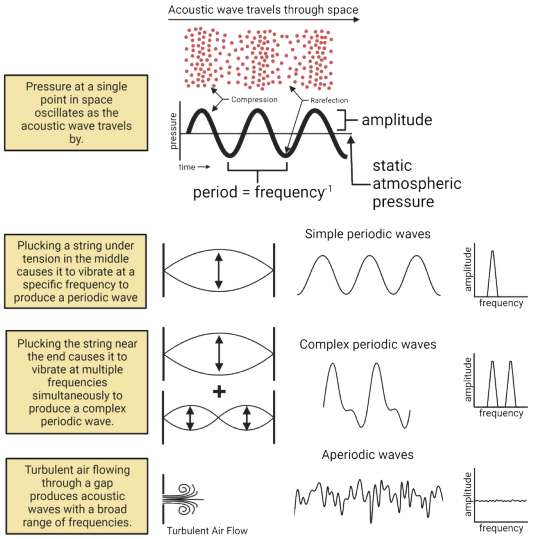


Figure 7.3 Physical properties of acoustic waves

The frequency of a wave is a measure of how rapidly the air at one location changes from compressed to rarefied and back (Figure 7.3). Frequency is measured in Hertz (Hz), the number of cycles that occur each second. The frequency of a sound wave is perceived as pitch. Low-frequency waves sound deep and rich, whereas high-frequency waves are perceived as sharp and thin.

The phase of a wave is a measure of time relative to the cycles of compression and rarefaction. Phase is not perceived directly, but it affects how different waves interact with each other.

Almost any process that displaces air molecules will result in an acoustic wave. One of the most common sources of sound is periodic vibration. You can generate periodic motion by plucking or striking a string that is under tension (for example, on a guitar, piano, or harp). Pluck it right in the middle, and listen to the sound while watching the string. The vibration will probably be too fast for your eyes to track, so the string will appear wide in the middle and narrow at the ends, as illustrated in Figure 7.3. As it vibrates, the string compresses the air while moving in one direction and rarefies it while moving in the other. The vibrations tend to occur at a specific frequency that depends on the mass of the string, its length, and how tightly it is tensioned. The motion of the string and the sound wave it produces are described by a simple mathematical function called a sinusoid (or sine wave) with a single frequency and amplitude. The form of this function and its relationship to the physical properties of the string will be covered in most elementary physics texts.

Amplitude		
dB SPL	Pa	Example
0	0.00002	Mosquito 3 m away in silent room (human hearing threshold)
10	0.000063	Calm breathing
30	0.00063	A quiet office with computer off
50	0.0063	Normal conversation 1 m away
70	0.063	Comfortable music listening level
90	0.63	Traffic on a busy roadway
100	2	Jackhammer 1 m away
120	20	Jet engine 100 m away (risk of instantaneous noise-induced hearing loss)
170	6300	Firecracker 0.5 m away

Table 7.1 Properties of sound

Now press the string down or pinch it at its midpoint before plucking it. The half that you pluck will vibrate twice as fast as the

whole string did, producing a sound wave with twice the frequency. You might notice that the higher note sounds similar even though the frequency is higher. If you pinch the string three-quarters of the way and pluck the short part, the frequency will be four times as high, but the note will still sound similar. This is an illustration of how the perception of frequency is logarithmic, as we'll discuss more later.

What happens if you pluck the whole string, but nearer to one end? You might notice that the note sounds richer and more complex, and that the movement of the string looks more complicated, without one clear wide part in the middle. Just as white light is composed of electromagnetic waves with frequencies spanning from red to violet, sounds can be composed of multiple waves with different frequencies. When the guitar string is plucked nearer the end, it will vibrate at the frequency corresponding to the full length of the string but also at twice that frequency (corresponding to half the length), three times that frequency (corresponding to one third of the length), and so on. A series of integer multiples like this is called a harmonic series. The lower-frequency and higher-frequency sound waves add together to produce complex harmonic motion. The specific combination of frequencies in a complex sound is called its spectrum. Most simple and complex periodic sounds are perceived as tones with a defined pitch that corresponds to the lowest frequency in the harmonic series.

Take a moment to think about this: you hear the string on the guitar as a single note, yet it is composed of several waves with different frequencies. As we will see later, each of these waves activates a different set of receptors in the inner ear and a different set of neurons that transmit information into the brain. In order for us to understand how audition works, we will need to understand how these different channels of information are combined by the brain to produce a single unified percept or split apart to distinguish between different sources, as when a person is singing along to the guitar.

Many species of animals generate sounds through periodic motion. The chirp of a cricket is produced by rubbing two textured surfaces on their wings together. The vocal folds in the mammalian larynx and the avian syrinx vibrate periodically as air is exhaled, and the frequency of the vibrations can be controlled by muscles that increase or relax the tension. In human speech (and even more so in singing), the vowels are produced by periodic movement of the vocal folds.

Sounds that do not have a regularly repeating pattern are not perceived as having pitch and are called aperiodic. The main sources of aperiodic sounds are transient collisions between surfaces and continuous, turbulent air flow. In turbulent air flow, the molecules are not all moving at the same speed and direction. This causes eddies and ripples to form as faster-moving air collides with slower-moving air, and the pressure variations in the ripples propagate outward as acoustic waves. Turbulent flow tends to occur whenever air is forced through narrow openings or disorderly obstacles like trees. You can make turbulent air flow by lightly pursing your lips and exhaling forcefully (but not forcefully enough to make a whistle). Aperiodic sounds do not contain a single frequency or even a regular combination of frequencies as in complex harmonic sounds. Instead, the pressure fluctuates at random across a broad range of frequencies. This is perceived as noise. A continuous sound that has equal amplitude across all frequencies is called white noise. Aperiodic sounds are also commonly used in acoustic communication. In human speech, many of the consonants are produced by aperiodic sounds.

How does sound travel and interact with objects?

Sound's ability to travel through the air is what allows the auditory system to sense cues and signals coming from a distance. In this respect, the sense of hearing shares certain similarities with vision, but acoustic waves are much slower and have longer wavelengths than visible light. Humans can hear sounds with frequencies between approximately 20 and 20,000 Hz. In air, these frequencies correspond to wavelengths between 17 m and 17 mm. In contrast, visible light has wavelengths between 400 and 780 nm. In other words, whereas light waves are much, much smaller than most behaviorally relevant objects, sound waves are around the same size. As a consequence, acoustic waves exhibit a number of phenomena that are important to understanding how sound works.

First, sound waves can diffract around common objects. You can illustrate diffraction by placing a stone about 1 cm in diameter in the center of a shallow bowl of water. Tap the water near the edge of the bowl and watch how the ripples seem to pass right through the stone. This is diffraction. Waves can diffract around objects that are around the same size or smaller than the wavelength, which means that lower frequencies (longer wavelengths) are less likely to be blocked. Thus, a predator may be impossible to see when it hides behind a rock or a tree, but most of the noises it makes will simply pass around the object.

Second, solid objects are more likely to transmit sound waves than visible light waves. Low-frequency sounds in particular are more easily transmitted through solids, which is why you can hear construction noises through solid walls and the bass line from your downstairs neighbor's music. At higher frequencies, solids tend to reflect sound. Reflections cause an acoustical phenomenon called reverberation, in which echoes of a sound reach the same point at slightly different times. For example, if you are in a large room with a concrete floor and metal walls, and someone a few meters away from you claps, you will hear not only

the wave coming directly from the source to your ears, but all the other waves that reflect off the floor and the walls. The reflected waves have longer to travel, and because the speed of sound is around 343 m/s, there can be a perceptible delay between the time when the direct wave and its reflections arrive. Reverberations with long delays are heard as distinct echoes. Reverberations with short delays tend to fuse with the main sound, making it sound more “alive”. Surfaces that are soft or uneven are better able to absorb sound, reducing the intensity of the reverberation, and rooms that have little reverberation sound muffled or “dead”. With practice, people can learn to use the acoustical characteristics of different materials as cues to their location within a room, an ability akin to the specialized echolocation of bats and dolphins.

The long wavelengths and reflectiveness of sound cause another phenomenon called resonance. If sound waves enter a space where they can reflect back and forth between two surfaces, they will interact with each other through interference. If the sound has a wavelength the same as the distance between the two surfaces (or an integral fraction of the distance), the peaks and valleys of the wave going in one direction will overlap with the wave going in the other direction, leading to constructive interference. Wavelengths that are not an integral fraction of the difference will not overlap, leading to destructive interference. For complex sounds comprising waves of multiple frequencies, resonance boosts certain frequencies (wavelengths) while attenuating others. This effect is also known as filtering. When you blow across the mouth of a bottle, the aperiodic noise produced by turbulence resonates in the bottle, boosting a single frequency (and its harmonics) to produce a tone.

Filtering is important to the production of speech. Recall that vowels are produced by periodic motion of the vocal folds. But how do we make different vowels? You can illustrate this by singing “aah” and then changing to “ooh” while holding the same pitch. If you pay close attention to your tongue and lips, you’ll notice that the shape of your mouth changes as you transition between different vowels. What’s happening as you move those muscles is that the sizes of the oral and pharyngeal cavities in your airway are changing to create different resonances that boost and suppress specific frequencies in the sound coming from your larynx.

A consequence of these phenomena is that it is common for a listener to hear many different sound sources simultaneously. This is an advantage in that it is possible to hear sounds without having to look at them, to take in an entire auditory scene in full 360-degree surround, and to hear multiple instruments or singers making music together. It also makes a difficult task for the auditory system, which has to separate out multiple sound sources and determine their locations. As we shall see, the structure of the ear performs a part of this task, separating complex sounds into their component frequencies, but the central nervous system still has an enormous amount of work to do to transform auditory scenes into coherent perception.

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6.2.2: How Does Acoustic Information Enter the Brain?

Learning Objectives

By the end of this section, you should be able to

- Identify the major anatomical parts of the ear and describe their function.
- Explain how the cochlea separates complex sounds into their component frequencies and transduces acoustic energy into neural signals.
- Describe how neural information ascends to the cerebral cortex through the major nuclei and fiber tracts of the classical ascending auditory pathway.

In the previous topic, we've seen how the air is full of acoustic waves carrying cues and signals vital to survival. These waves consist of minute variations in air pressure that can be up to 10 billion times smaller than the overall pressure exerted by the atmosphere. In this topic, we will examine how the incredibly sensitive organ known as the ear is able to detect these tiny fluctuations and convert them to neural signals that the brain can process.

The ear consists of three main parts, shown in Figure 7.4: the external ear, the middle ear, and the inner ear. Auditory stimuli enter through the external ear as acoustic waves and exit the inner ear as neural impulses.

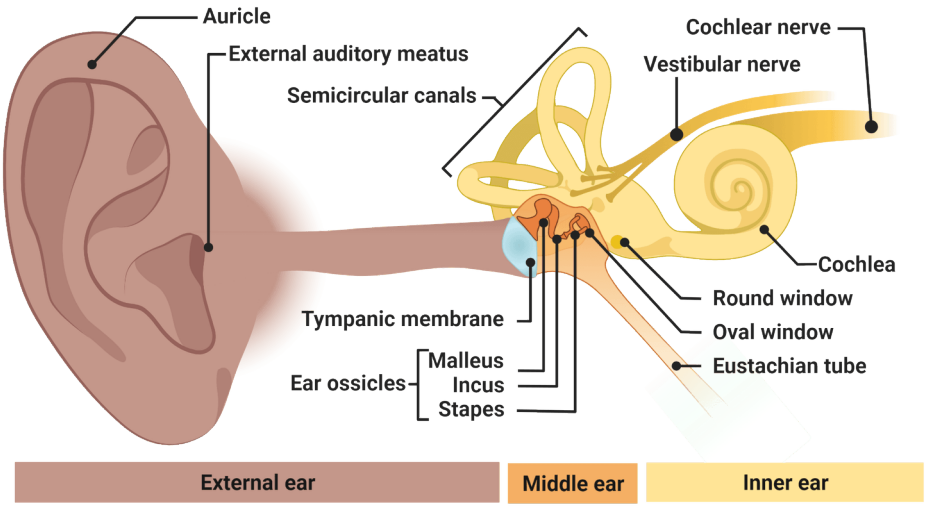


Figure 7.4 Ear anatomy Ear anatomy

External ear

When someone is asked to point to their ears, they will usually indicate their auricles, structures of skin and cartilage on either side of their head. The shape of the auricles (also called pinna), differs greatly among species. Some species, like cats, can manipulate the shape of their pinna using muscles on the skull, while many other species, including most birds, amphibians, and reptiles, have no pinna at all.

The auricle serves two functions. The first is to funnel acoustic waves into the external auditory meatus (ear canal). This amplifies the waves by compressing them into a smaller opening, increasing the sensitivity of hearing by up to 10 dB. The second function is to aid in localizing sound sources. The ridges and folds in the auricle create resonant cavities that filter out specific frequencies that depend on the direction from which the sound is coming. As a simple experiment, filling the cavities of the auricles with modeling clay makes it considerably more difficult to tell where a sound is coming from with your eyes closed (Oldfield and Parker 1984).

Middle ear

Separating the external auditory meatus from the middle ear cavity is the tympanic membrane, a thin sheet of tissue. Like the tightly stretched surface of a drum, the tympanic membrane vibrates in response to acoustic waves in the ear canal. As compressed air reaches the membrane, it pushes it inward, because the pressure in the ear canal is slightly higher than the pressure in the middle ear. Similarly, when the air in the ear canal is at a lower pressure (rarefied), the tympanic membrane is pushed outward by the air in the middle ear.

In order for the tympanic membrane to vibrate effectively, the static pressure in the ear canal and the middle ear cavity need to be equal. The external atmospheric pressure depends on altitude, and a rapid change of altitude, as in a descending or ascending airplane, creates an imbalance that reduces hearing sensitivity, particularly for high frequencies. The Eustachian tube, which connects the middle ear to the oral cavity, allows the balance to be restored. Sometimes it is necessary to encourage the Eustachian tube to open by "popping your ears". A bad cold or sinus infection can cause the Eustachian tube to close. This results in a persistent imbalance that can be acutely painful and even cause damage to the tympanic membrane. Infections of the middle ear, called otitis media, can cause the middle ear cavity to fill with fluid, causing a pressure imbalance if the fluid is unable to drain through the Eustachian tube.

In mammals, the middle ear cavity contains three bones: the malleus (hammer), the incus (anvil) and the stapes (stirrup). These bones are the smallest in the human body. Their function is to transmit the vibrations of the tympanic membrane to the inner ear, specifically the oval window of the cochlea. The middle ear bones form a mechanical lever that compensates for the large difference in the impedance of the air in the ear canal and the fluid inside the cochlea. As illustrated in Figure 7.5, when air is on both sides of a barrier like the tympanic membrane, acoustic energy is efficiently transferred from one side to another because the molecules have the same size and density. They collide like billiard balls: one ball comes to a stop while the other absorbs its momentum and moves on with the same speed. However, when an acoustic wave in air collides with a fluid, the water molecules are densely packed, and much of the energy is reflected, like ping-pong balls bouncing off a bowling ball. The ear compensates for this impedance mismatch through mechanical advantage. The tympanic membrane has a surface area around ten times the size of the oval window. Its vibrations are captured by the stiff middle ear bones, which add further mechanical advantage by acting as levers. Without the middle ear, only a thousandth of the energy in airborne acoustic waves would make its way into the fluid filling the cochlea (Wever and Lawrence 1948).

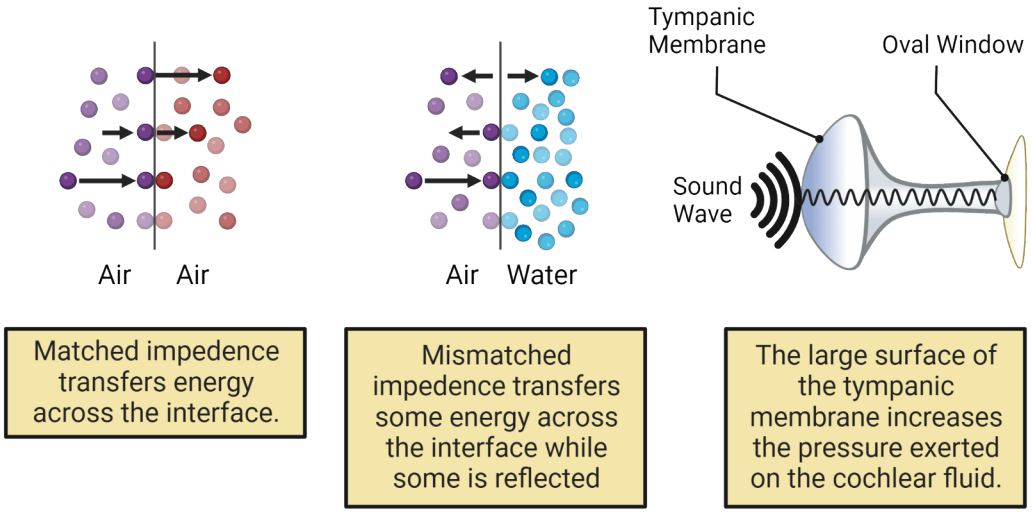


Figure 7.5 Acoustic impedance

The impedance-matching of the middle ear can be compromised by buildup of scar tissue from repeated middle ear infections or by immobilization of the ligaments supporting the middle ear bones. This condition can result in a severe loss of hearing.

The middle ear also contains two muscles that attach to the middle ear bones, the tensor tympani and the stapedius (Figure 7.6). These muscles adjust the tension of the tympanic membrane and the stiffness of the connection between the incus and stapes, respectively. These muscles allow the brain to control the gain of the middle ear. The stapedius reflexively contracts in response to high-intensity sounds and during self-vocalizations, causing a reduction in transmission through the inner ear by up to 25 dB

(Pang and Peake 1986; Rosowski 1991). This reflex is an important protection against the damage that intense sounds can do to the inner ear, but like every reflex, there is some delay. Very sudden sounds like gunshots can therefore do significant harm.

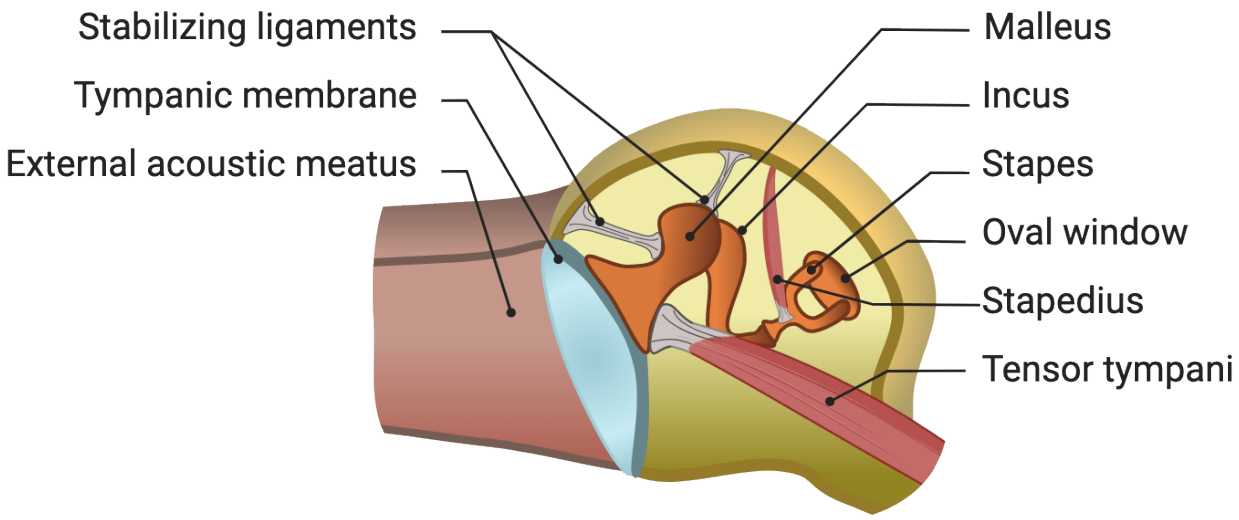


Figure 7.6 Acoustic reflex The stapedius muscle contracts in response to loud noises, attenuating sound transmission through the middle ear.

Inner ear

The inner ear is a hollow bony structure that contains epithelial tissue and fluid. It comprises the cochlea, which is involved in hearing, along with the semicircular canals, the utricle, and the saccule, which are part of the vestibular system. The cochlea gets its name from the Greek for “snail” because it is shaped like a spiral (in mammals).

Cochlea

The interior of the cochlea (Figure 7.7) has a circular cross-section, divided into three fluid-filled compartments that run the length of the cochlear duct: the scala vestibuli, the scala media, and the scala tympani. The scala vestibuli begins at the base of the cochlea at the oval window, a membrane-covered opening that contacts the foot of the stapes. It connects to the scala tympani at the apex, the tip of the innermost spiral of the cochlea. The scala tympani terminates at the base of the cochlea in the round window, another membrane-covered opening. The fluid found in the scala vestibuli and scala tympani is called the perilymph. The scala media is a separate compartment filled with a different fluid called endolymph.

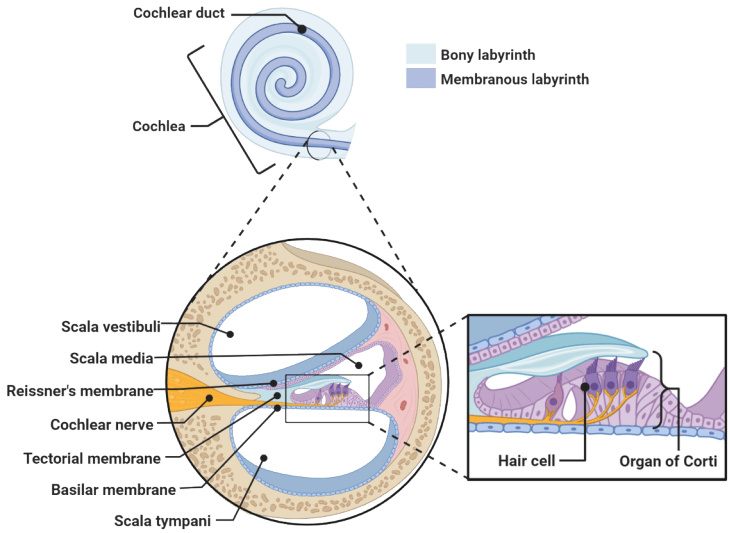


Figure 7.7 Inner ear and cochlea

Basilar membrane

Acoustic waves enter the cochlea through the oval window via the stapes. As the stapes vibrates in and out, it pushes and pulls on the perilymph in the scala vestibuli and scala tympani, which in turn displaces the membrane covering the round window. Some of the energy of this wave, however, is absorbed by the basilar membrane, which stretches between the two walls of the cochlear duct and is able to move up and down. The basilar membrane varies systematically in thickness and width over its length. It is thickest and narrowest at the base and thinnest and widest at the apex (Figure 7.8). These physical properties translate into tuning for different frequencies, a phenomenon called resonance. Near the base, the basilar membrane resonates at high frequencies, around 20,000 Hz. Vibrations in the acoustic wave at these frequencies are absorbed into vertical displacements of the basilar membrane, while the lower-frequency components continue to travel down the scala vestibuli. The resonance of the basilar membrane becomes progressively lower, to about 20 Hz at the apex, so as the acoustic wave travels toward the apex, each segment of the basilar membrane absorbs energy at its resonant frequency (von Békésy G 1960; Rhode 1971).

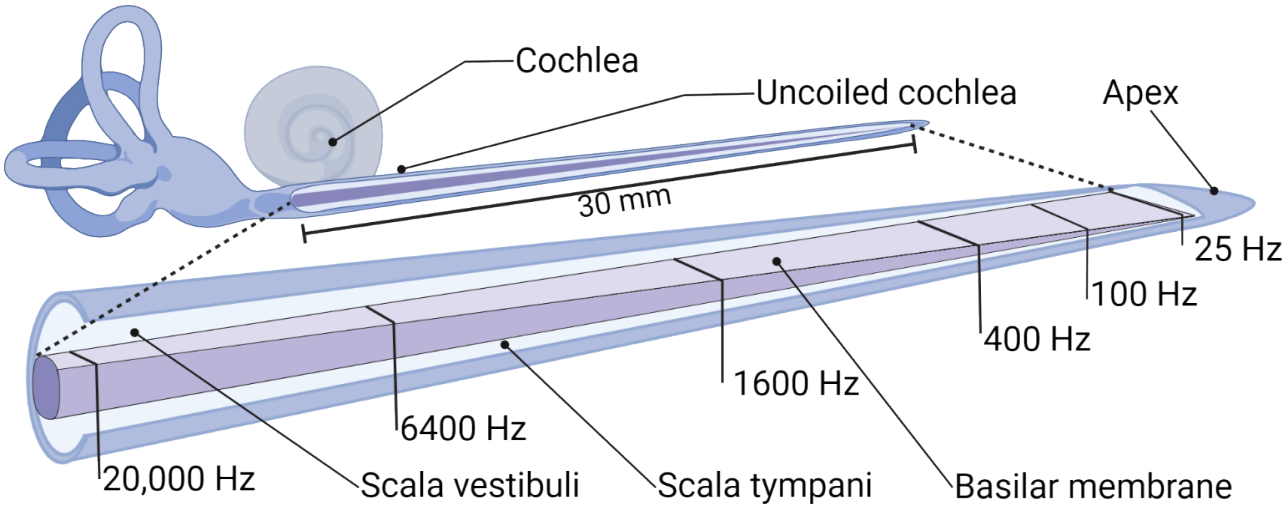


Figure 7.8 Unrolled cochlea

Take a moment to notice in Figure 7.8 how the frequencies are spaced along the basilar membrane. About half of the length is dedicated to the frequencies between 25 and 1600 Hz; the other half goes from 1600 to 20,000 Hz, a much larger range. In other words, the relationship between frequency and position is not linear but (approximately) logarithmic. This organization may be

related to how frequencies in a harmonic series are spaced logarithmically (i.e., integer multiples of the fundamental frequency). In humans, it may also reflect the fact that most of the information in speech is carried by relatively low frequencies (see 7.3 How Does the Brain Process Acoustic Information?).

Although the physical principles are different, the way the basilar membrane separates complex sounds into waves of different frequencies is analogous to the way a prism can separate white light into its component frequencies (or colors). It is an essential first step in how the brain analyzes complex sounds. The organization of frequency (a non-spatial property of the sound) along the axis of the basilar membrane (a spatial dimension) is an example of topography. Because the ear contains a map of frequency, this topography is also known as tonotopy.

On top of the basilar membrane sits the organ of Corti, the epithelial membrane that transduces mechanical movements of the basilar membrane into neural impulses. The organ of Corti comprises four rows of hair cells along with a large number of various kinds of support cells. Hair cells are characterized by stereocilia arranged in a stairstep bundle that protrudes into the endolymph filling the scala media (Figure 7.9; . The organ of Corti is attached at one side to the tectorial membrane, forming a hinge. The tectorial membrane is a gelatinous structure that floats just above the tips of the hair cells' stereocilia.

There are two types of hair cells in the organ of Corti. The inner hair cells form a single row nearest the hinge with the tectorial membrane. They are responsible for sensing the movement of the basilar membrane and transducing those movements into neural impulses. The other three rows are the outer hair cells. Their function is not to sense movement, but to help amplify low-intensity sounds.

Inner hair cells

The inner hair cells are in many ways the most important cells in the auditory system, because they are the sole point at which the physical energy of acoustic waves is converted into the electrochemical signals used by the nervous system. On one end, called the apical end, are the stereocilia, whereas the basal end makes a synapse with an afferent terminal from a single bipolar neuron in the spiral ganglion. There are about 3500 inner hair cells in the human cochlea.

As the basilar membrane vibrates up and down, the tectorial membrane slides back and forth in the transverse direction. The fluid between the organ of Corti and the tectorial membrane tends to remain stationary because of inertia, causing the stereocilia of the inner hair cells to deflect toward and away from the hinge. The tips of the inner hair cell stereocilia contain ion channels that are physically attached to the next-tallest cilium by a tip link. As illustrated in Figure 7.10, deflection of the stereocilia toward the taller edge of the bundle puts tension on the tip links, opening the ion channels and permitting potassium and calcium ions to enter the cell from the endolymph. This depolarizes the cell, causing voltage-gated calcium channels at the basal end of the hair cell to open, which in turn causes synaptic vesicles to fuse with the plasma membrane and release neurotransmitter into the synapse. Deflection of the stereocilia in the other direction relieves tension on the tip link, closing the ion channels, hyperpolarizing the cell, and stopping neurotransmitter release (Hudspeth 1985; Fettiplace 2017).

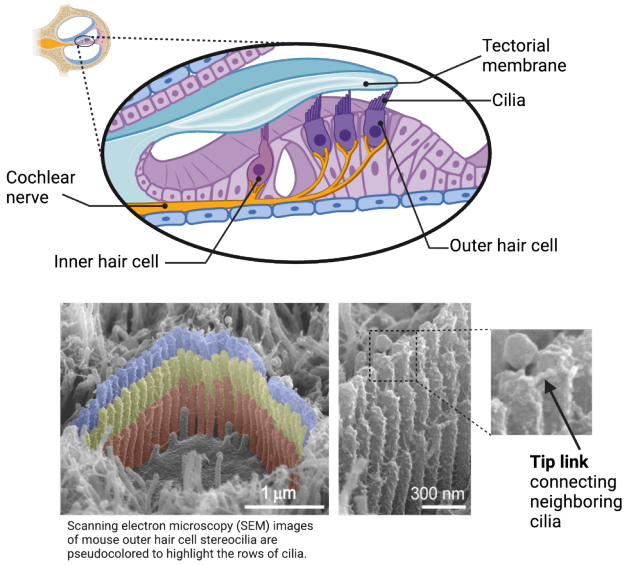


Figure 7.9 SEM of cilia Image credit: SEM cilia images from: Velez-Ortega et al., 2017, eLife https://elifesciences.org/articles/24661. CC BY 4.0.)

The transduction process in inner hair cells is exceptionally sensitive and fast. Sounds at the threshold of hearing produce basilar membrane movements of about 0.1 nm, about the diameter of a hydrogen atom, and movements of the stereocilia may be even smaller. The membrane potential of the hair cell responds to stereocilia deflection in as little as 10 µs, and a specialized ribbon synapse (Figure 7.10) allows neurotransmitter to be rapidly released onto the afferent fiber. The speed and fidelity of neurotransmission allows auditory nerve fibers to track frequencies as high as 1000 Hz or more, firing only at a specific phase of a periodic sound (Dynes and Delgutte 1992). Phase-locking is critical to one of the mechanisms the brain uses to determine the direction of a sound.

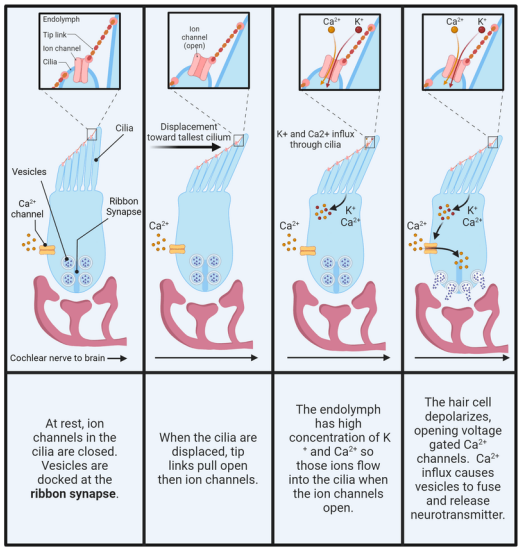


Figure 7.10 Tip link channel transduction

Outer hair cells

The other three rows of hair cells in the organ of Corti comprise the outer hair cells. Outer hair cells have a similar appearance to inner hair cells, but serve a different function. Whereas the inner hair cells primarily receive afferent connections that carry neural signals into the brain, the outer hair cells primarily receive efferent connections carrying signals out from the brain. When an outer hair cell is stimulated, either by deflection of its stereocilia or by synaptic transmission from efferent fibers, it changes its shape. This electromotive response, which is generated by the molecular motor prestin, can occur at frequencies up to 50 kHz,

among the fastest cellular movements known (Zheng et al., 2000). Because the stereocilia of outer hair cells are embedded in the tectorial membrane, these movements are translated into the basilar membrane. This allows the brain to selectively amplify very weak sounds at specific frequencies (Dallos 1992). This is one of the major reasons why we are able to detect extremely low-intensity sounds. However, as anyone who has heard what happens when a microphone is placed directly in front of a loudspeaker can attest, amplifiers are sensitive to overstimulation. This means that the outer hair cells are easily damaged, leading to hearing loss.

Developmental Perspective: Noise, hearing loss, and tinnitus

Hearing loss affects one in eight people aged 12 and older in the US (Lin et al., 2011). Many of these cases are termed conductive hearing loss, because they are related to deficits in how acoustic energy is transmitted from the air to the cochlea. Common causes of conductive hearing loss include occlusion of the ear canal, damage to the eardrum, otitis media, and damage or congenital defects in the middle ear bones. Other cases may involve damage to a component of the nervous system, such as hair cells in the inner ear, the auditory nerve, or an auditory area of the brain. These are termed sensorineural hearing loss. In humans and other mammals, hair cells cannot regenerate, so sensorineural hearing loss is almost always progressive and irreversible (Wagner and Shin 2019). Exposure to excessive noise is one of the most common causes of damage to hair cells. This damage can be easily prevented with appropriate hearing protection. High-intensity acoustic waves cause large displacements of the basilar and tectorial membranes, generating shearing forces strong enough to break tip links, which can be repaired, even in mammals, or loss of stereocilia, which cannot. Blows to the head, aging, genetic defects, and certain ototoxic drugs (including some antibiotics), can also damage hair cells. Outer hair cells are particularly sensitive to noise-induced hearing loss, perhaps because of electromotive feedback or because their tips are directly embedded in the tectorial membrane. Loss of outer hair cells not only makes it more difficult to hear low-intensity sounds, but also impacts the ability to understand speech in noisy conditions, because the brain is no longer able to selectively amplify specific frequencies of interest. Thus, although hearing aids can correct for some of the loss of sensitivity, they are less effective at restoring intelligibility.

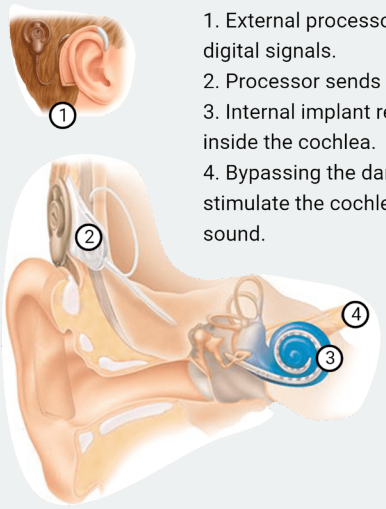
Exposure to intense noise can also produce a hearing disorder called tinnitus, a perception of a tone or buzzing sound in the absence of an external stimulus. Although the mechanisms of hearing-loss-related tinnitus remain unclear, one hypothesis is that the illusory tones are the result of overcompensation by central brain areas for regions of the organ of Corti where hearing loss has occurred (Knipper et al., 2021).

Neuroscience in the Lab

Cochlear implants

Most cases of deafness are caused by conductive hearing loss, by sensorineural damage to hair cells, or by a combination of the two. What if it were possible to bypass these parts of the ear and directly stimulate the afferent auditory nerve fibers? In recent decades, the technology to do just that has restored hearing for hundreds of thousands of individuals, including some who were unable to hear from birth.

A cochlear implant consists of two main parts (Figure 7.11). A thin array of electrodes is surgically implanted in the cochlear partition, close to the afferent terminals of the auditory nerve. When an electrical pulse is delivered to one of these electrodes, it depolarizes the axons directly, causing them to generate action potentials that travel into the brain. Electrodes near the base of the cochlea activate the axons associated with high frequencies, while electrodes near the apex activate the axons associated with low frequencies.



1. External processor captures sound and converts it into digital signals.
2. Processor sends digital signals to internal implant.
3. Internal implant relays the signal to an electrode array inside the cochlea.
4. Bypassing the damaged hair cells, the electrodes stimulate the cochlear nerve and the brain perceives the sound.



A child wearing a cochlear implant

Figure 7.11 Cochlear implant Image credit: Cochlear implant image modified from by BC Family Hearing www.bcfamilyhearing.com/%20my...lear-implants/, CCBY-SA 4.0,commons.wikimedia.org/w/inde...curid=48252363; Child image from Image by Matt Ralph - Flickr, CC BY 2.0

The second part of the implant is a controller placed outside the skull. It has a microphone to sense acoustic waves, and a digital processor that separates the acoustic signal into its component frequencies and converts the signal in each frequency band into a sequence of electrical pulses that are sent to the appropriate electrode.

Cochlear implants are an almost miraculous technology. They enable many individuals to more fully participate in societies that place great emphasis on verbal, acoustic communication. Deaf children who are fitted with implants early in life, before the onset of sensitive periods for learning the acoustic structure of speech, can achieve close to normal language development (Kral and Sharma 2011). Cochlear implants are not without their limitations, however, and research continues to improve their sensitivity and fidelity. As of this writing, typical cochlear implants have around 12–24 electrodes (Dhanasingh and Jolly 2017). This is much less than the approximately 3500 inner hair cells, so each electrode stimulates a large number of fibers and the spectral resolution is low. Fortunately, much of the information in speech is contained not only in which fibers are activated, but also in their rate and relative timing. Because of this, the sophisticated signal processing in cochlear implants is generally able to produce an intelligible percept of speech. Other kinds of signals for which the ability to resolve distinct frequencies is critical, like music, remain difficult for cochlear implants to transmit to the brain with fidelity (Fowler et al., 2021). Another limitation of cochlear implants is the absence of the dynamic amplification provided by outer hair cells, which impairs intelligibility of speech in noisy conditions or when there are multiple speakers.

Ascending auditory pathways

After the inner hair cells of the organ of Corti have transduced the mechanical deflection of their hair bundles into the release of neurotransmitter, the auditory stimulus propagates as neural impulses through a number of brain regions and fiber tracts on its way to the cerebral cortex. This ascending pathway is more complex than the pathways for other sensory systems, so there are more names and connections to learn. One reason for this complexity may be that information about the location of sound sources, arguably one of the most important tasks for the auditory system's function in predator avoidance, needs to be extracted from the stimulus early on.

This section will focus on the anatomy of the classical ascending auditory pathway, the most prominent and best studied route by which auditory information enters the brain (Figure 7.12). Although we may briefly note the function of some brain regions and pathways, a full discussion of the physiology and neural computations will be deferred to 7.3 How Does the Brain Process Acoustic Information?.

Auditory nerve

The inner hair cells form synapses with the dendrites of auditory nerve cells, which are bipolar neurons with their cell bodies in

the spiral ganglion, a thin strip of gray matter within the spiraling interior wall of the cochlea. The axons of these cells course together in the center of the cochlea to form the auditory branch of cranial nerve VIII. The auditory nerve also contains many efferent axons descending from the brain to the cochlea; these primarily make synapses with the outer hair cells.

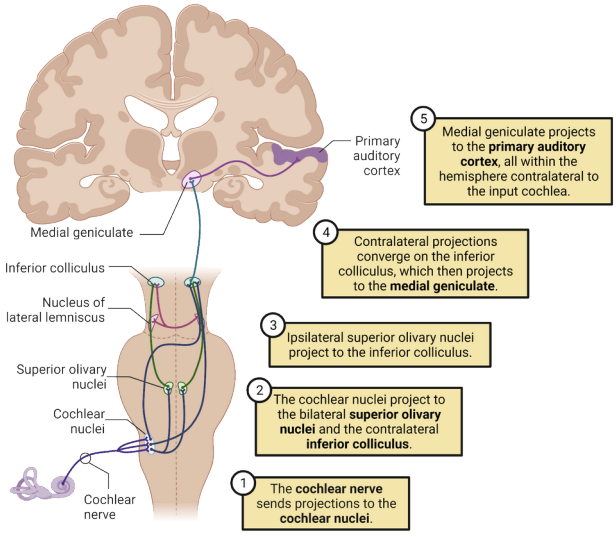


Figure 7.12 Central auditory pathways

Cochlear nucleus

All of the afferent axons in the auditory nerve terminate in the cochlear nucleus, located right at the junction between the medulla and the pons. The cochlear nucleus has three subdivisions: dorsal, posterior ventral, and anterior ventral. Each auditory axon branches twice to make synapses in all three subdivisions. The tonotopic organization of the cochlea is preserved in these projections, resulting in three complete maps of frequency within the cochlear nucleus, one per subdivision (Figure 7.13). Almost all of the stations in the classical auditory pathway have a complete tonotopic map.

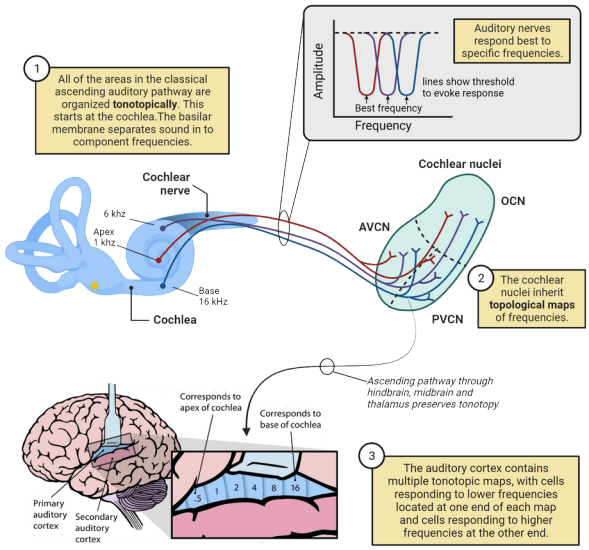


Figure 7.13 Tonotopic oragnization auditory cortex Image credit: Primary auditory cortex image from: Chittka L. and Brockmann A. - Perception Space—The Final Frontier, A PLoS Biology Vol. 3, No. 4, e137 doi:10.1371/journal.pbio.0030137 ([1]/[2]), CC BY 2.5, https://commons.wikimedia.org/w/inde...?curid=5929021

The neurons within the cochlear nucleus give rise to three major output pathways that cross the midline and then ascend up the brainstem through a bundle of axons called the lateral lemniscus.

Superior olivary complex

The superior olivary complex is the first station in the auditory pathway that receives input from both ears. It is located in the pons and comprises three main nuclei: the medial superior olive (MSO), the lateral superior olive (LSO), and the nucleus of the trapezoid body (NTB). These areas primarily receive input from the cochlear nucleus, and all three are involved in determining the location of sound sources using differences in the timing and level of stimuli arriving at the two ears.

Lateral lemniscus and nuclei

The lateral lemniscus is a tract that includes axons from ipsilateral and contralateral cochlear and superior olivary complex nuclei. Some of these axons form synapses in the nucleus of the lateral lemniscus (NLL), while others continue to ascend to the inferior colliculus.

Inferior colliculus

All the axons in the lateral lemniscus terminate in the inferior colliculus, the first midbrain auditory area and a major relay station. There are three major auditory areas within the inferior colliculus: the central nucleus, the external nucleus, and the cortex. Only the central nucleus is considered to be part of the classical pathway. Its main output is via the brachium of the inferior colliculus to the medial geniculate body, a nucleus in the thalamus. The central nucleus of the inferior colliculus also projects to the superior colliculus, an important midbrain area that integrates auditory, visual, and somatosensory input to create a unified map of space relative to head location. This map facilitates rapid orientation of the eyes and head to startling sounds.

Medial geniculate body

The medial geniculate body is a nucleus in the dorsal thalamus, and is the primary gateway for auditory information to reach the cerebral cortex. As such, it plays an important role in suppressing these inputs during sleep and boosting them during arousal. Like the inferior colliculus, the medial geniculate body has three main subdivisions: dorsal, ventral, and medial. Only the ventral medial geniculate body is considered to be part of the classical pathway. It receives input from the ipsilateral central inferior colliculus and sends its output to the ipsilateral auditory cortex, the primary auditory cortex.

Auditory cortex

Ascending auditory information in the classical pathway reaches the cerebral cortex in a region called primary auditory cortex, or A1. In humans, this area is located in the temporal lobe. As in other primary sensory areas, thalamic afferents primarily form synapses in layer 4. There are also inputs from the medial geniculate body onto two neighboring areas, secondary auditory cortex, and auditory association cortex.

The primary auditory cortex and its neighboring areas (sometimes called the core) together make up the first stage in a hierarchy of cortical areas. They each have a tonotopic map representing the full range of audible frequencies, and receive input from both ears. The core is surrounded by secondary cortical areas that receive auditory input via the core and also show tonotopic organization (shown in the bottom portion of Figure 7.13). The secondary areas are heavily interconnected with each other, and appear to be involved in processing more complex acoustic features and in storing auditory memories. The secondary areas project to higher-order sensory association areas that receive input from more than one sensory modality (e.g., visual and auditory) and, in humans, to areas that are specialized for perception and production of speech. These higher-order areas project back to primary and secondary auditory areas. These top-down connections feed back information about context that can help parse complicated scenes by suppressing specific frequency bands and boosting others.

Bilateral processing and descending pathways

Auditory perception is inherently binaural, because one of its most essential and probably primitive functions is to localize acoustic cues. As we will see, this requires input from both ears. It is therefore unsurprising to find many connections between the hemispheres at multiple levels of the auditory pathway. For example, the cochlear nucleus not only makes connections to the superior olivary complex on the same side of the brain (ipsilateral), it also projects to structures on the opposite (contralateral) side of the brain, including the contralateral cochlear nucleus, superior olivary complex, nucleus of the lateral lemniscus, and inferior colliculus. There are also cross-hemisphere connections (called commissures) in the midbrain and in the cortex. One

consequence of this extensive interconnection between hemispheres is that damage to one hemisphere of the auditory system, such as lesions caused by strokes, typically do not result in deafness on either side, though there may be deficits in localization.

Many of the ascending connections discussed in this section are paralleled by descending connections, axons traveling in the opposite direction from cortex to periphery. Indeed, descending connections from cortex to thalamus and other lower stations can far outnumber the ascending ones (Winer et al., 1998; Winer et al., 2001). These connections can modulate processing at almost every level down to the cochlea, where dynamic control of outer hair cells is thought to support dynamic amplification and filtering of signals of interest (de Boer et al., 2012).

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6.2.3: How Does the Brain Process Acoustic Information?

Learning Objectives

By the end of this section, you should be able to

- Describe how circuits in the auditory system determine the location of sound sources by comparing the inputs arriving at each ear.
- Relate the physical characteristics of sounds to auditory perception.
- Describe how speech perception changes in early childhood and the role of experience-dependent neural plasticity in this process.

It is remarkable to consider how the flapping of a mosquito's wings can set in motion a process that involves thousands if not millions of neurons. We have traced the pathway this process takes from the outer ear to the cerebral cortex, exploring the exquisitely sensitive mechanisms for amplifying acoustic waves, breaking them down into component frequencies, and converting them to neural impulses. We have followed these impulses as they jump from neuron to neuron along the auditory pathway, crossing the midline one or more times. This process is not just the passive transmission of information, however: at each station in the pathway, signals are filtered, refined, and compared between ears. This section will explore the complicated relationship between acoustic properties and perception.

Location

One of the most important functions of the auditory system is to locate nearby animals. If the other animal is a predator, knowing its location may enable it to be escaped. If the other animal is prey, knowing its location may allow it to be captured. In behavioral tests, humans can reliably pinpoint the location of sound sources to within several degrees (Oldfield and Parker 1984). The acuity of sound localization is highest in front of the head along the horizontal axis. In our own experience, the reflexive turning of the head to look at an unexpected sound is so natural and automatic, it may be difficult to appreciate how difficult the underlying calculations are. Yet evolution has solved this problem with incredible precision.

Interaural timing and level differences

The fact that animals have two ears is not simply a consequence of bilateral symmetry. Depending on the location of a sound source, the two ears will receive slightly different inputs. By comparing the inputs between the ears, the brain is able to determine the location of the source.

When we discuss auditory spatial cues, we are referring to location relative to the head (Figure 7.14). More specifically, what the brain needs to determine is the angle of the source relative to some reference direction, which by convention is usually taken to be the front of the head. The angle of the source has two components: the azimuth, which is the angle to the left or right on a horizontal plane, and the elevation, which is the angle up or down from that plane. Because the ears are separated from each other by the head along the plane of the azimuth, the azimuth of a sound source will affect the relative level and timing at which the sound reaches each ear.

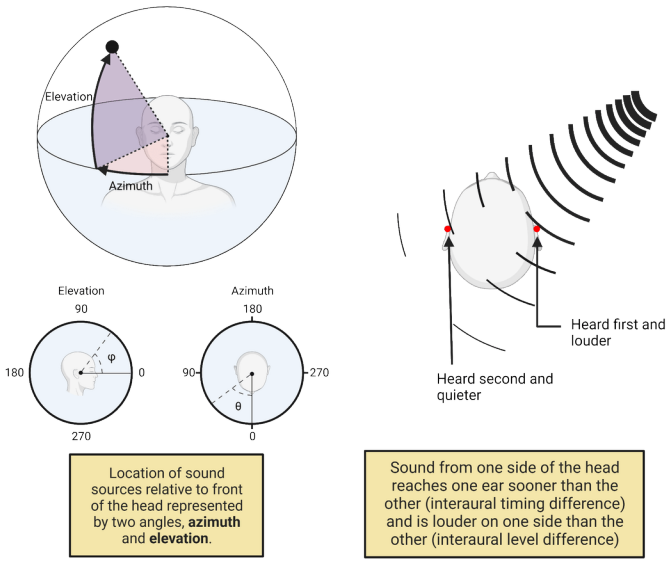


Figure 7.14 Locating sources of sound

Level differences between the ears arise because the head casts an acoustic shadow. Incoming sound waves tend to reflect off the head or to be absorbed by it, so the ear that is closer to the sound source will receive pressure waves with a higher amplitude. This effect is more pronounced for higher frequencies, because low-frequency sounds can more easily transmit through the head and diffract around it. The interaural level difference is greatest when the sound source is 90 degrees to the left or the right, and zero when it is directly in front of (0 degrees) or behind (180 degrees) the head.

Timing differences between the ears arise because the speed of sound is finite (343 m/s at sea level). At 90 degrees azimuth, the distance between the ears in humans is around 0.2 m, corresponding to a delay of about 600 µs. By comparing the timing at which sound arrives at the two ears, it is possible to determine its azimuth. For transient sounds, this comparison involves the difference between the times when the pressure wave's onset arrives at either ear. This difference is called the interaural time delay. Interaural time differences are more relevant cues for the location of low-frequency sounds, whereas interaural level differences are more important at high frequencies.

The elevation of a sound source does not produce interaural differences in level or timing. Nevertheless, humans and many other species can determine the elevation of sound sources thanks to the irregular shape of the auricles. The cavities and ridges of the auricle create resonances that selectively amplify some frequencies while dampening others, creating "notches" in the sound spectrum. These resonances depend on both the elevation and azimuth of the sound source (Oldfield and Parker 1984). Thus, by determining where there are notches in the sound spectrum, it is possible for the brain to determine elevation.

The cues for distance are subtle, and much less is known about how this percept is formed (Kolarik et al., 2016). Without any obstacles, sound attenuates with the square of the distance, so there is no difference in intensity between a source two meters away from one that is twice the distance but four times the amplitude. However, sounds coming from greater distances have the opportunity to interact with more objects, resulting in greater reverberance. It is likely that the perception of distance relies on such cues.

Neural circuits involved in decoding location

The superior olivary complex is the primary brain structure involved in determining azimuthal location. The medial superior olive compares timing between the two ears, whereas the lateral superior olive compares levels between the ears (Figure 7.15).

Top: Left: Line graph od Response v ITD in micro-seconds, showing an oscilating wave. Right: a diagram of a section of brainstem with pathways from the right and left cochlea to the AVCN, which then project to the MSO. Bottom: Left: Line graph od #spikes v ILD in decibels with I

Figure 7.15 Neural circuits for decoding sound location

One of the earliest models for how the brain might calculate timing differences is the coincidence detector. As proposed by Jeffress (1948), if a neuron receives input from both ears, neither of which alone is enough to make it spike, then it will only fire

when the two inputs are active coincidently (i.e., at the same time). If the pathways from the ipsilateral and contralateral ear are the same length, then coincidence will only occur when the sound arrives at both ears simultaneously, from directly in front (0 degrees) or behind (180 degrees). If the ipsilateral pathway is slightly shorter, then the neuron will respond best when the input arrives at the contralateral ear slightly before the ipsilateral one. By systematically varying the relative lengths of the axons, an array of such coincidence detectors would be able to represent timing differences as a place code, much as different frequencies are represented in a tonotopic map. In birds, the medial superior olive appears to implement just such a detector (Figure 7.16). It receives inputs from the contralateral and ipsilateral cochlear nucleus, and the incoming axons, in many species, branch to form an orderly array, with the shortest paths from the ipsilateral side at one end and the longest paths at the other. In further support of this model, electrophysiological recordings from the medial superior olive reveal that neurons in this area respond preferentially to specific interaural time differences (Joris et al., 1998). The calculation of interaural time differences in mammals uses a similar principle, but is implemented differently (Lesica et al., 2010).

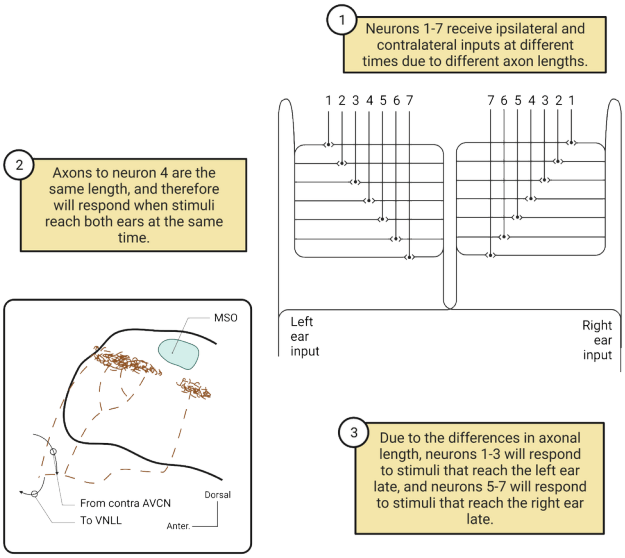


Figure 7.16 A model of coincidence detection for sound localization

Differences in level between the two ears are computed by the lateral superior olive, which receives excitatory input from the ipsilateral ear and inhibitory input from the contralateral ear (via the nucleus of the trapezoidal body). The firing rates of these inputs are proportional to the sound level in each ear. Neurons in the lateral superior olive add together the excitatory (positive) and inhibitory (negative) inputs, so their firing rate represents the difference in the sound level between the ears.

Spatial information from the superior olivary complex propagates forward through the auditory pathway, and as it does, inputs from the medial and lateral superior olive combine to integrate information about timing and level differences. This results in a coherent, unitary perception of sound location.

Perceptual contents

In addition to determining the locations where sounds originate, the auditory system also has to determine what is making the sounds. These complex identifications are based on patterns of simpler spectral and temporal features of the sounds. In other words, we can describe complex sounds like “bird singing” or “lion roaring” in terms of simpler perceptual features. In this section, we will examine some of these perceptual features and how they relate to the physical properties of the sound, then describe some of the neural circuits involved in decoding these features.

Loudness, pitch, and timbre

In 7.1 Acoustic Cues and Signals, we learned that acoustic waves can be described in terms of three quantities: amplitude, frequency, and phase. Simple, sinusoidal sounds have a single value for each of these quantities. Complex sounds are combinations of simple sinusoids, which means that they can be described as a spectrum of frequencies, each with its own amplitude and phase. The basilar membrane decomposes complex sounds into their constituent frequencies, but how are these complex patterns of activation perceived?

Acoustic amplitude (or intensity) is perceived as loudness. Sounds with higher amplitudes sound louder. The relationship between physical amplitude and perceived loudness is geometric (also called logarithmic), which means that proportional increases in amplitude are perceived as linear increments in loudness. Because intensity is usually reported using the logarithmic decibel (dB) scale (see Table 7.1), a linear step in decibels of intensity corresponds to a linear step in perceived loudness. In other words, the perceived difference in loudness between a 65 dB tone and a 75 dB tone is the same as the perceived difference between a 70 dB tone and an 80 dB tone. This relationship only holds if the cochlea is healthy and undamaged, and if the intensity is within the range of human hearing. Below 0 dB, sounds are inaudible, and above 120 dB, the perception of loudness is distorted by saturation (i.e., overstimulation) of the physical and neural processes of transduction.

Frequency is perceived as pitch. Similarly to loudness, this is a geometric relationship. A doubling of frequency corresponds to a perceived pitch interval of one octave, regardless of where you are on the musical scale.

Periodic sounds usually contain multiple frequencies. It is very rare to hear pure sinusoidal tones. When physical objects vibrate, they often produce a harmonic series. consisting of frequencies that are integer multiples of the lowest frequency. Such sounds are perceived as having a pitch corresponding to the lowest frequency in the series, the fundamental frequency. The numerical relationship between harmonics influences the perception of tonality, or how different pitches sound in relation to each other. For example, tones that are an octave apart sound “the same” because the harmonics of the higher note overlap completely with the harmonics of the lower note.

The higher harmonics (also called overtones) are not heard as distinct tones, but instead influence perception of timbre. Timbre is a qualitative rather than a quantitative percept (McAdams 2019). It may be difficult to describe how a clarinet sounds in words, but it is easy to distinguish it from a violin or a French horn, even when they are playing notes of the same pitch. This is because, as illustrated in Figure 7.18, the relative distribution of amplitude in the harmonics a clarinet produces is different from the distribution of amplitude in the same harmonics produced by a violin.

Surprisingly, the perception of pitch does not require hearing the fundamental frequency. Even when the fundamental frequency is filtered out from a note, listeners perceive the sound as having the same pitch (Plack and Oxenham 2005). This observation clearly shows that the perception of pitch is constructed by the auditory system and that it requires neural circuits to integrate information across multiple frequencies.

Neuroscience in the Lab

Psychoacoustic experiments

The study of how physical properties of acoustic stimuli relate to perception is called psychoacoustics. It is a branch of a broader field called psychophysics. Although psychoacoustics does not directly examine the brain, it has yielded many important insights into how the brain processes sound purely by examining behavior.

Psychoacoustic experiments require precise control over how stimuli are presented. They usually take place in specially constructed acoustic isolation chambers that strongly attenuate extraneous sounds. Stimuli are generated by computer programs that can synthesize sounds or manipulate digital recordings. Computers are also used to control presentation of different stimuli and to record the subject’s responses, which usually involve pressing keys rather than making qualitative descriptions. Human subjects can be instructed about how to respond, but nonhuman animals can also be used in psychophysics using operant conditioning or other forms of behavioral training.

Figure 7.17 illustrates two common psychoacoustic paradigms.

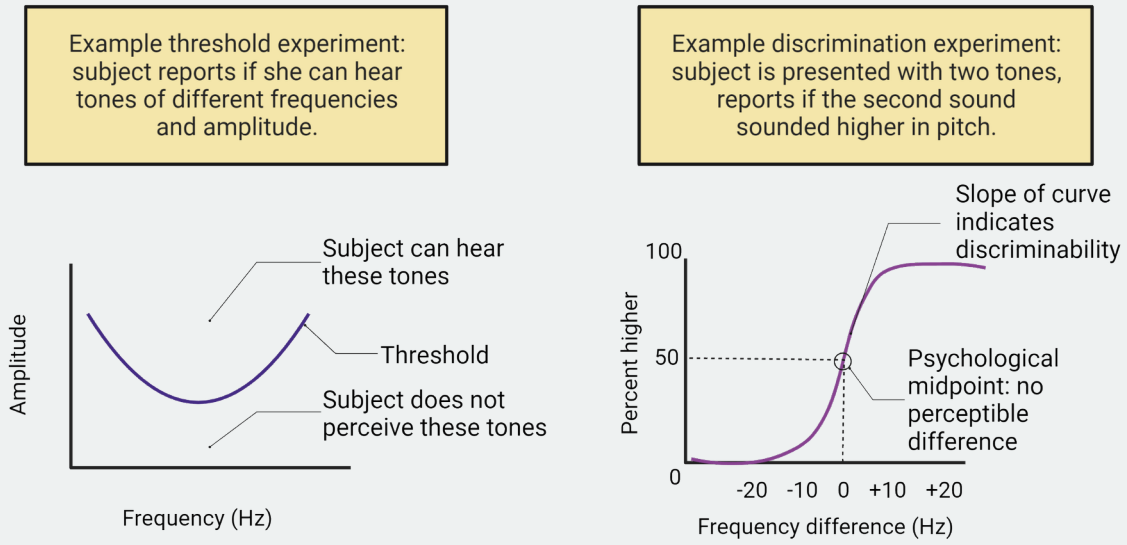


Figure 7.17 Psychoacoustic experiments

In a threshold experiment, subjects report whether they can hear a stimulus or hear the difference between two stimuli. A threshold plot is used to show the minimum value or difference required to elicit a response. In a discrimination experiment, subjects report whether stimuli belong to a group. For example, a subject might be required to indicate whether the second tone in a series is higher than the first. This type of experiment produces a psychometric curve showing the proportion of times the subject or subjects gave a specific response. Psychometric curves typically have a sigmoidal shape. The midpoint of this curve indicates the "psychological midpoint" at which the subject cannot discriminate which category the stimulus belongs to, and the slope of the curve indicates how sharply the subject discriminates between the categories.

Neural circuits decoding contents

Much less is known about how the brain decodes the perceptual contents of auditory stimuli. Natural sounds often comprise multiple frequencies and extend over time, so the neural circuits that decode contents and identify sources need to integrate over multiple frequencies and over time. Even the perception of loudness, though it primarily depends on amplitude, is not entirely straightforward. Amplitude is encoded at the earliest stages of audition. Amplitude affects the displacement of the basilar membrane and hair cell stereocilia, and the firing rate of auditory nerve fibers is proportional to amplitude. This representation of amplitude is maintained throughout the auditory pathway, with most neurons firing more rapidly to more intense stimuli. However, the perception of loudness also depends on duration. Shorter bursts of white noise sound quieter than longer bursts even when they are the same amplitude (Scharf 1978). This implies that the auditory system is keeping a memory of intensity over short intervals of time through temporal summation (or integration).

Conversely, the perception of pitch and timbre requires integration across multiple frequencies. Auditory nerve fibers are tuned to single frequencies corresponding to the region of the basilar membrane they innervate. Many neurons throughout the ascending auditory pathway share this selectivity, but increasingly larger proportions of neurons respond strongly to more than one frequency. These "multi-peak" neurons are prevalent in the auditory cortex (Winter 2005); interestingly, many of these neurons are tuned to frequencies that are integer multiples of a fundamental frequency, just like the harmonics in a complex periodic sound (see Figure 7.18). This suggests that these neurons may be involved in the perception of pitch (Wang 2013).

The auditory cortex is also likely to be the site where short-term and long-term memories of specific sounds and acoustic patterns are stored. Electroencephalography and neuroimaging studies in humans consistently show that responses to complex sounds or to deviations from expectations (a form of memory) are centered in the auditory cortex (Demany and Semal 2008) (see Methods: Electroencepahology). In nonhuman animals, training to recognize or discriminate complex sounds results in neural plasticity within the auditory cortex, implying that the memories associated with the animals' newly acquired perceptual abilities are formed within the cortex (Bao et al., 2013).

Speech and other communication signals

Acoustic communication signals are often complex, consisting of periodic and aperiodic sounds. The frequency and amplitude of these components are often dynamic, changing over time. To illustrate, Figure 7.21 shows a spectrogram of a song sparrow singing (top) and the author speaking a phrase (middle). Spectrograms are two-dimensional plots of how the spectrum of a complex sound changes over time. Frequency is shown on the y-axis, time on the x-axis, and the relative amplitude by the intensity or color of the plot. The sparrow song consists of a series of different kinds of tonal (periodic) sounds in rapid succession. Some of the tonal sounds have clear harmonics, indicated by parallel lines at integer multiples of the lowest frequency. In other sounds, there is only a single frequency, but it is rapidly modulated up or down to produce chirps and trills. The human speech consists of long tonal components, corresponding to vowels, transients spanning the whole range of frequencies, corresponding to consonants like “t”, “b”, and “k” where the flow of air is stopped by the tongue or lips, and broadband aperiodic noises, corresponding to consonants like “s” where turbulent air is passing through the teeth.

In this section, we will focus on human speech, one of the most important stimuli our auditory system has to process.

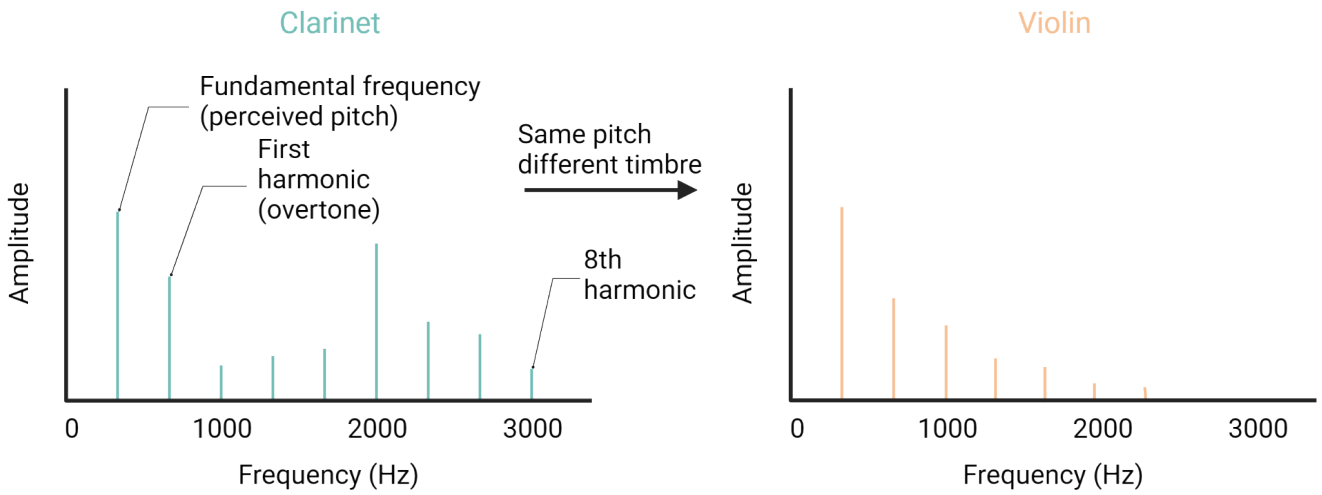


Figure 7.18 Perception of auditory features

The acoustic and phonetic structure of speech

Human speech consists of a series of periodic and aperiodic sounds. Speech sounds are produced by the movement of air through the vocal tract. The parts of the vocal tract that are moved to shape the air stream and produce speech sounds are called articulators.

The main articulator for speech is the larynx, and more specifically, the vocal folds, bands of muscle tissue in the center of the airway. In normal breathing, the vocal folds are relaxed, and air is able to pass through freely. In speaking or singing, the folds are tightened and the air pressure from the lungs increases, causing them to vibrate open and closed. This vibration, also called phonation, produces a periodic wave that forms the basis for vowels.

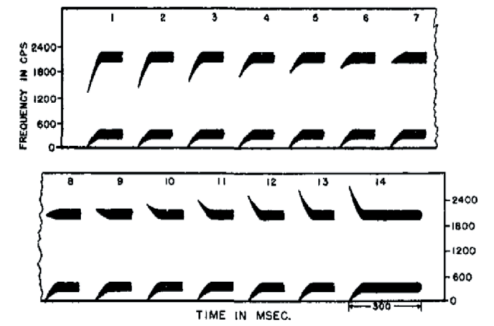
In most languages, vowels are distinguished not by the fundamental frequency of the vocal fold vibrations, but by how this sound, which is rich in harmonics, is filtered in the upper vocal tract. Positioning the tongue and lips creates cavities of different sizes and shapes. The resonances of these cavities act as filters, producing peaks in the vocal spectrum called formants.

Consonants are phonemes that occur at the beginnings and ends of vowels. They can be produced by starting and stopping air flow through the vocal tract, or by restricting its flow through a narrow opening, producing turbulence.

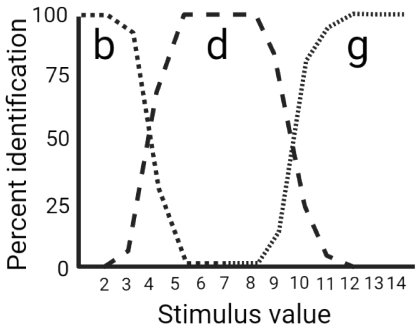
As you might imagine, the human vocal system can produce a great variety of different vowels and consonants. Not every speech sound, or phone, is used in every language, however, and different phones may be used interchangeably. A group of phones that can be used interchangeably is called a phoneme. In English, the phones [r] and [l] are distinguished from each other: switching [r] for [l] causes the meaning of a word to change (for example “right” and “light”). The same is not true in Japanese: there is only

a single phoneme that includes the whole range of sounds between [r] and [l].

Phonetic perception is categorical: acoustically dissimilar stimuli can be perceived as identical. This phenomenon was demonstrated by Alvin Liberman and Ignatius Mattingly, two pioneers of speech perception, using synthetically generated speech (Liberman et al., 1957; Liberman and Mattingly 1985). As illustrated in Figure 7.19, when the shape of the onset of a consonant-vowel syllable is systematically shifted, English-speaking listeners report hearing either “ba”, “da”, or “ga”. Even though the acoustic difference in each step is the same, this linear acoustic relationship is not reflected in what listeners perceive. Rather, listeners hear sudden transitions from one phoneme to another (there is no percept midway between “ba” and “da”), and they are unable to distinguish sounds within the same category from each other.



Liberman and Mattingly (1957) presented subjects with synthetic speech sounds with systematic changes in the shape of the onset.



Subjects perceive the stimuli as belonging to one of three distinct categories.

Figure 7.19 Categorical perception of phonemes Image credit: Data re-traced and image reused from Liberman, A. M., Harris, K. S., Hoffman, H. S., & Griffith, B. C. (1957). The discrimination of speech sounds within and across phoneme boundaries. Journal of Experimental Psychology, 54(5), 358–368. doi.org/10.1037/h0044417. Article in the public domain (CC0).

Categorical perception results in a many-to-one mapping between the acoustic structure of speech and phonetic perception. At some level of the auditory pathway, the brain must be responding the same way to different stimuli (Holt and Lotto 2010). This is a critical feature of vocal communication, because it allows us to understand the same words and phonemes produced by different individuals despite wide variations in pronunciation. It also allows us to understand the same phoneme produced by the same individual in different contexts, at different frequencies, and with different emphases.

Developmental Perspective: Normal development of phonetic perception

Different languages have different sets of phonemes, and categorical perception tends to follow the phonetic structure of the listener’s native language. In other words, individuals who grow up hearing English may not be able to hear the difference between sounds that form two distinct phonemes in another language. This observation suggests that phonetic perception is shaped by experience. Moreover, the older people get, the more difficult it is for them to learn to perceive the phonemes of a new language. They hear the new language through the lens, so to speak, of their native language, which makes it more difficult to rapidly process speech or correct an accent. These observations imply that the effect of experience on perception is limited to a narrow window during development, i.e. a critical period.

Work by Patricia Kuhl and Janet Werker has revealed how phonetic perception is established early in life (Werker and Tees 1984; Kuhl et al., 2006). Prior to about 6 months of age, infants from all over the world, raised in environments where different languages are spoken, can discriminate between all of the phonemes found in all languages. However, by 9–12 months of age, infants become better at discriminating phonemes in the language of their parents or caregivers and worse at discriminating phonetic contrasts not found in that language (Figure 7.20). Children raised hearing Japanese lose the ability to distinguish [r] from [l]. In contrast, children raised in English-speaking environments stop being able to tell apart “dental” [t], made by placing the tongue against the teeth, from “retroflex” [T], formed by placing the tongue against the roof of the mouth; these sounds are distinct phonemes in Hindi but not in English. This shift, which commits the infant to a certain way of hearing speech, is echoed by changes in how the brain responds to native and nonnative phonemes (Bosseler et al., 2013). This commitment is necessary for normal language

development (Tsao et al., 2004), but it makes it increasingly difficult for children to hear other languages as native speakers do. This could explain why children who begin learning a language later in life are more likely to speak with an accent (Piske et al., 2001), because they would have a harder time hearing their own mispronunciations and correcting their errors.

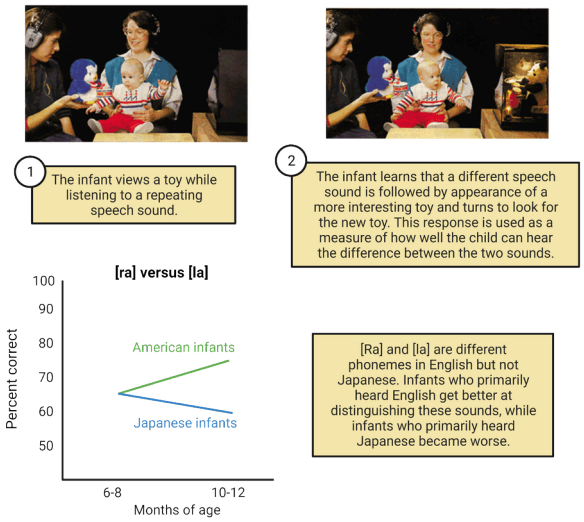


Figure 7.20 Infant perception of phonetic contrasts Image credit: Data based on findings from: Kuhl, P.K., Stevens, E., Hayashi, A., Deguchi, T., Kiritani, S. and Iverson, P. (2006), Infants show a facilitation effect for native language phonetic perception between 6 and 12 months. Developmental Science, 9: F13-F21. doi.org/10.1111/j.1467-7687.2006.00468.x. Photos from: Kuhl, P.K. (2007), Is speech learning 'gated' by the social brain?. Developmental Science, 10: 110-120. doi.org/10.1111/j.1467-7687.2007.00572.x. Images published by permission from John Wiley & Sons.

Neuroscience in the Lab

Measuring perception in infants and nonverbal animals

How is it possible to measure what an infant is hearing before it can speak or even understand questions? Kuhl, Werker, and their colleagues devised a clever technique that takes advantage of basic mechanisms of perception and learning (Werker and Tees 1984; Kuhl et al., 2006). As illustrated in Figure 7.20, infants sit on their mother's lap while viewing a toy. As the infant watches the toy, experimenters play a series of consonant-vowel pairs like "ka". At random intervals, the "ka" sound is replaced by a different sound like "ba", and a few seconds later, a more exciting toy is revealed in a different direction. The infant's gaze is drawn to the new visual stimulus, a natural *orienting response* that can be observed almost immediately after birth. Within several such trials, the infant learns that the change in sound predicts the exciting toy, and will turn its head to look at the toy even before it appears. The proportion of trials when the infant shifts its gaze is therefore a measure of how perceptually dissimilar the "oddball" is from the standard. Using this approach, Werker and Kuhl were able to show that native phonemes become more easily discriminated at 9–12 months of age, while nonnative phonemes become harder to tell apart.

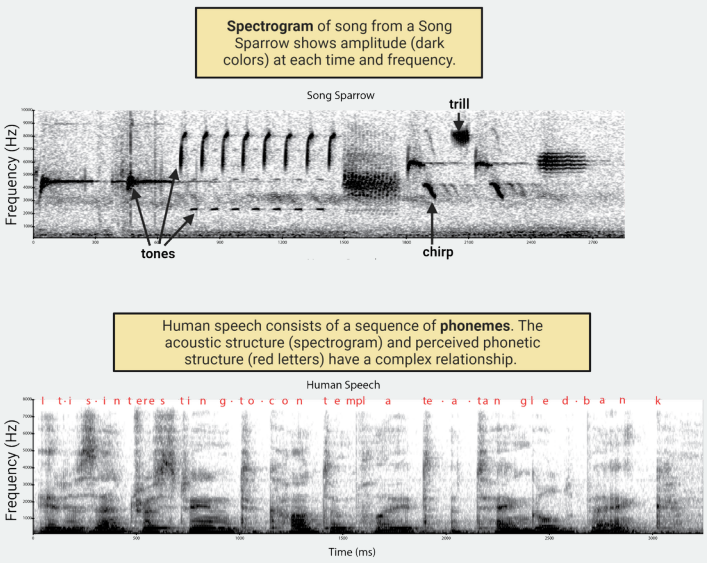
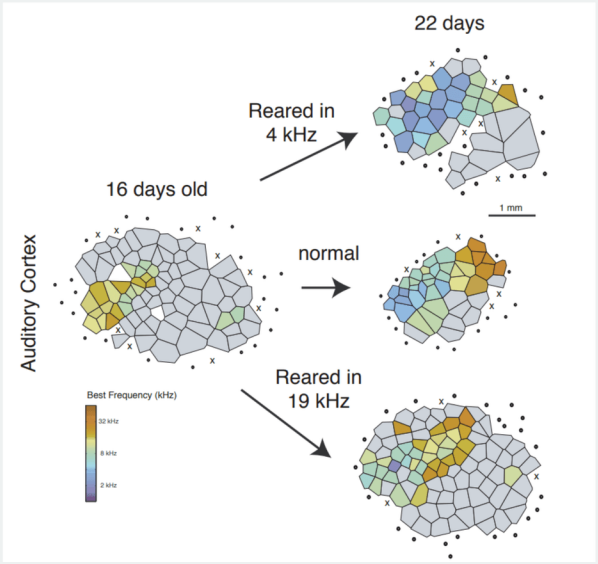


Figure 7.21 Spectrograms of birdsong and human speech

Neuroscience Across Species: Experience-dependent plasticity in animal models

What happens as a child's brain commits itself to a particular set of phonemes? Although it is not possible to study this at a cellular or molecular level in humans, work in nonhuman animal models has shed light on how experience could be reshaping how the auditory system processes sounds.

The auditory cortex in rats, as in other species, is organized by frequency in a tonotopic map (Figure 7.22). This organization is seen throughout the classical auditory pathway, so a reasonable hypothesis would be that the cortical organization is inherited via topological connections from earlier stations. This does not mean that the map is not able to change: work from Michael Merzenich and his colleagues has shown that the map is plastic early in life, subject to alteration by experience (Zhang et al., 2001). When a rat is raised in an environment dominated by tones of a single frequency, the map that results is dominated by that frequency. In other words, repeated exposure to 4 kHz tones results in more neurons over a larger area of cortex responding preferentially to that frequency. Similar effects are seen with other features like rhythm (Zhou et al., 2008). However, the map is only plastic for a limited period during development. The same treatment has little effect on older animals. This closely resembles what is seen in humans: once a child's brain has committed to a specific language's phonetic map, it becomes much more difficult to change (Kuhl et al., 2006; Bosseler et al., 2013).



In rats exposed to constant 4 kHz tones, a large portion of the tonotopic map is dedicated to that frequency.

In normally reared rats, all the frequencies from 2-32 kHz are represented about equally.

In rats exposed to 19 kHz tones, it is the higher frequencies that are overrepresented.

Figure 7.22 Experience and spatial tuning Image credit: Maps made based on data from Zhang, L., Bao, S. & Merzenich, M. Persistent and specific influences of early acoustic environments on primary auditory cortex. Nat Neurosci 4, 1123–1130 (2001). https://doi.org/10.1038/nn745)

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6.3: THE CHEMICAL SENSES

6.3.1: The Chemical Senses are Several Distinct Sensory Systems

6.3.2: The Gustatory System

6.3.3: The Olfactory System

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6.3.1: The Chemical Senses are Several Distinct Sensory Systems

Learning Objectives

By the end of this section, you should be able to

- List the basic taste modalities, and for each, provide examples of the type of molecules they represent; for these examples describe why it might be important for an organism to detect those types of molecules.
- Describe behaviors that rely on olfactory cues in their environment and how these behaviors promote survival.

Signal integration is arguably the most fundamental function of the nervous system. While our brain can integrate information from any of our senses, our perception of taste and smell is likely the most profound sensory integration a human commonly experiences. One often-used example of this phenomenon is how a head cold alters the perception of food. Who among us has not sought the comfort in a favorite food while unwell only to be shocked at the incredible blandness? We might have even thought or said: "I cannot 'taste' anything today." However, this perception is typically not the result of dysfunction in any signaling proteins, receptor cells, or sensory neurons of the "taste" neural system. Instead, in this example, our perception of altered taste is caused by the absence of the olfactory signals that typically occur while feeding. Our brains so tightly interweave the signals produced by the chemical senses during feeding that the common definitions of taste and smell lack the precision needed for describing the underlying neurobiology.

The complex connections between taste and smell can also make communicating about these systems challenging. While the common definitions of taste and smell are imprecise, they are helpful in accurately describing human perceptions that motivate fundamental animal behaviors. Thus, in this chapter, we use the term smell when referring to the chemosensory perception of inhaled air but use olfaction when describing the chemosensory system housed primarily in the nasal cavity. Similarly, the term taste commonly refers to the chemosensory perception of the oral cavity, but gustation specifically refers to the chemosensory system housed primarily in the oral cavity. To make this distinction even more explicit, flavor is the preferred term neuroscientists use to refer to the perception of oral chemosensation, which is produced when the brain integrates signals from the gustatory, olfactory and somatosensory systems. Comprehending these distinctions is the first step in understanding the neuroscience of the chemical senses and the vital behaviors they mediate. In this section, we will use the above vocabulary to explain the basic functioning of chemosensory systems before we explore how each system produces specific sensations in subsequent sections.

Taste-mediated behaviors

The primary role of the sense of gustation is to determine the chemical composition of substances we are about to ingest. The gustatory system is capable of detecting only a few specific types of molecules when in high concentration at close proximity with receptor cells, and it triggers only a handful of sensations or modalities (Sweet, Umami, Salty, Sour, Bitter, etc.). While this is relatively few modalities compared to olfaction, gustation is essential for survival. It is the final mechanism by which animals decide if materials are full of life-giving nutrients or life-threatening poisons.

Acquiring molecules essential for life

All animals consume food for energy and to obtain the chemical building blocks used to construct and repair their bodies. In humans and most other species, there are several broad classes of molecules that must be identified by the organism and ingested. Specifically, the detection of carbohydrates and/or protein (strings of amino acids) in food are critically important for most animals. Many animals also require a source of essential fatty acids that they cannot synthesize *de novo*, as well as external sources of salts to help maintain healthy fluid balance. The ability of animals to perceive carbohydrates, amino acids, fatty acids, and salts in food is largely mediated by the gustatory system. Each of these molecules plays an indispensable role in the fundamental physiological and metabolic processes of animals and must be acquired through ingesting food. Thus, one of the most important roles the gustatory system plays in animal behavior is to allow an animal to determine the nutritive value of a particular food before it is ingested and mediate decisions about which food sources to pursue. For humans, the positive hedonic experience provided by consuming sweet, umami, fatty, and salty foods drives food choices that exacerbate some of the

most prevalent diseases in the developed world. Therefore, understanding how the gustatory system and brain work in concert to decide which foods an animal seeks out is of primary importance to understanding animal behaviors and managing human diseases.

Rejection of potentially toxic or poisonous chemicals

Of equal importance to the gustatory system's role in the selecting of nutritious foods is its capacity to detect dangerous chemicals. Consuming essential molecules is a constant necessity for animal life, but mistakenly ingesting toxic, poisonous, or infectious materials only once can be a fatal error! Accordingly, the detection of compounds that indicate contamination with microorganisms or potential poisons can trigger the rejection or avoidance of those foods. For example, many vertebrate animals, including human infants, find sour foods aversive. Humans describe the taste of acids as being sour. Weakly acidic compounds are often produced in high concentrations by microorganisms metabolizing biomolecules—a process called fermentation. A possible explanation for the tendency of most animals to avoid sour substances is that foods with a high concentration of weak acids were likely decaying and were possibly dangerous to consume. Nevertheless, most adult humans readily consume foods that are fermented, like alcoholic beverages, yogurt, miso, kimchi, sauerkraut, garum, and certain types of sausages and cheeses. However, almost all these foods are thought of as "acquired tastes" that are avoided by inexperienced eaters. This phenomenon highlights the plasticity of the gustatory system and is an indication of how experience can shape the hedonic valence of the foods we consume.

Another example of a taste that potentially signals danger is bitterness. Humans perceive several classes of molecules as being bitter. These molecules are usually found in plants and are likely to have physiological or psychoactive effects on animals. Analogous to "acquiring a taste" for fermented foods, many humans also acquire a taste for bitter compounds that alter their physiology; alcohol, caffeine, nicotine, and cocaine are all perceived as being intensely bitter, but humans commonly will learn to tolerate the bitter taste of these drugs in pursuit of the psychoactive effects. Conversely, the bitter taste of many pharmaceuticals can cause individuals to avoid ingesting therapeutic drugs, and some green vegetables that have health benefits are also avoided because of their bitter taste. Despite these last two examples, perceiving compounds as bitter likely warns of a substance that could detrimentally alter an animal's health.

The primary behavior mediated by the gustatory system is the acceptance or rejection of particular foods. However, it is the integration of these signals with olfactory signals and even the somatosensory system (see 8.2 The Gustatory System) by the brain that creates the sensation we refer to as "taste" or more precisely flavor.

Olfactory-mediated behaviors

The function of the olfactory system stands in contrast to the gustatory system. While the gustatory system detects only a handful of molecules, the olfactory system can detect almost any type of volatile (e.g. air-borne) organic molecule, producing a seemingly inexhaustible collection of different types of smells by detecting specific motifs in those molecules. The olfactory system is also sensitive to incredibly small concentrations of molecules and can therefore detect sources of volatile molecules at great distances. Our sense of smell does more than just add sensory complexity to the flavor profile of a meal or allow us to enjoy the scent of a spring flower. Across the animal kingdom, the olfactory system is an important sensory modality for numerous sensory-guided behaviors. Below, we describe three olfaction-dependent behaviors: navigation, nutrient finding, and mate selection/communication.

Navigation

Navigation occurs on many scales. Bacteria climb chemical gradients to traverse mere fractions of an inch. Insects, like ants and honeybees, travel dozens of meters to find food and nectar. And salmon return hundreds of kilometers to spawn in the very same river from which they hatched. While these examples occur on vastly different spatial scales, they each rely on interactions with chemical cues in the environment. It has long been a mystery how salmon know to return to the exact location they hatched from an egg. We now know that the local olfactory or chemical composition of a river plays an important role in their migration. Fish can smell underwater by detecting waterborne chemicals, much like we do for airborne odors.

Nutrient finding

Nutrients are found in food sources that provide animals with energy and essential compounds for their growth. We discussed above the critical role of gustation in helping animals to assess the nutrients in food they might ingest, but olfaction is essential

to locating these nutrients. A crying baby searching for its mother's milk is a familiar example of nutrient sensing that relies on olfaction. Milk is especially rich in lipids (fats) and all mammals rely on it for their caloric intake early in life. Because of this, it is critical that animals can locate and obtain this important food source. Many mammals, like rodents, begin life without the ability to see or hear and must find their way to milk in order to thrive. These animals rely on their sense of smell to find their mother and her milk. Similarly, not all fats and sugars carry the same nutritional content; olfaction helps babies and adults are able to distinguish between them.

Mate selection and communication

The selection and identification of mates is a universal need for all animals that reproduce sexually. When selecting a mate, animals must gauge both the receptiveness and fitness of potential reproductive partners. These cues can be delivered through numerous behavioral displays; however, olfactory cues often play an important role in bringing mates together. Many signals related to reproductive behaviors are conveyed by chemicals called pheromones, which are sensed using their own specialized olfactory system, separate from smells associated with things like nutrients. Pheromones are powerful substances that can signal sexual receptivity between animals, influence physiological responses like the estrus cycle, and be used to coordinate other behaviors among animals. Behavioral responses to pheromones are innate rather than learned. Later in this chapter we will discuss how pheromones may even play an important role in human partner selection.

Chemesthesis-related behaviors

Many of the culinary ingredients we call spices contain chemicals that stimulate the somatosensory system to produce warming and cooling sensations. The technical term for the chemical stimulation of the somatosensory system is chemesthesis. Many plants produce chemicals that simulate thermal stimuli to alter the behavior of predatory animals. However, because our brains integrate chemesthetic with olfactory and gustatory signals to produce the perception of flavor, human beings cultivate these plants to use as flavor enhancers. The sense of chemesthesis is essential to describing the distinct culinary traditions around the world, but increasingly research indicates that the sense of chemesthesis is important for monitoring parts the body for growing bacteria.

The Jelly Bean Experiment: How can you tell the difference between Taste and Smell?

Without training, it can be difficult to distinguish between gustatory, olfactory and chemesthetic sensations. This simple experiment highlights the differences between the senses of olfaction, gustation and chemesthesis discussed in this chapter, and the role the olfaction plays in our perception of flavor. It requires only paper, a writing utensil, jellybeans, mints, and a way to pinch your nose closed.

Materials

- Paper and writing utensil to record your results. You will likely have to record your observation with one hand if you are using the other to pinch your nose, so phones and keyboards are not ideal equipment.
- A couple fruit-flavored jellybeans. The experiment will not work if you use jellybeans flavored with licorice, mint or flavors you might describe as being "spicy."
- A few mints. The more intense the spicy flavor, the better the experiment will work. Cinnamon flavored mints work particularly well.
- A way to pinch your nose. The easiest way will likely be to use your non-dominant hand to squeeze your nose shut just hard enough that it makes your voice increase in pitch. Other options include having a friend pinch your nose closed for you or purchasing specialized padded clips (like the sort made for swimmers) for comfortably holding your nose closed for an extended time.

Methods:

- Step 1: Draw two lines on your paper (one down the center, the other across), dividing the paper into four quadrants. Label the four quadrants "Jellybean/Pinched," "Jellybean/Open," "Mint/Pinched," and "Mint/Open."

Part 1: Gustation and Olfaction:

- Step 2: Tightly pinch your nose. While your nose is pinched you will breathe through your mouth.
- Step 3: Place a jellybean in your mouth on your tongue for at least 5 seconds and chew it a few times.
- Step 4: Write down words to describe the sensations caused by the jellybean in the “Jellybean/Pinched” section of your paper. Don’t swallow the jellybean yet!
- Step 5: Start chewing the jellybean, release your nose and exhale through it. Try to chew the jellybean for at least 5 seconds while breathing through your nose. During this time write down words to describe the sensations caused by the jellybean in the “Jellybean/Open” section.
- Step 6: You can finish chewing the jellybean and swallow it now if you want. If it is convenient, the quality of the experiment is improved by taking a few sips of water here to cleanse your palate.

Part 2: Chemethesis:

- Step 7: Tightly pinch your nose again. While your nose is pinched you will breathe through your mouth.
- Step 8: Place a mint in your mouth on your tongue for at least 5 seconds and chew it a few times.
- Step 9: Write down words to describe the sensations caused by the mint in the “Mint/Pinched” section of your paper. Don’t swallow the mint yet!
- Step 10: Start chewing the mint, release your nose and exhale through it. Try to chew the mint for at least 5 seconds while breathing through your nose. During this time write down words in the “Mint/Open” section to describe the sensations caused by the mint.
- Step 11: You can finish chewing the mint and swallow it now if you want. If it is convenient, the quality of the experiment is improved by taking a few drinks sips of water here to cleanse your palate.

Part 3: “Smell” or Orthonasal Olfaction:

- Step 12: Find a jellybean of the same flavor you used in Part 1. Hold the jellybean in front of your nose and sniff its odor (if you cannot smell the jellybean, try mashing it between two fingers). Write down words to describe this sensation on the back of your paper.
- Step 13: If you did this experiment with a group of people, combine the data you all have collected and discuss how the types of sensations and the words you used to describe them are similar and different for each experience. What patterns do you see?

What you will likely notice when you do this experiment is that the descriptive words used to describe the “Jellybean/Pinched” experience tend to be synonymous with the five basic taste qualities (e.g. Sweet, Sour, Salty, Bitter, Savory). However, once your nose is released, the “Jellybean/Open” descriptors become much more diverse, perhaps even identifying exactly the flavor of the jean bean. While your nose is pinched, very little air is moving from your oral cavity to your nasal cavity through your pharynx, so the chemicals from food cannot reach the olfactory system in the nasal cavity. However, when you exhale out of your nose while chewing, chemicals from your oral cavity can easily travel from your oral cavity into your nasal cavity to stimulate the olfactory system; a process called retronasal olfaction.

These differences highlight that stimulation of the gustatory system is only capable of producing a few very specific sensations that correspond to a few specific classes of molecules; conversely the olfactory system can detect the presence of an almost limitless number of different compounds and the language we use to describe those sensations is similarly diverse. Additionally, you can begin to determine the different sensations mediated by the gustatory and olfactory systems by comparing how similar your description of sniffing the jellybean was to the other experiences. Likely, the sniffing description was very similar to what was recorded for the “Jellybean/Open” experience. There are some foods, however, that may produce different sensations from orthonasal olfaction (e.g. sniffing) and retronasal olfaction. For example, some cheeses (e.g. parmesan cheese or blue cheeses) are famously stinky when perceived by orthonasal olfaction but produce a different sensation when perceived retronasally.

When you compare the description of the mint to the jellybean, you will likely notice the addition of words like burning, cool, pungent, or painful in the description of the mint. These sensations are due to chemicals in the mint stimulating the free nerve endings of the trigeminal nerve—part of the somatosensory system, your sense of chemesthesis.

The jellybean experiment is easy to do with most foods, and, by practicing it, you can become better at perceiving the difference between gustation, olfaction, and chemethesis. Eventually you may even be able to tell the difference without pinching your nose closed!

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6.3.2: The Gustatory System

Learning Objectives

By the end of this section, you should be able to

- Describe the functional anatomy of the gustatory system from cellular receptors to neural pathways in vertebrates.
- Describe the molecular pathways required for the detection of a taste modality
- List some of the ways gustation can be parallel and different across species

Imagine it is a cool fall evening at a street festival, and you are hungrily wandering through the food trucks trying to find the perfect snack. You have been looking forward to this moment all week; even planning lighter meals today to facilitate your guiltless indulgence of the calorically rich food. Suddenly you see just what you have been looking for: at least a cubic foot of pink, blue, and mauve spun sugar on a stick. Salivating, you purchase the snack and are filled with joy as handfuls of the cotton candy instantaneously liquefies into sweetness as it hits your tongue. In this section, we will explore how the gustatory system is able to distinguish between different classes of molecules to produce different sensations (e.g. Sweet, Umami, Salty, Sour, Bitter) and current theories about how these signals are processed in the CNS.

Gustation and peripheral anatomy to receptors

The primary role of the gustatory system is to assess the quality and concentration of chemicals before they are allowed entrance into the digestive tract. This process begins with bringing chemicals into the mouth where they can interact with specialized receptors on sensory cells.

The tongue and oral cavity

The sensory cells of the gustatory system are typically concentrated in the oral cavity. These sensory cells are found in clusters called taste buds. The exact distribution of taste buds will vary among species. In most mammals, taste buds are concentrated on the tongue (Figure 8.2), but are also found on the soft palate, epiglottis, larynx, upper esophagus, and associated with salivary glands behind the molars.

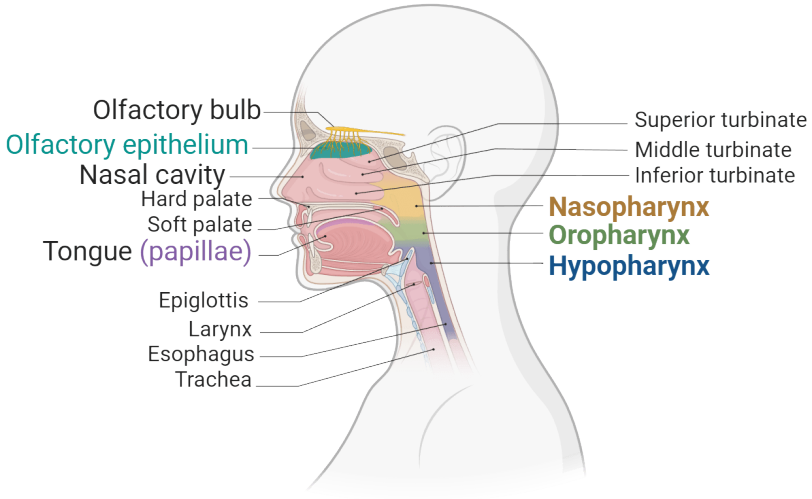


Figure 8.2 Gross anatomy of gustatory and olfactory systems

Many species of fish, in contrast, possess taste buds in the oral cavity but also on their lips and on the skin of their bodies—indeed,

taste buds are so prevalent on the bodies of catfish that they are sometimes described as being “swimming tongues.” Conversely, marine mammals (e.g. dolphins, seals) that feed by swallowing prey whole typically have a reduced number of taste buds throughout the oral cavity and tongue. These anatomical adaptations all facilitate the specific feeding behaviors of each species. Despite the observed anatomical variation, chemicals in food are detected by sensory cells in taste buds, and this information is subsequently passed on to homologous regions of the central nervous system.

While there is great variation in the anatomy of the oral cavity between species, the tongue of most vertebrates is a sensory organ specialized for both chemosensation and somatosensation. If you have ever looked at your tongue closely in the mirror, you might have noticed that its anterior surface appears rough, except for scattered bumps which have a smooth texture (Figure 8.3).

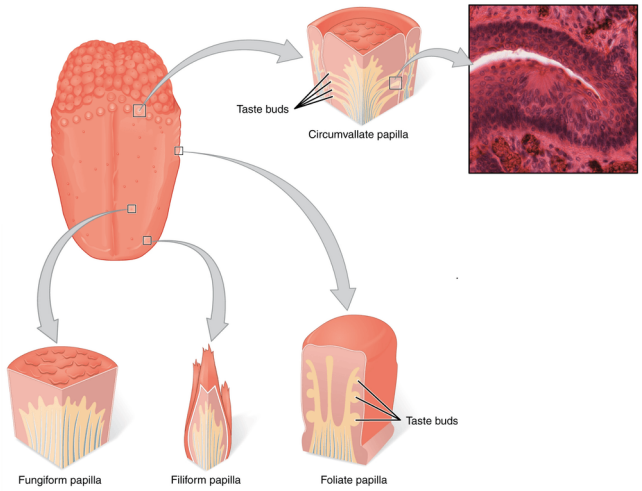


Figure 8.3 Tongue and papillae anatomy Image from: By OpenStax - https://openstax.org/books/anatomy-and-physiology-2e

Both the rough areas and smooth bumps are made up of structures called papillae, which enhance somatosensation on the tongue. The rough areas of the tongue are covered in filiform papillae, which are cone-shaped, come to a point, and do not contain taste buds. The three other types of papillae contain taste buds: the smooth round bumps on the tongue are called fungiform papillae and often have 1 to 5 taste buds at their apex. On either side of your tongue there are 4 to 6 groves lined with hundreds of taste buds called foliate papillae. And at the very back of your tongue are 4 to 8 circular troughs containing taste buds called circumvallate papillae. The exact number of papillae varies across vertebrate animals, but most have each type of papillae to facilitate exploring the textures of food and channeling the biomolecules towards taste buds.

Behind the tongue is a space called the pharynx. Figure 8.2 shows the three major divisions of the pharynx. In most terrestrial animals, this space connects to the oral cavity, esophagus, trachea, nasal cavity, and even the inner ear. This anatomical arrangement allows for the chemicals in food to be sampled with both the gustatory and olfactory systems simultaneously. The co-simulation of these systems when eating strengthens and facilitates our perceived integration of these senses.

Taste buds and taste receptor cells

Papillae are visible with the naked eye, while taste buds are so small they require a microscope to see. People without formal anatomical training sometimes mistakenly equate fungiform papillae (0.5 to 0.8 millimeters or 500 to 800 micrometers across) with taste buds (30 to 100 micrometers across). Taste buds resemble an onion or bulb of garlic in cross-section (Figure 8.4).

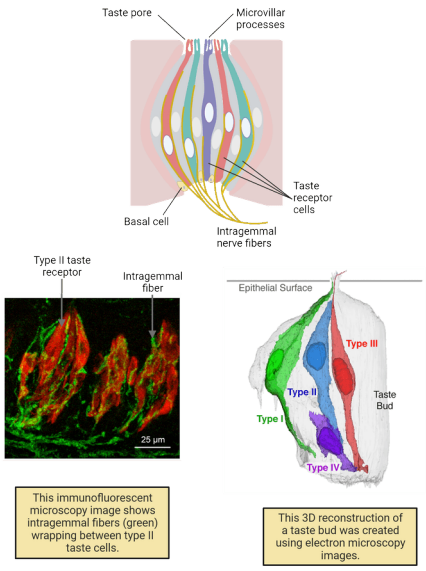


Figure 8.4 Taste bud anatomy Image credit: Taste bud diagram adapted based on: By OpenStax. Taste bud immunofluorescence: Kinnamon SC and Finger TE (2013) A taste for ATP: neurotransmission in taste buds. Front. Cell. Neurosci. 7:264. doi: 10.3389/fncel.2013.00264 CC By 3.0. 3D taste bud rendering from: Recent advances in taste transduction and signaling [version 1; peer review: 2 approved]. F1000Research 2019, 8(F1000 Faculty Rev):2117 (https://doi.org/10.12688/f1000research.21099.1) CC BY 4.0

Each taste bud is a collection of 50 to 150 neuroepithelial cells and associated nerve fibers. These neuroepithelial cells are spindle-shaped or bottle-shaped with apical microvillar tufts that open into the lumen of the oral cavity in a structure called a taste pore. For the gustatory system to detect particular chemical stimuli, a chemical must first enter the taste pore so it can interact with proteins in the cell membrane of the microvillar process of these cells. Because these cells are the first element of the gustatory system that responds to chemicals, they are referred to as taste receptor cells (TRCs).

Anatomists studying the cells of taste buds have grouped them into three types based on characteristics observed by transmission electron micrography (Farbman, 1965) (see Methods: Transmission Electron Microscopy). These classifications based on micro-anatomy turn out to be functional, as different classes of chemicals activate Type I, Type II and Type III taste receptor cells. Type II and Type III cells will make occasional cytoplasmic contact with each other or nerve fibers but Type I cells enwrap the other cell types supporting them and helping degrade neurotransmitters released by the other cells. These functions have caused scientists to describe Type I cells as “glial-like.” Type IV cell is a designation given to basal cells in the bud that divide to replace the other taste receptor cell types that are lost to damage. The specialized anatomical arrangement of taste receptor cells allows taste buds to detect chemicals and selectively modulate either other cells in the taste bud or the associated nerve fibers to ultimately produce the familiar taste qualities of sweet, umami, bitter, salty, and sour.

Taste receptor cells and taste receptor proteins

But how does a taste receptor cell in a taste bud turn a chemical in your mouth into a signal that your brain can understand? Decades of research have helped us understand that the mechanisms for detecting and transducing a chemical into a neural signal are different for each of the half dozen or so taste qualities. This stands in dramatic contrast to the mammalian olfactory system, where hundreds of genes belonging to the same receptor family using the same basic transduction paradigm allow you to perceive an incomprehensible number of olfactory qualities. In the mammalian taste system, at least 4 different families of receptors are implicated in detecting the chemicals we perceive as sweet, umami, bitter, sour, and salty. An overall summary of these receptors and how those signals are transduced is provided in Figure 8.5.

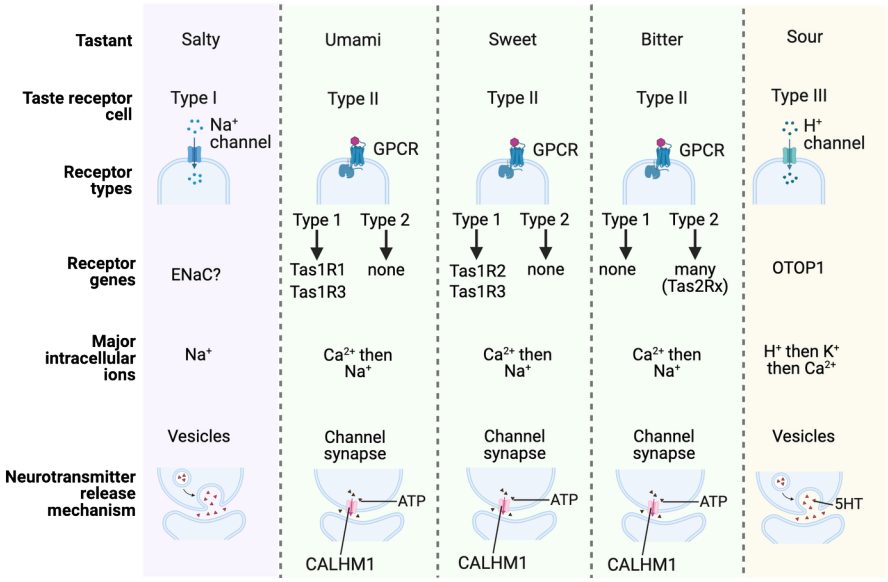


Figure 8.5 Taste receptor cell comparison

Three distinct groups of Type II taste receptor cells are responsible for detecting sweet, umami, and bitter chemicals using receptors from the GPCR super-family. The sweet and umami-sensitive taste receptor cells detect chemicals using taste receptors from subfamily 1, which is made up of 3 individual receptor genes designated Tas1R1, Tas1R2, and Tas1R3. To produce a functioning receptor protein from this family of receptors—either sweet or umami—two different receptor genes must combine to make a heterodimer: The sweet receptor requires both Tas1R2 and Tas1R3; while an umami receptor requires Tas1R1 and Tas1R3. The third group of type II taste receptor cells detects bitter compounds via taste receptor subfamily 2 (Tas2Rs), which consists of many more genes than subfamily 1 (e.g. humans have 25 Tas2R genes). Thus, sweet-sensitive type II receptor cells will express Tas1R2+Tas1R3, umami-sensitive type II receptor cells will express Tas1R1+Tas1R3, and bitter-sensitive type II receptor cells will express some combination of Tas2Rs. Activation of any of these receptors triggers lipid secondary messenger signaling that ultimately results in the release of ATP to activate gustatory nerve fibers.

Ion channels are responsible for the detection of sour and salty chemicals. Most sour chemicals are acids that dissociate to produce a proton (e.g. hydrogen ion) in solution. Type III taste receptor cells that are sensitive to sour chemicals express a proton channel Otopetrin 1 (Otop1). Protons flow into these cells through Otop1 and ultimately trigger a change in membrane potential resulting in the vesicular release of serotonin (5HT).

While scientists are still searching for the precise mechanism of salt detection, Epithelial Sodium (Na) Channels (ENaC) are widely considered to play an essential role in the depolarization of Type I taste receptor cells in the presence of sodium ions.

Identifying the receptor proteins TRCs utilize to detect chemicals is a prerequisite for a complete understanding of the taste modalities the gustatory system is capable of detecting. The involvement of at least four different families of receptor proteins and distinct transduction mechanisms in taste receptor cells highlights the inherently molecular nature of gustatory perception.

Taste transduction in depth

Part I: Umami, sweet, bitter

The chemicals we perceive as umami, sweet or bitter are detected by Type II taste receptor cells (TRCs). However, three distinct subsets of Type II cells in a taste bud respond to the amino acids, carbohydrates, and bitter chemicals that generate these tastes. The three subsets of Type II cells are defined by which combinations of two sub-families of G-protein coupled receptors or GPCRs they express.

Taste receptors in subfamily 1 (abbreviated either Tas1R or T1R) are responsible for detecting sweet or umami molecules. Type II cells that respond to sweet or umami molecules require the expression of two of the three different T1Rs genes to make a functional taste receptor. Umami-responsive receptors that bind amino acids like glutamate are produced by combining T1R1+T1R3. Sweet-responsive receptors that bind sugars, carbohydrates, and other compounds that taste sweet are produced by combining T1R2+T1R3. While there are 3 T1R genes in humans, there are 25 taste receptor genes in

subfamily 2 (abbreviated either Tas2R or T2R). Some T2Rs appear to be selectively activated by a single compound or class of compounds while others appear to be broadly tuned to multiple compounds. Type II taste receptor cells will either express one pair of T1Rs (either T1R1+T1R3 or T1R2+T1R3) or some combination of T2Rs. The table in Figure 8.6 shows how combinations of taste receptor genes will make a particular Type II taste receptor cell sensitive to sweet, umami or bitter molecules.

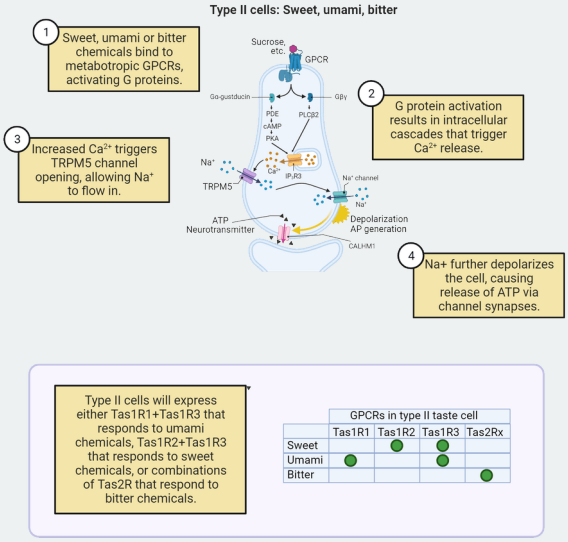


Figure 8.6

Regardless of receptor, when a Type II taste cell is stimulated by a tastant, the signaling pathway leads to an increase in intracellular calcium, via a pathway shown in the top of Figure 8.6. Two proteins in this pathway are particularly important to researchers because they can be targeted to modify Type II receptor cell signaling for experiments. The first of these proteins is gustducin, the G-protein subunit that couples to GPCRs. The other of these proteins is TRPM5, which is a cation channel primarily responsible for depolarizing type II cells. Knockout mice for gustducin or TRPM5 show major deficits in the ability to discriminate between umami, sweet and bitter foods suggesting that these proteins are essential for proper gustatory system functioning (see Methods: Transgenic Organisms). Since the gustducin-TRPM5 pathway is largely conserved among Type 2 taste receptor cells, these genes are commonly used as markers of Type II cells for neuroanatomy experiments or to drive genetic constructs for taste behavioral studies (see Methods: Immunohistochemistry, Methods: Optogenetics).

Part II: Salty and sour

In contrast to the molecules we perceive as umami, sweet and bitter, the chemicals we perceive as sour and salty are typically simple ionic compounds. Ionic compounds dissociate in water to produce at least one monatomic ion (e.g. H+ or Na+). Where other classes of tastants interact with GPCRs, these ions are detected by TRCs via direct interaction with ion channels. For decades, electrophysiological and physiological imaging have implicated Type III taste receptor cells as the sensory cell responsible for sour taste. However, over that period, several ion channels expressed by Type III taste receptor cells have been proposed as candidate sour receptors. After much speculation and experimentation, the proton-selective ion channel Otopetrin 1 (Otop1) has been identified as essential for the sour response of Type III taste receptor cells (Figure 8.7).

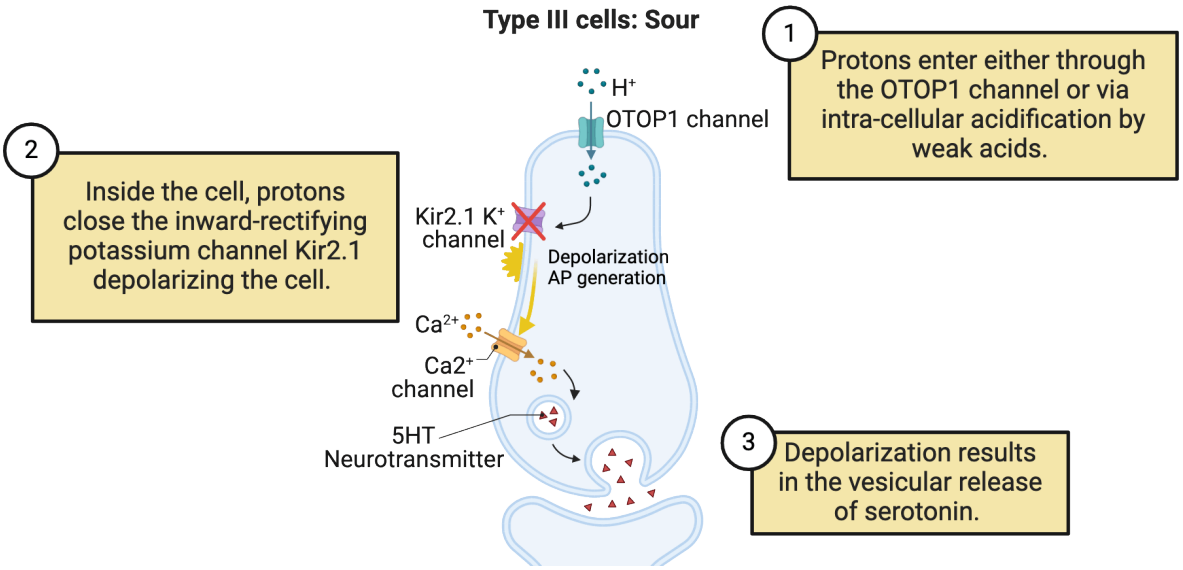


Figure 8.7

In sour taste, extracellular hydrogen ions enter the cytoplasm of Type III taste receptor cells through Otop1 channels and ultimately trigger an action potential and neurotransmitter release. When protons flood through Otop1 channels they lower the pH of the cytoplasm and block the inwardly rectifying potassium channels. In response to the blocked potassium currents, Type III taste receptor cells depolarize, an event that triggers voltage-gated sodium channels to generate action potentials that ultimately cause serotonin release.

While the molecular mechanism responsible for sour taste appears to have been elucidated, the molecular mechanisms underlying salty taste are arguably the least well understood of the five traditional taste modalities. Multiple factors contribute to the complexity of salty taste, not the least of which is the apparent existence of two distinct mechanisms that detect high and low concentrations of salt.

At lower concentrations, most terrestrial animals find salt appetitive (i.e. tasty). Most models of salt taste focus on epithelial sodium channels (ENaC) in Type I cells. The hypothesized mechanism is that Na+ from salt flows into the cell via ENaC, causing a depolarization that triggers opening of further Na+ channels in the Type I cell (Figure 8.8). That amplified depolarization from additional Na+ influx triggers neurotransmitter release.

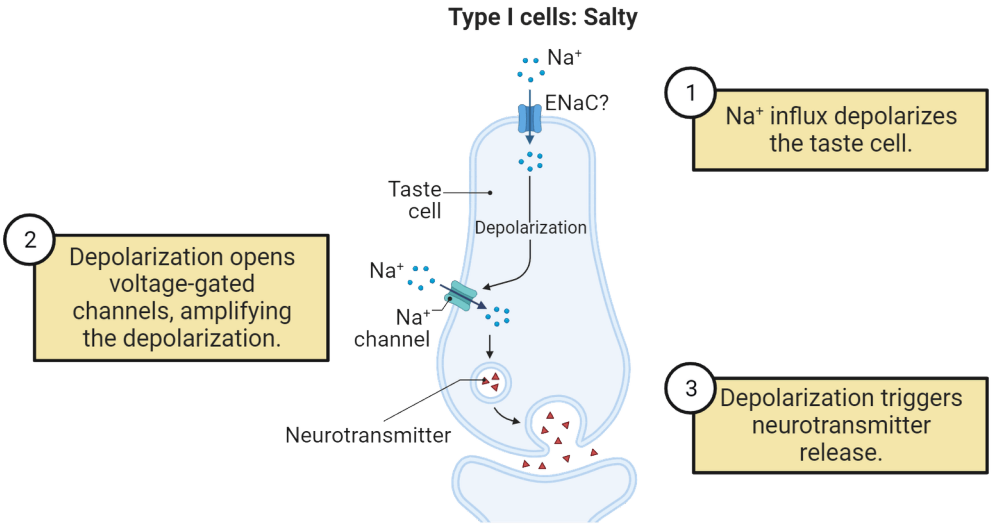


Figure 8.8

While low, appetitive salt levels require ENaC to stimulate Type I taste receptor cells, the taste of high concentrations of salt

is aversive, even after genetic knockout of ENaC subunits. This type of salt taste appears to involve both Type II and III taste receptor cells but our understanding of the mechanisms responsible for our ability to distinguish between heavily brined and slightly salted foods is incomplete.

Other possible taste modalities

Neuroscientists are continuously designing experiments to determine precisely what chemicals are detected by the gustation system. For example, given that carbohydrates and proteins are associated with primary taste qualities, the hypothesis that the gustatory system would also respond to energy-rich lipids is appealing. Several candidate receptors for fat taste have been identified in taste receptor cells and work in this area is ongoing (Besnard et al., 2016). The mechanisms by which the gustatory system may detect the flavor qualities described as astringent (Wu et al., 2022), metallic (Wang et al., 2019), kokumi/richness, or fatty is an active area of research.

Previously, there was a great scientific debate surrounding the perception of glutamate and if it met the criteria for a primary taste modality (Kinnamon and Finger, 2019). Ultimately, the identification of the T1R1+T1R3 heterodimer (Nelson et al., 2002) allowed genetic tools to be combined with anatomical, electrophysiological, and behavioral experiments to address this question. We can taste glutamate and we call this primary taste umami. Over the past decades, the Japanese loan-word umami has been so popularized that it is regularly mentioned on gourmet menus, on foodie blogs, and by celebrity chefs around the world. In contrast to its current popularity, the concept of umami and the identification of chemicals that produce the sensation was largely ignored in the English-speaking scientific community for nearly a century (Kurihara, 2015; Stańska and Krzeski, 2015). The scientific discoveries identifying T1R1+T1R3 as essential for the perception of umami have helped place it as one of the main tastes on menus around the world.

Gustation - neurotransmission and the central nervous system

After taste receptor cells detect chemical stimuli in the oral cavity, this signal must be transmitted to the nerves innervating the taste bud. These intragemmal (from the Latin gemma meaning bud, gem, or cup) nerve fibers enter the taste buds (shown in Figure 8.4), detect neurotransmitters released from taste receptor cells and conduct this information into the brain regions where the perception of umami, sweet, bitter, sour, and salty are represented. Before reaching gustatory cortex, taste information passes through 2 relays along the way: the nucleus tractus solitarius in the medulla and the posteroventral nucleus of the thalamus (Figure 8.9). Once this information has arrived in the gustatory cortex, an animal can make decisions about the palatability of the substances in the oral cavity. How the primary taste qualities are represented between the taste buds and brain remains one of the great open questions in sensory neuroscience.

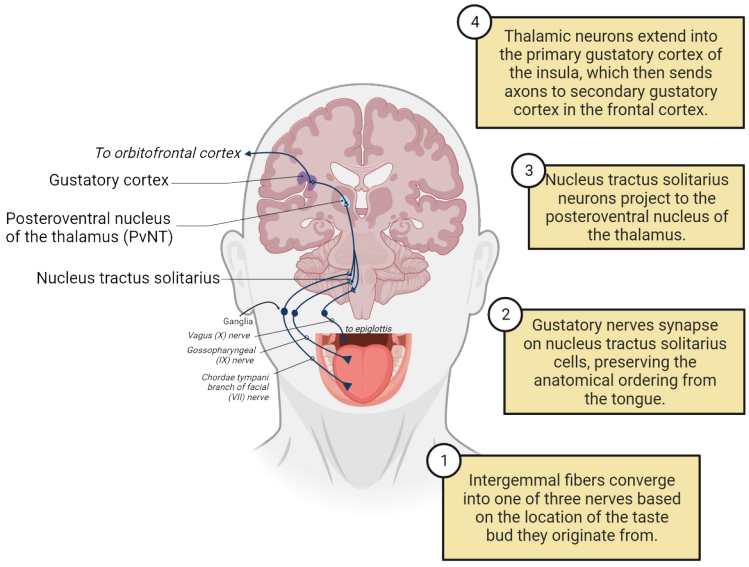


Figure 8.9 Neural pathways of taste

While the broad pathway of gustatory information is known, exactly how that pathway encodes different tastes remains uncertain. Historically, most hypothesized models for how the nervous system encodes primary taste qualities can be classified as either

labeled line coding or across-fiber pattern coding. In labeled line coding, there is a discrete pathway or circuit from the receptor cells to the afferent neurons, to higher brain regions for each of the primary taste qualities. In this coding model, a sweet chemical of adequate concentration would result in activity through the sweet “line” and would not trigger substantial activity in the circuits for other primary tastes. A classic example of a sensory system that uses label line coding is the somatosensory system.

In across-fiber pattern coding, any given pathway (e.g. receptor cells, nerve fibers, higher brain regions) is not associated with any individual primary taste quality; rather, a specific pattern of activity among overlapping neural pathways codes for each of the primary tastes. Across-fiber pattern coding allows the vertebrate olfactory system to represent an overwhelming number of olfactory modalities.

Figure 8.10 diagrams these two opposing models, using circles to represent neurons that might respond to sour, salt or both. As technological advancements allow scientists to examine the activity in gustatory circuits at an ever-increasing resolution, new refinements are constantly being made to theories of gustatory system coding.

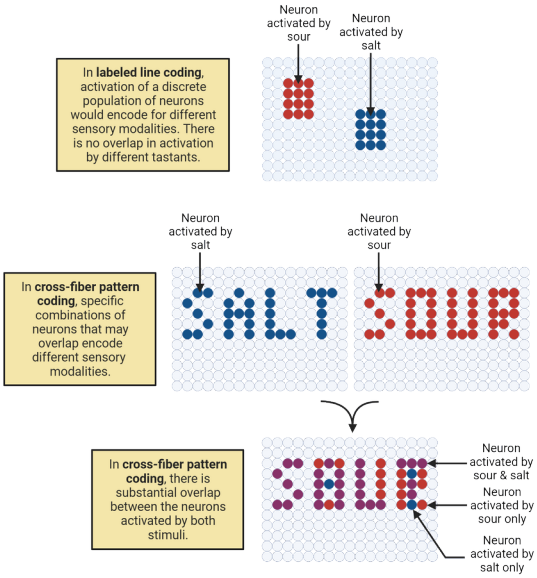


Figure 8.10 Labeled line coding Image credit: adapted from Wayne Silver (Wake Forest University).

Neuroscience in the lab: Studying taste receptor cell to neurotransmission

Recording action potentials from a nerve that primarily makes connections with taste buds provides an important assay for determining if chemicals are activating the gustatory system. The chorda tympani branch of the facial (VII) nerve and the glossopharyngeal (IX) nerve innervate the taste buds on the rostral ⅔ and caudal ½ of the tongue, respectively. In contrast to behavioral data, chorda tympani and glossopharyngeal nerve recordings in ATP receptor knockouts or animals treated with an ATP receptor blocker show decreased activity not just for umami, sweet and bitter tastants, but also for salty and sour compounds (Figure 8.11). Conversely, while knockout or pharmacological blockade of serotonin receptors results in no taste-related behavioral deficits in mice, it does decrease chorda tympani nerve response to MSG, sucrose, salts, and both weak and strong acids. Taken together, these data suggest that ATP release is necessary for taste receptor cell nerve neurotransmission for all taste modalities, while serotonin acts synergistically to intensify the neural response to certain taste qualities.

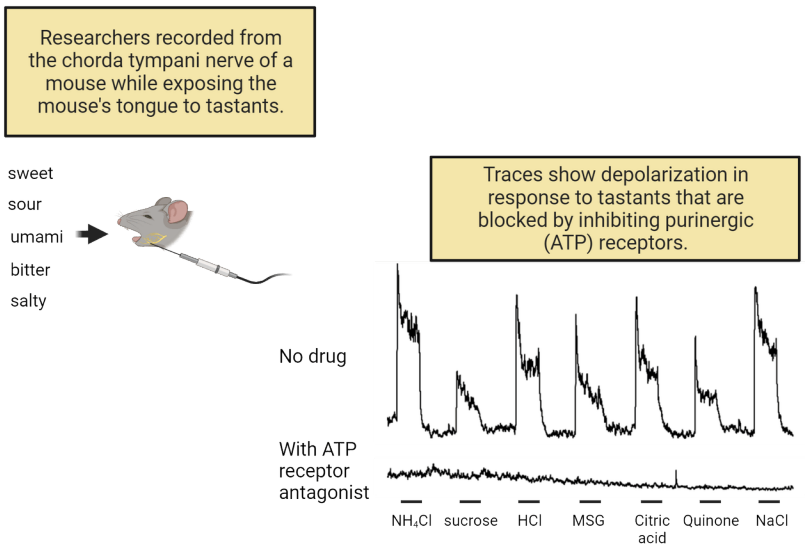


Figure 8.11 Chorda tympani nerve recording Image credit: Nerve recording data provided by Aurelie Vandenbeuch (University of Colorado, Anschutz Medical Campus).

However, this interpretation is difficult to resolve with the observation regarding transmitter release from taste receptor cells. Specifically, what is the source of ATP, if only type III cells are activated by sour tastants and those cells do not appear to release ATP or possess the proteins necessary for ATP's release? One hypothesis, which would explain these results, would be the existence of a currently unknown mechanism by which low levels of ATP could be packaged alongside serotonin. Another explanation is that the limited cell-to-cell contacts between type II and type III cells allow for serotonin signaling directly between taste receptor cells to modulate ATP release from type II cells in the presence of sour stimuli. However, this model must account for the serotonin's apparent inhibitory action on type II cells making ATP release from these cells less likely in the presence of sour stimuli.

Science as a process: Taste nerves and the nucleus of the solitary tract

As intergemmal nerve fibers exit taste buds, they merge into larger bundles until ultimately joining cranial nerves, which conduct taste information to the brainstem. A recently published connectome (a complete map of cellular and neural connections) of taste buds determined that 97% of intergemmal fibers innervate one taste receptor cell or the same taste receptor cell type (Wilson et al., 2022). Thus, each intergemmal nerve fiber is passing information from only one taste receptor cell type to the nucleus of the solitary tract in the brainstem.

Three cranial nerves innervate taste buds in distinct regions of the oral cavity: Taste buds on the rostral or anterior 2/3 of the tongue are innervated by the chorda tympani branch of the facial (VII) nerve, taste buds on the caudal 1/3 of the tongue and palate are innervated by the glossopharyngeal (IX) nerve and taste buds found on the epiglottis are innervated by the vagus (X) nerve. Chemosensory information from all three of these nerves is conducted to a region of the brainstem called the nucleus of the solitary tract.

The nucleus of the solitary tract (NTS, from the Latin nucleus tractus solitarii) is the primary gustatory and visceral chemosensory nucleus of the central nervous system. Gustatory information to the central nervous system projects to the most rostral portion of the NTS (Figure 8.12). Within the rostral NTS (rNTS) or gustatory nucleus, projections from the facial, glossopharyngeal, and vagal nerves are arranged rostrally to caudally reflecting their innervation of taste buds in the oral cavity. Chemosensory afferents projecting to the caudal NTS (cNTS) carry information from visceral chemoreceptors. This anatomy creates a rostral to caudal topographic map of chemosensory inputs from the mouth to the alimentary canal (i.e. digestive tract) and other internal organs along the NTS.

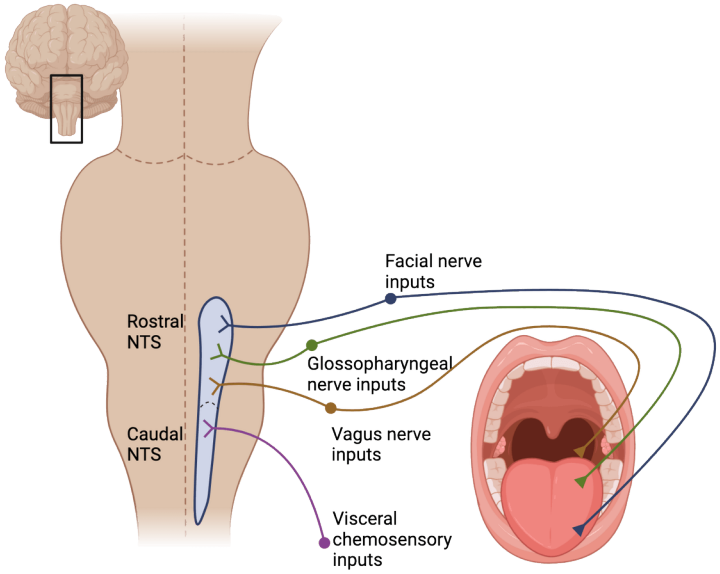


Figure 8.12 Nucleus of the solitary tract Inputs to the NTS, or gustatory nucleus, are arranged anatomically by the incoming nerve and which part of the oral cavity it innervates.

In addition to its anatomical map, investigators continue to define the chemotopic map or coding logic for taste qualities within the NTS. For example, most chemicals perceived as bitter trigger activity in neurons located in the medial rNTS. MSG and NaCl, which taste savory and salty, both activate the intermediate zones of the rNTS. Sweet chemicals produce diffuse activity along the nucleus. Sour chemicals, like citric acid, trigger activity in lateral-rostral and mid-NTS. One major challenge that researchers attempting to define the chemotopic map of the NTS face is determining the influence that non-gustatory inputs play in the coding logic of these taste qualities.

While the rNTS is the first relay of gustatory information in the central nervous system, it also receives and integrates other signals that can influence our perception of flavor. For example, contrary to its moniker as the gustatory nucleus, the rNTS also receives oral somatosensory information from the trigeminal nerve. The temperature of solutions with identical chemical composition can modulate the firing neurons of the NTS, presumably through these somatosensory inputs. The result is that a particular rNTS neuron that fires action potentials at a specific rate to a specific chemical solution may increase or decrease its activity as the temperature of that solution changes. Figure 8.13 shows an example of this phenomenon.

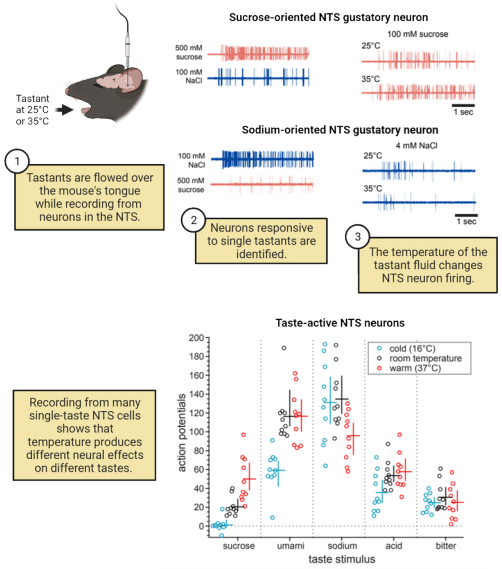


Figure 8.13 Mouse NTS response to tastants at different temperatures Image credit: Recordings and data panel provided by Jinrong Li and Christian Lemon (University of Oklahoma). Top panel based on data from Li J, Lemon CH. Influence of stimulus and oral adaptation temperature on gustatory responses in central taste-sensitive neurons. J Neurophysiol. 2015 Apr 1;113(7):2700-12. doi: 10.1152/jn.00736.2014. Epub 2015 Feb 11. PMID: 25673737; PMCID: PMC4416558. Bottom panel based on data from Wilson DM, Lemon CH. Modulation of central gustatory coding by temperature. J Neurophysiol. 2013 Sep;110(5):1117-29. doi: 10.1152/jn.00974.2012. Epub 2013 Jun 12. PMID: 23761701; PMCID: PMC3763089.

In this experiment, the activity of neurons in the NTS was recorded while fluids of different temperatures, containing different tastants were flowed over a mouse's tongue. The top of the figure shows firing of a sucrose-oriented NTS neuron in response to room temperature sucrose and warm sucrose, which results in more firing than the room temperature solution. The responses of NTS neurons to temperature are not all the same, though. The salt-oriented NTS neuron fires less to warm salt than room temperature salt, for example. The bottom on the figure shows more evidence of this variability across NTS neurons, with some tastants leading to more firing when warm, some leading to less and some seeming relatively insensitive to this temperature change. This anatomical and physiological arrangement is one biological explanation for the observation that temperature and other sensory information can have a profound impact on flavor perception.

Gustatory pathway and cortical processing

Ultimately the gustatory information from the NTS is relayed to the primary gustatory cortex (GC), where the conscious perception of taste occurs. In humans and other primates, fibers from the NTS project directly into the parvocellular division of the ventral posterior medial nucleus of the thalamus (VPMpc), and then into the GC.

The conscious perception of taste occurs in the GC. This cortical region can be viewed by separating the lateral sulcus and is found along the anterior insular lobe and frontal operculum (see Figure 8.9). In a variety of vertebrates, techniques from electrophysiology to cellular and functional imaging have established that neurons of the gustatory cortex demonstrate differential activity in responding to chemicals with different tastes. Additionally, some neurons in the region fire different patterns of action potentials in response to changing concentrations of tastants. Thus, both the identity and intensity of the chemical stimuli detected by the taste receptors of the tongue can be represented in the GC. From the GC, a large portion of gustatory information passed on to the secondary gustatory cortex, located in the caudolateral section of the orbitofrontal cortex and ultimately integrates gustatory signals with other sensations, including those of satiety.

Gustatory information is not just a one-way street to the primary and secondary GC, though. Interconnection with other sensory modalities, and even other non-sensory systems, occurs throughout the gustatory neural pathways. The gustatory connections to the limbic system are one, particularly important example of this cross-talk. Along the gustatory neural pathway, collateral and descending fibers pass gustatory signals back to the NTS and into the limbic system, modulating the limbic system's regulation of feeding behaviors. For example, the neural connections between the GC and the lateral hypothalamus allows for gustatory signals to immediately modulate feelings of satiety.

Additionally, neural inputs to the amygdala mediate negative associations with foods that might have poisoned an animal. For

example, it is common for people who have suffered from food poisoning to avoid the food that has made them sick for a long time. This is a phenomenon called conditioned taste aversion and is observed in a variety of animals. In the lab, rodents will avoid a novel tastant if it is paired with a subcutaneous injection of KCl (which makes the animal feel sick) just a single time. A conditioned taste aversion is an important tool for designing experiments to assess if an animal perceives two chemicals as having similar tastes; specifically, if an animal that has a conditioned taste aversion to one chemical also avoids a different chemical, then the animal likely perceives the two chemicals as having the same or a very similar taste. This behavioral assay has been an essential tool for studying taste perception in animals.

Neuroscience Across Species: Non-mammalian gustatory systems

Across species, chemosensory cells that detect the same broad classes of biomolecules are almost always concentrated around the entrance to the digestive tract. So far, we have talked mostly about taste in animals like mammals, which sense chemicals they might ingest using taste buds in the interior of their mouth. In contrast, in the common model organism *Caenorhabditis elegans* (a roundworm of phylum Nematoda), chemosensory neurons are found associated with the lips that physically gate the digestive tract. Segmented worms like leeches and earthworms are literally covered in chemoreceptors (on their skin), but these cells are most concentrated on the prostomium—the scoop-like first segment with functions analogous to a tongue or proboscis. In radially symmetric octopodes, chemosensory cells are present inside the suckers on the 8 arms surrounding their beaked mouths (van Giesen, et al., 2020). Even among hydra (phylum Cnidaria), whose nervous system consists of a simple neural network, chemical cues triggering feeding reflexes are influenced by internal metabolic states (Grosvenor, et al., 1996). Even filter feeders are often capable of modifying behavior in response to the chemical contents of their feeding substrate.

We know an especially large amount about how gustation occurs in the commonly-studied fly species *D. melanogaster*. The *D. melanogaster* exoskeleton is covered in hair-shaped sensory organs called sensilla. While hair on a human's body can provide mechanosensory information, an individual sensillum on a fly may be specialized for mechanoreception or *chemoreception*. Gustatory sensilla can be found on their wings, tarsi (legs), and body but are concentrated on the proboscis. This anatomical arrangement allows fruit flies to "taste" any surface they land on and, if appetitive chemicals are present, reflexively extend their proboscis (mouth parts) to feed.

While the anatomical location of gustatory sensilla in the fly is quite different than that of mammalian taste buds, how the two sensory cell systems work is analogous. Like taste buds, each sensilla contains neurons analogous to taste receptor cells; these gustatory receptor neurons (GRNs) detect different classes of chemicals. Each GRN is a bipolar neuron, whose cell body is inside the sensillum with an axon projecting to the insect's central nervous system, and a dendrite projected towards a taste pore at the sensillum tip. GRNs detect chemicals using a different receptor family than vertebrates—they are ligand gated ion channels, not GPCRs. These receptors are expressed in combinations that make different GRNs sensitive to sugars, simple ionic compounds (salts), pure water and alkaloids or other compounds humans perceive as bitter. It is worth noting here that despite this nomenclature, we do not know if a fly's gustatory experience of alkaloids (or any of these other compounds) is at all like what we humans would describe as "bitter!" We can say that flies typically avoid these and that their behavioral response to these compounds is similar to that of vertebrates. Notably, while there is controversy over how gustatory information gets organized centrally in mammals, in flies there is good evidence that information follows a labeled line coding model, where specific pathways mediate specific tastes all the way to the higher centers of the CNS.

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6.3.3: The Olfactory System

Learning Objectives

By the end of this section, you should be able to

- Define the relevant anatomy and cell types of the olfactory system.
- Describe the neural circuitry involved at each layer of the processing hierarchy of the olfactory system and its relationship to odor perception.

Imagine the smell of freshly baked bread or a cup of coffee on a lazy weekend morning. Now turn your attention to the visual scenery that accompanies this thought. Your mind has probably already filled in many of the details for you. For many people, the sense of smell is so powerful it can even transport us back in time, conjuring vivid memories of people, places, and events.

The sense of smell, or olfaction, has a direct input to the emotional centers of the brain. With its direct input to the limbic system (see amygdala), the sense of smell is also critically involved in social behaviors across the animal kingdom. Olfaction arises from interactions between specialized sensory receptors and chemicals we encounter in the environment. In this section, we will explore how molecules inhaled into the nose are detected and encoded by the brain and how odors might elicit powerful memories and behaviors in some animals.

The nasal cavity

The primary sensory organ for the olfactory system is a sheet of tissue found deep within the nasal cavity called the olfactory epithelium (Figure 8.14). The olfactory epithelium within the nose is responsible for detecting airborne odorous molecules. These molecules, also called odorants, are the basic unit that can elicit the sensation of an odor.

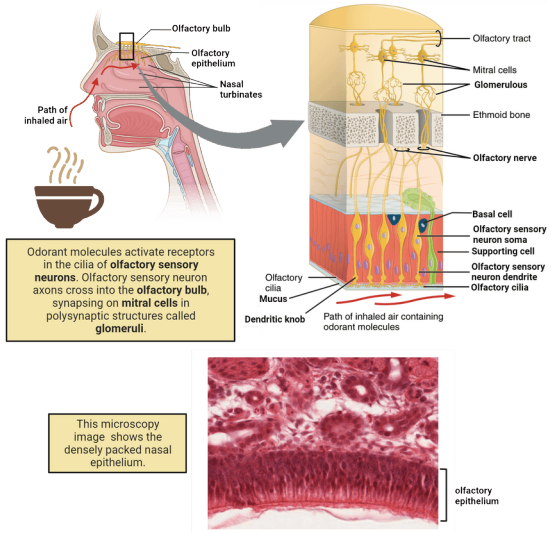


Figure 8.14 Olfactory epithelium anatomy Image credit: Modified from original image by adding/removing labels, adding basal cell, and reconstructing top left panel. Original image by OpenStax.

Odorants are typically small enough that they can become suspended in the air and drawn into the nasal cavities. Inside, odorants travel through intricate caverns called turbinates, which are formed of bone and cartilage. These structures filter, humidify, and warm inhaled air, but they also play a critical role in directing odorants onto the relatively restricted area of the nasal cavities which contains the olfactory epithelium.

The structure of the nasal cavities is highly variable between animal species. For example, many mammal species, like dogs and

bears, have evolved intricate nasal passages that play an important role in their ability to detect extremely low concentrations of an odorant. The large surface area of their turbinates ensures that small amounts of odorants are forcefully propelled onto the olfactory epithelium. In addition to specialized turbinates, dogs, bears, and many other animals have a larger olfactory epithelium than humans do, which contributes to their excellent sense of smell.

Olfactory epithelium and sensory neurons

Located deep within the nose, the olfactory epithelium is a specialized portion of the nasal cavity. The placement of this important tissue ensures that it is protected from damage caused by inhaling toxins and positions it close to the brain. There are three main cell types that make up the olfactory epithelium. Olfactory sensory neurons are the cells tasked with detecting odorants, supporting cells provide structure and surround the sensory neurons, and basal cells are the precursors from which regenerating sensory neurons arise (Figure 8.14)

Olfactory sensory neurons each have a single enlarged dendrite that extends outwards from the epithelium and terminates at the epithelial surface in a specialized structure called a knob. The knob is an integrative hub for fine hair-like structures known as cilia extending through the mucus lining that coats the olfactory epithelium. The cilia are important structures because olfactory receptors, the proteins that interact with odorant molecules, are found along the length of each of these projections. The olfactory receptors are part of a large gene family that varies by species. Humans have ~300-400 receptor genes, while mice and dogs have more than 1000! (Malnic et al., 2004; Zhang and Firestein, 2002).

Signal transduction in olfactory sensory neurons

Olfactory receptors are metabotropic receptors, meaning that they are coupled to a G-protein second messenger on the intracellular side of the neuron. The binding sites for odorants are, of course, on the extracellular side, exposed to the nasal cavity. In olfactory receptors, the G-protein is a specialized stimulatory G-subunit (G_{olf}). Figure 8.15 shows the intracellular signaling activated by odorant binding and G_{olf} activation.

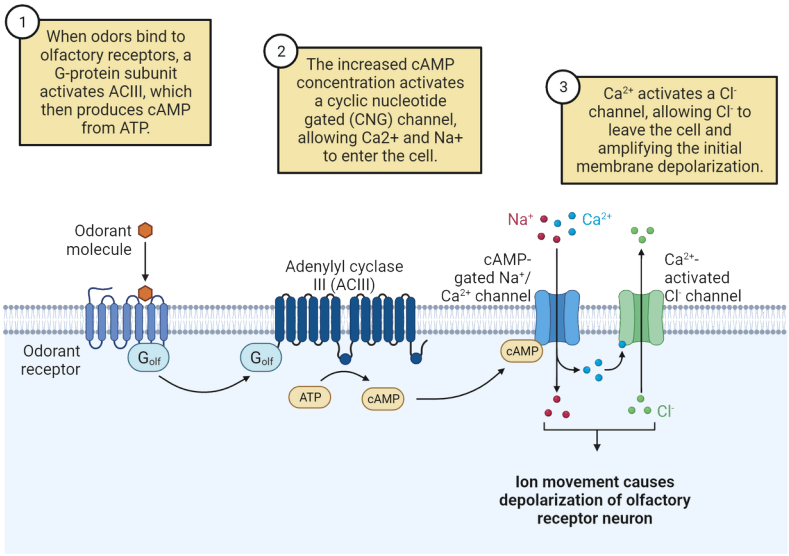


Figure 8.15 Olfactory receptor signaling

Once bound to an odorant, the olfactory receptor complex releases G_{olf} to the intracellular side of the membrane. When released from the receptor complex, G_{olf} then stimulates the activity of the catalytic enzyme adenylyl cyclase III (ACIII). The role of ACIII in this series of events is to then convert adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). cAMP then serves as a ligand to cyclic nucleotide gated (CNG) channels, which are an entry point for Na^+ and Ca^{2+} ions into the sensory neurons. Because both Na^+ and Ca^{2+} carry a positive charge, this results in a membrane depolarization of the sensory cells bringing them toward the action potential threshold.

However, there is an additional step that has been proposed to amplify these initial membrane depolarizations through the CNG

channels. The increased intracellular abundance of Ca^{2+} ions begins to act on calcium-activated chloride channels (CaCC). With respect to the mucous that surrounds cilia, the internal cellular concentration of chloride is elevated. This means that when CaCCs are activated by Ca^{2+}, negatively charged Cl- ions flow out of the cell, thus amplifying the initial membrane depolarization from the CNG channels.

This molecular chain of events results in action potentials being generated near the soma of the sensory neurons that contain the receptor proteins on their cilia. We can think about odorant molecules as being similar to neurotransmitters that generate electrical activity between neurons within the brain. The signals then travel down sensory neuron axons that extend through perforations in the cribriform plate, a bony structure that separates the brain from the nasal cavities. The axons and their electrical signals then arrive at the brain in the olfactory bulb, where they synapse with the central processing circuitry of the olfactory system.

A key organizing principle of the olfactory system is the molecular logic by which the cilia of olfactory sensory neurons express olfactory receptor proteins. The genome of most animals encodes hundreds of olfactory receptors, each of which has a unique binding site that will recognize only a narrow range of chemical shapes. Though there are hundreds of receptor genes, only a single type is expressed on the cilia of each sensory neuron. Although each sensory neuron may express thousands of receptor proteins, each of them will be exactly alike (Figure 8.16).

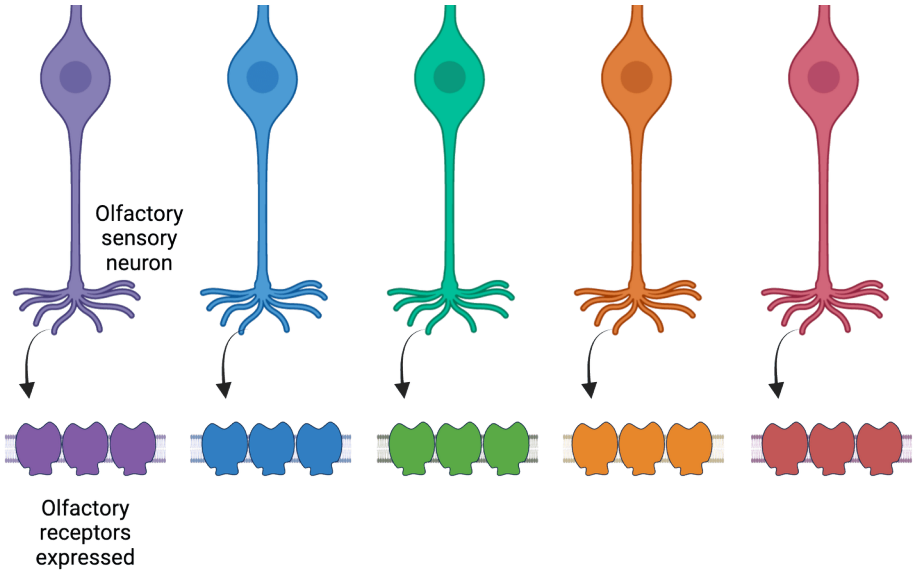


Figure 8.16 One receptor type per neuron in the olfactory system There are hundreds of unique olfactory receptor genes but an individual olfactory sensory neuron only expresses 1 receptor gene.

People behind the science: The discovery of olfactory sensory neuron genetics

We now know that the genes that encode the olfactory receptor proteins are the largest class of G-protein coupled receptors, including hundreds of unique protein types in humans, and over a thousand in rodents! However, the identity and function of these proteins were once a mystery in the field of biology. In 1991, Dr. Linda Buck, then a postdoctoral fellow, was working in the Laboratory of Dr. Richard Axel at New York's Columbia University. With the help of a then newly developed technology called polymerase chain reaction, she not only solved the mystery of how many receptor types there are in the olfactory system but also demonstrated that they came from a previously unknown superfamily of G-protein coupled receptors (Buck and Axel, 1991). Her discovery revealed the molecular diversity that underlies the peripheral olfactory system and the incredible wiring logic by which the system assembles during development.

This revelation was not only foundational for understanding the olfactory system but also had far-reaching implications across biological domains to fields including drug discovery, gene regulation, and the wiring logic of the brain. In 2004, Drs. Buck and Axel were awarded the Nobel Prize in Physiology or Medicine for their discovery.

OSNs are renewed throughout life

A special feature of the olfactory system is that, unlike other senses including vision and hearing, olfactory sensory cells are constantly regenerating. In fact, even without specific or acute damage, olfactory sensory cells are constantly turning over. It is speculated that, because the nose draws in numerous potentially damaging agents from the environment (dust, germs, pollution, etc.), frequent turnover of the sensory cells is a mechanism to ensure that the system remains in good working condition.

In the olfactory epithelium, stem cells line the nasal passages and give rise to newly generated sensory neurons that incorporate with the existing circuitry. As you will read below, sensory neurons of a common subtype must find a highly targeted and specific region of the brain to terminate. Exactly how newly regenerated sensory neurons find their way to the olfactory bulb is still a mystery, but some work tells us that the expression of receptor proteins outside of the sensory cilia may play an important role.

Unfortunately, as we age our body begins to lose its ability to regenerate sensory neurons. This ability is impacted by inflammation, disease, and injury, all of which accumulate as we get older. Because sensory neurons do not replenish with the same regularity, many people begin to lose their sense of smell in old age. In a later section, we will discuss how some well-known diseases affect our sense of smell.

Olfactory bulb circuitry

The olfactory bulb is responsible for the first stages of processing electrical signals as they arrive from the nose. Before arriving in the olfactory bulb, the axons of all sensory neurons that express the same type of receptor protein converge. Once in the bulb, the axons then form a spherical structure of nerve endings, dendrites, and synapses called a glomerulus. Because each glomerulus receives input from only a single type of olfactory sensory neuron, the input to these structures is receptor type specific. Each odorant activates a subset of olfactory sensory neuron types; therefore, many glomeruli are activated at the same time by a given odor. We can think of this as similar to how letters in the alphabet group together to form words. In this case, each letter represents an activated glomerulus, and their grouping as a word represents the perception of an odor. Importantly, words can be simple or complex depending on the number of letters they contain, just as an odor depending on the number of activated glomeruli.

It is still unknown how or if glomeruli are arranged in the physical space of the brain with respect to the chemical structure of the odorants that activate them. However, there is some evidence that there exist coarse groupings of glomeruli. Those that are activated by broadly similar odorant molecules tend to be located closer together. Furthermore, among animals of the same species, glomerular positioning and grouping is conserved (Soucy et al., 2009)

Glomerular layer neurons

Glomeruli are innervated by a number of cell types in addition to the nerve endings of olfactory sensory neurons. These cells include glutamatergic projection neurons that relay information to higher-order processing centers and inhibitory cells that help to process odor information within the olfactory bulb.

Projection cells of the olfactory bulb fall into two sub-classes of cells, mitral cells, and tufted cells. Mitral cells are the largest cells in the olfactory system and are found in a single row of cells sitting beneath the glomeruli. Each cell has a single apical dendrite that extends to one glomerulus where it ramifies extensively and receives input from olfactory sensory neurons, as well as other neurons within a glomerulus. While each mitral cell contacts only a single glomerulus, each glomerulus is innervated by ~10-20 mitral cells (Liu et al., 2016). Mitral cells also have characteristic lateral dendrites that extend deeper within the olfactory bulb, where they receive inhibitory input. Tufted cells share many of the same morphological characteristics as mitral cells, though their distribution is different. They also serve to relay information about odorants, as mitral cells do, but are more broadly tuned to odors and often can respond to lower concentrations than mitral cells.

In addition to these projection cells, the olfactory bulb hosts several classes of local interneurons. In general, these cells are thought to play an important part in refining the number of active glomeruli following an odorant encounter and coordinating the synchronous activity of olfactory bulb output neurons.

Cortical processing

Output from the olfactory bulb travels along the axons of the two classes of projection neurons: mitral cells and tufted cells.

Although these cells share many common features, they differ in both their responses to odorant stimuli and their projections to downstream processing centers of the brain. The primary targets of olfactory bulb output are the olfactory cortex, limbic system, and ventral striatum.

Piriform cortex

Mitral cells target a number of different brain regions, but perhaps the most predominant among them is the piriform cortex, also called the olfactory cortex. The organization of the piriform cortex is different from other sensory modalities because it contains three layers rather than the six typically found in other sensory cortices. Mitral cell axons from the olfactory bulb travel as a nerve bundle in the lateral olfactory tract and most densely target the anterior portion of the piriform cortex where they target broadly distributed and overlapping populations of neurons. Because neurons in the piriform cortex receive input from many different mitral cells, and each mitral cell can be associated with a different glomerulus, this is the first point in the olfactory system where stimulus information from the periphery is blended (Figure 8.17). However, unlike the olfactory bulb where some coarse relationship exists between glomeruli, the spatial distribution of cells in the piriform cortex has a minimal relationship to the odorants which activate them. This stands in contrast to other sensory modalities, like audition and somatosensation, where similar stimuli are represented in adjacent cortical fields. Despite this seeming disorganization within the olfactory system, the ensemble of neurons that become activated in the piriform cortex upon encountering an olfactory stimulus is related to how the stimulus is identified, categorized, and perceived by an animal.

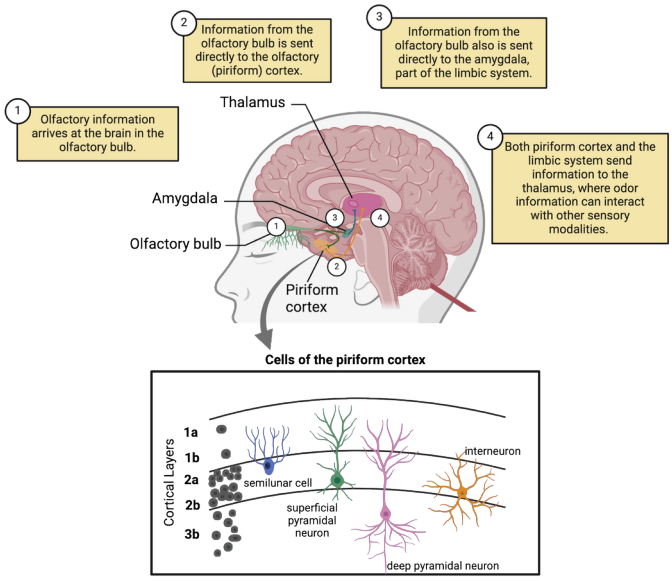


Figure 8.17 Neural pathways of olfaction

In addition to direct inputs from the olfactory bulb, the piriform cortex is a dense recurrent network and has extensive interconnections, called associational connectivity. The piriform cortex also contains local inhibitory connections that can oppose both inputs from the olfactory bulb and associational input. The local connectivity within the piriform cortex, both excitatory and inhibitory, allows the structure to perform important analytical functions like pattern completion, prediction, and odor categorization. While these functions allow animals to accurately interpret their environment, they also provide a mechanism for animals to make decisions about stimuli with only partial or incomplete information about a stimulus.

Anterior olfactory nucleus

The primary target of axonal projections from tufted cells is a structure known as the anterior olfactory nucleus (AON), which is found directly behind, or posterior to the olfactory bulb. The olfactory system is different from other sensory modalities in how the processing hierarchy is structured. While information from most senses is processed in the opposite brain hemisphere from which it was detected by sensory cells at the periphery, the olfactory system is lateralized. For example, the right olfactory bulb sends most of its projections to cortical areas in the right hemisphere, and the left olfactory bulb to the left hemisphere.

A key feature of the AON is that it sends projections that cross the brain through a nerve tract called the anterior commissure and terminate at contralateral brain hemispheres. Since this is one of the few places in the olfactory system where lateralization

is broken, it allows the AON to make comparisons between odor information arriving at each of the nostrils and may thereby play a role in orienting animals to an odor source. Similarly, because each AON receives bilateral input, it is thought that this structure may play an important part in odor navigation by allowing animals to make comparisons of stimuli that arrive at each of the two nostrils.

Amygdala and entorhinal cortex

Projections from the olfactory bulb target other brain regions that layer the rich texture that accompanies olfactory perception. Earlier, we discussed how odors can be linked with powerful memories and emotional states. These feelings arise through direct connections between the olfactory bulb and brain areas associated with memory, emotion, and reward. In addition to their projections to the piriform cortex, the axons of mitral cells branch and terminate in two structures contained within the limbic system, the amygdala and entorhinal cortex (Figure 8.17).

The amygdala is a powerful emotional center of the brain and its direct connection with the olfactory system is the reason that certain odors can provide powerful reminders of the emotional state in which they were encountered. For example, the smell of your grandmother's homemade soup may precipitate a feeling of comfort and safety. The same is also true for negative emotions and may provide an important mechanism for animals to avoid predation or other dangers.

The entorhinal cortex is strongly tied to memory formation, consolidation, and recall. In addition to the input it receives from other memory structures, like the hippocampus, it also receives direct input from the olfactory bulb via mitral cells. In the introduction of this chapter, we described how smells can conjure vivid memories of people and places — connectivity between the olfactory bulb and the entorhinal cortex helps this to happen. When smelling your grandmother's homemade soup, in addition to your emotional state, you likely recall other details of how you experienced the soup. For instance, the wallpaper in grandmother's kitchen or the pattern on the dishware that the soup was served in. These details are filled in and completed by the entorhinal cortex.

Adaptation

Have you come home from school and noticed that the trash in the kitchen smelled bad? Maybe you got distracted and then forgot to take the garbage out, but after a while, you no longer notice the smell. Some people call this perceptual phenomenon "nose-blindness", which is a common name for the physiological process called adaptation. There is actually a very important reason for "nose-blindness", in addition to saving you from the smelly scent of your forgotten garbage. Adaptation helps animals pay attention to changing features in their environment rather than focus on constant but otherwise distracting stimuli.

In the olfactory system, adaptation arises from physiological processes at the two ends of the system, the nose at the front and the piriform cortex at the back end. In the nose, adaptation results from the desensitization of olfactory receptor proteins for the odorant ligands. The abundant presence of an odorant molecule results in conformational changes to the receptor protein, thereby decreasing its efficacy in binding with a ligand and transducing a message about the stimulus. In the olfactory cortex, the precise mechanism of adaptation is not clear, but nonetheless, the overall effect is that ensembles of principal cells become less responsive to odor stimuli upon repeated presentation of the stimulus, and the perception of an odor decreases (Kadohisa and Wilson, 2006).

The accessory olfactory system

Many animals secrete chemical signals called pheromones that trigger social responses in animals of the same species. Reptiles, amphibians, and mammals, including some non-human primates, have evolved a division of the olfactory system, called the accessory olfactory system, dedicated to detecting these substances. This system operates using many of the same principles as the main olfactory system but uses anatomically distinct structures with different cellular organization and projections to deep brain structures that guide behavior and physiological states.

Many pheromones are oily substances and are therefore unable to be carried through the air. This creates a problem where these compounds are incapable of reaching the olfactory epithelium. The vomeronasal organ is a collection of sensory cells found near the entrance to the nasal passages that detect pheromones and other social odors (Figure 8.18). For compounds to reach this structure, it is necessary for an animal to touch its nose to another animal, or a secretion it has left behind. Many of us have observed this behavior before. When dogs greet each other on the sidewalk, often their first instinct is to touch their nose to the other dog. Here they are using pheromonal cues to communicate.

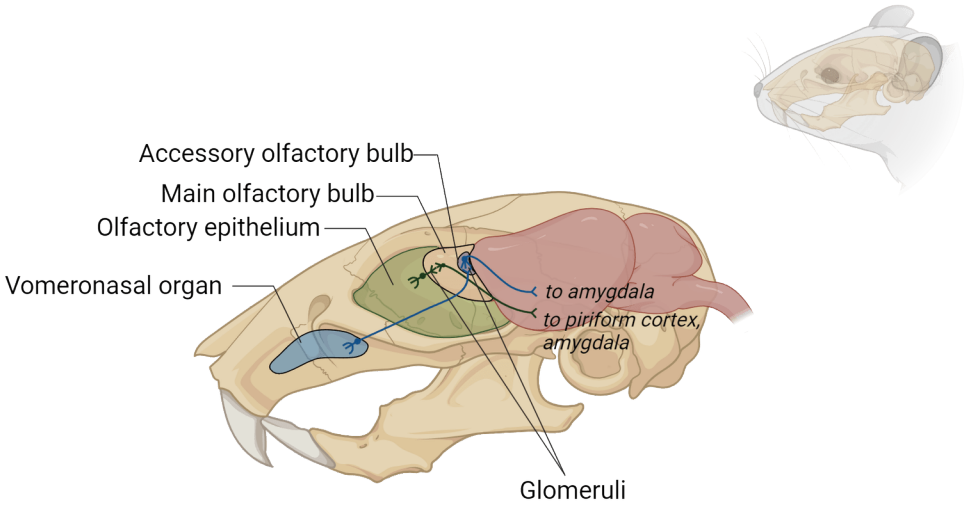


Figure 8.18 Accessory versus main olfactory bulb and epithelium connection

The vomeronasal organ is divided into two halves, one on each side of the nasal septum. Like the olfactory epithelium, it contains basal cells, supporting cells, and sensory neurons. The sensory neurons of the vomeronasal organ contain G-protein coupled receptors that are sensitive to specific social compounds depending on the type of receptor protein that they express. The sensory cells of the vomeronasal organ project axons to the dorsal posterior portion of the olfactory bulb where an accessory subdivision is found (accessory olfactory bulb) (Figure 8.18). The accessory olfactory bulb contains many of the same cell types as the main olfactory bulb; however, the circuit organization is somewhat different.

Neuroscience in the lab. Sex as a biological variable: Social odor detection in humans

It is quite intuitive how our sense of smell influences our food preferences or even the type of perfume that we like. But can our sense of smell also influence how we interact with other people, and does olfaction play a role in human mate selection as it does in many animal species? A Swiss biologist named Claus Wedekind set out to answer this question in an experiment known as the "sweaty T-shirt study." In his study, men were asked to wear a t-shirt for two days without bathing. Then, women participants were asked to sniff a hole in a box containing each shirt and rate the shirts as more or less appealing. When the genetic makeup of the men and women was compared, it was revealed that women selected t-shirts from men who had the most divergent genetic sequence for a set of genes called the major histocompatibility complex (MHC). MHC genes are part of the adaptive immune system, and in effect, women were selecting men in a way that might boost the fitness of their potential offspring by conferring greater immune selectivity. Although the exact mechanism is still a mystery, MHC genes are speculated to be linked to a body scent that can be detected by the opposite sex, even if subconsciously. Though it might be tempting to think this effect relies on pheromones and the vomeronasal organ, the vomeronasal organ is often absent from the nasal passages in humans. And if one is present, it likely only exists as a vestigial organ. In the case of humans, social odors are detected by the main olfactory system.

The olfactory system and disease

You might not think that the inability to smell would impact your day-to-day life; however, you would be woefully wrong. Do you remember the jellybean experiment? This would become your reality for every meal. Food would lack depth and your favorite meal would become uninteresting. Earlier, we learned about several animal behaviors that strongly rely on olfaction: navigation, nutrient sensing, and mate selection. Without the ability to smell, an animal's survival would be at risk. People with the inability to smell are also at a survival disadvantage. People with anosmia, the inability to smell, face a lifetime mortality rate four times higher than the average person (Pinto et al., 2014). These differences arise through difficulties in detecting hazardous circumstances like natural gas leaks, fires, chemical vapors, and decayed food. Unfortunately, for humans, there are several circumstances through which we may lose the ability to smell. These include normal aging, damage from a head injury, and disease. Below, we will discuss two causes of anosmia: neurodegenerative disease and Covid-19.

Olfactory dysfunction in neurodegenerative disease

Reduced olfactory capabilities and the loss of olfactory acuity is a leading indicator of two well-known neurodegenerative diseases. Alzheimer's disease is widely known for a profound deficit in both short and long-term memory, which has become a hallmark of the disease. In addition, disrupted olfactory sensation and anosmia are frequently reported by patients with Alzheimer's disease before they begin to experience memory deficits. Because of this, olfactory dysfunction is a leading indicator of the disease and there is great interest in using olfactory capabilities as a disease biomarker. Parkinson's disease is another neurodegenerative disorder that manifests with early olfactory deficits. In Parkinson's disease, dopaminergic neurons die, leading to that disease's hallmark motor deficits. The olfactory bulb also contains many dopaminergic neurons, as well as dopaminergic projections from other areas of the brain. Nearly all patients with Parkinson's disease experience deficits in their sense of smell, which often occurs years before the onset of motor symptoms. These symptoms can be used as a warning sign and if treatment is started early enough, medication can delay the progression of the disease.

Covid-19

The coronavirus pandemic that started in 2019 has brought increased attention to olfactory dysfunction. A symptom of many coronavirus infections has been transient anosmia that generally resolves as the viral infection is cleared. However, for some particularly unlucky people, a coronavirus infection has left them with persistent anosmia or sensations of unpleasant odors from otherwise innocuous smells.

Covid-19 is primarily transmitted as respiratory droplets, which means that as it is passed from person to person, it typically enters its next host through the nasal passages. Earlier in this section, we learned that the olfactory epithelium is found deep in the nasal cavities, and in addition to infecting and reproducing in respiratory tissues, coronavirus also infects cells in the olfactory epithelium. The receptor protein ACE2 is densely expressed in the supporting cells of the olfactory epithelium and is a target of Covid-19. When these supporting cells are infected, they become inflamed or damaged. Inflammation of the epithelium then disrupts the ability of nearby olfactory sensory neurons to transmit information about the odor environment to the brain. However, because sensory neurons themselves do not appear to be infected or destroyed by Covid-19, once the infection has passed, and inflammation of supporting cells subsides, normal olfactory function typically resumes.

Unfortunately, for some people, the Covid-19 induced inflammation of the olfactory epithelium becomes more than the tissue can handle and results in the death not only of the supporting cells, but also of the olfactory sensory neurons through indirect effects. We learned earlier that sensory neurons are constantly regenerating, and this is also true after a coronavirus infection. However, we also learned that sensory neurons must target their appropriate location in the brain for accurate odor recognition. When all or many of the olfactory sensory neurons die at the same time, they are no longer able to reliably find their correct location and glomeruli end up receiving mixed input from many different types of sensory neurons. When this happens, a person will regain their ability to smell, but it may not quite be the same. In this scenario, people often report unpleasant smells that accompany objects that otherwise would not smell bad. This is called parosmia. Some people will eventually recover from parosmia, while for others it can persist for years.

Insect olfaction and disease.

Neuroscience Across Speciess: Across the animal kingdom, different species have evolved unique strategies for sensing their chemical environment. Arthropods, including insects, lack sensory cells in their respiration pathways and instead have evolved olfactory sensors that are found along their body segments. In insects, olfactory sensors are found in specialized body segments attached to the head called antennae. Despite these differences, insects use the chemical senses for the same behaviors and functions as their vertebrate counterparts. Just as bees must find flowers to collect nectar, all insects seek to find nutrients, reproductive opportunities, and to avoid predation.

One of the most well-studied olfactory systems is the fruit fly, *Drosophila melanogaster*. You might be wondering, "why do scientists spend time thinking about a bug's sense of smell." It turns out there are some pretty good reasons. Insects like bees use olfaction to collect nectar from flowers, and at the same time spread pollen that helps to germinate fruit. Conversely, insects can also destroy food crops of all varieties through infestation. Developing aversive odorant-based repellents negates the need to use harmful pesticides to prevent these losses. Understanding insect olfaction is also an important public

health consideration. Infectious diseases including malaria, dengue, and Zika are spread by a remarkably common insect, the mosquito. As you may well have experienced, female mosquitoes require a blood meal before they can reproduce, and humans are often their target

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6.4: THE SOMATOSENSORY SYSTEM

6.4.1: Somatosensory Receptors
6.4.2: Somatosensation in the Central Nervous System
6.4.3: Pain and Itch

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6.4.1: Somatosensory Receptors

Learning Objectives

By the end of this section, you should be able to

- Describe the anatomical properties of different sensory receptors.
- Identify the physiological properties of different sensory receptors.
- Describe the anatomy and neurotransmitter usage of primary afferents to the spinal cord.

When you lift a hot pot of boiling water from the stove, not only do you feel the temperature but also vibration due to the boiling content. Further, you may also notice the texture of the handle. How does this happen? How can you sense so many properties at once? Among all five senses, the body sense (somatosensory system) starts with the largest variety of different unique receptors. Each receptor connects via an axon to the central nervous system to transmit information to our brain to enable perception. This section will review how these receptors transduce such a variety of skin signals into neural signals headed to the central nervous system.

Peripheral receptors and functional modalities

Each somatosensation starts with the activation of one or more types of peripheral somatosensory receptors. Peripheral receptors include several major types, such as the Merkel disk, Meissner's corpuscle , Ruffini endings, Pacinian corpuscle , free nerve endings, and hair cells (Figure 9.2). These different sensory receptors enable us to feel touch, pressure, vibration, pain, and temperature.

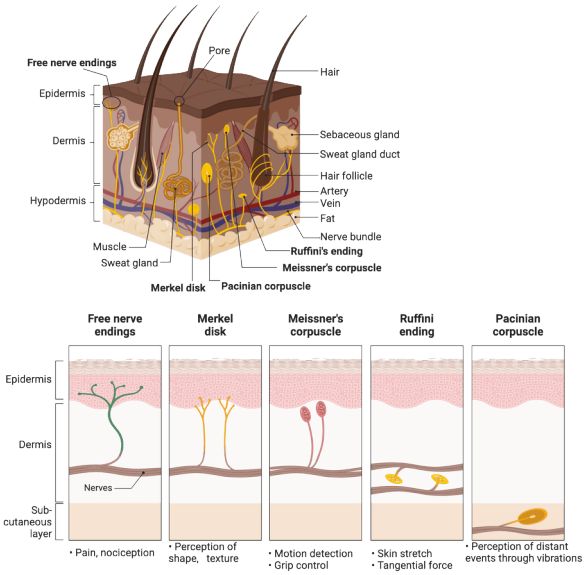


Figure 9.2 Mechanoreceptory types In this example from the skin, there are Merkel disks and Meissner's corpuscles in the superficial part of the skin. Hair follicles, Ruffini endings and Pacinian corpuscles sit in the deeper part of the skin. All of these use large myelinated Aβ-fibers. Unmyelinated C-fiber Free nerve endings are found throughout the skin.

Touch receptors

Merkel disk, Meissner's corpuscle, Ruffini endings, and Pacinian corpuscle all serve to transduce features of touch sensation. These disks and corpuscles are specialized structures in the skin that are connected to axons that send touch information to the spinal cord. These terminal structures are the starting points of the somatosensory system, so they are also called "sensory receptors". Here the term "receptor" is different from the neurotransmitter receptor on the cell membrane (much smaller, one

protein molecule). The sensory receptor is a much larger structure (composed of many proteins). Within these specialized endings sit mechanosensitive cation channels which activate in response to mechanical pull from sensations like touch, pressure, and vibration. These channels, also called piezo channels, are permeable to Na^+, K^+, Ca^{2+}, and Mg^{2+}, with a slight preference for Ca^{2+}. Figure 9.3 shows the protein structure of two major piezo channels. They both are made of 3 proteins that come together to form a central pore, through which ions move, with blade-like structures surrounding the pore. The discovery of piezo channels led to a Nobel prize in 2021 for Dr. Ardem Patapoutian, the scientist who first described them (Coste et al., 2010) (Figure 9.3). Figure 9.4 shows how these channels open in response to mechanical force. The influx of ions through these channels leads to the generation of action potentials which propagate via highly myelinated Aβ fibers to the spinal cord.



Figure 9.3 Piezo channel structure Signals responsible for mechanosensation are transmitted by piezo channels. Piezo channels are composed of three proteins forming blades around a central pore.

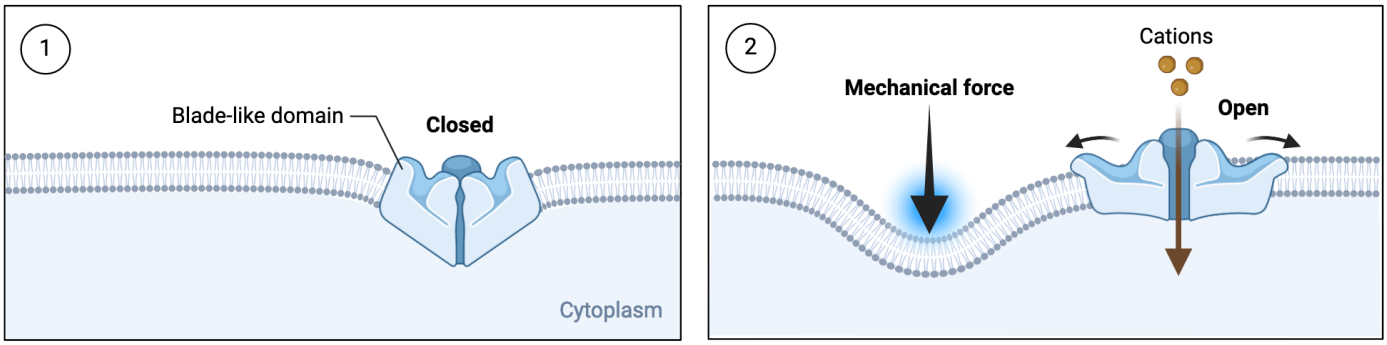


Figure 9.4 PIEZO Channels: How Do They Allow Mechanosensation? PIEZO1 and PIEZO2 are both mechanically-activated cation channels. Based on protein structure, it was predicted that the 'blades' of the PIEZO channels undergo a lever-like flattening motion upon application of mechanical stress. This opens up their central pore, allowing an influx on positive charge. The exact mechanism by which mechanical force leads to the central pore opening is not fully understood.

The four major mechanoreceptors (Merkel disks, Meissner's corpuscles, Ruffini endings, and Pacinian corpuscles) are each sensitive to different kinds of touch. The location and shape of each receptor structure supports these different sensitivities. Figure 9.5 summarizes these key features of the 4 receptor types. Next, we will review some key structural features of these receptors and how they support the receptor function.

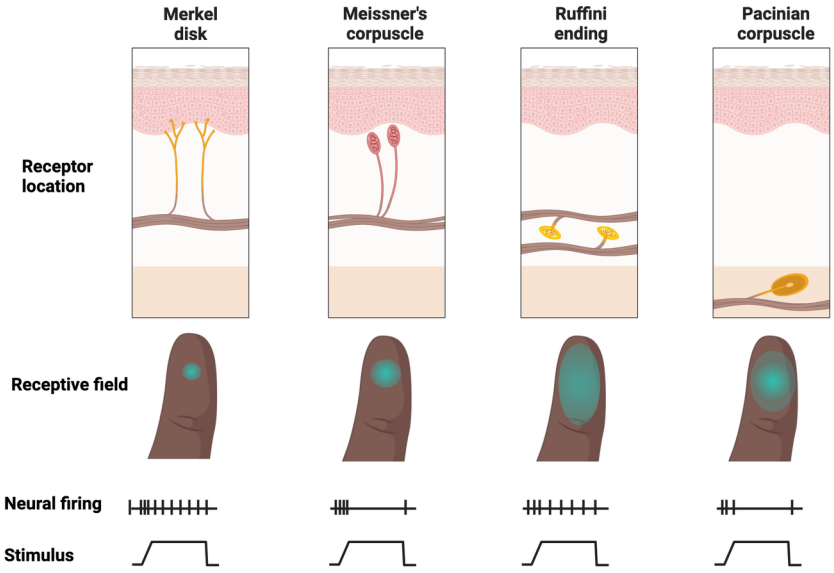


Figure 9.5 Mechanorecpetor receptive fields and adaptations

	Merkel disk	Meissner's Corpuscle	Ruffini ending	Pacinian corpuscle
Skin location	Superficial	Superficial	Deep	Deep
Adaptation	Slow	Rapid	Slow	Rapid

Table 9.1

First, their different locations in the skin help determine how large or small their receptive fields are, which for touch receptors means the area of the skin in which touch can activate them. Merkel disks and Meissner's corpuscles are located more superficially around the epidermis and therefore have a smaller and clearly-defined receptive field. Ruffini endings and Pacinian corpuscles are located more in the deeper part of the skin (with a larger, blurry receptive field), near where hair follicles are located.

Second, the shape and composition of each touch receptor help determine how long they respond to stimuli, dividing them into rapid adapting versus slowly adapting receptors. The slowly adapting receptors include Merkel disk and Ruffini endings. When a force or stimulus is applied in their receptive field, those receptors will be constantly activated and generate electrical activities (e.g., pressure). On the other hand, the rapidly adapting receptors such as Meissner's corpuscle and Pacinian corpuscle only respond or generate electrical activities when there is a dynamic change of forces or stimuli, such as vibration (Johansson and Vallbo, 1983; Koerber and Mendell, 1988). These adaptation properties combine with the receptive field to give the unique sensitivity of each of these 4 receptor types to specific touch modalities described in Table 9.1.

Nociceptors

The specific receptor for sensing a high-threshold stimulus that is damaging or threatens damage to normal tissues is called a nociceptor. Free nerve endings serve as nociceptors, or receptors that transmit pain signals related to mechanical, thermal, or chemical sources. Free nerve endings are different from the preceding four mechanoreceptors. The role of free nerve endings is related to sensing pain and temperature. Free nerve endings lack any specialized structures around their terminals and are connected to or in continuation with unmyelinated C-fibers and myelinated Aδ fibers. There are separate types of nociceptors responding to each modality (i.e., mechanical, thermal, and chemical), but also polymodal receptors that respond to all. Below we will discuss further how nociceptors sense tissue damage and temperature specifically.

Some free nerve endings transmit pain signals related to tissue damage (Figure 9.6). For example, if someone cut their finger, the direct and indirect damage of the nerve terminals (C- or Aδ fibers) at the primary injury site will excite and generate action potentials, which will not only propagate to the spinal cord (generating pain perception), but also propagate through the axonal branch points to spread to other axonal terminals that connect to the same main axon. The invasion of action potentials to the nearby uninjured axonal terminals will lead to the release of several key neural peptides, CGRP (calcitonin-gene related peptide) from Aδ fiber and SP (Substance P) from C-fiber, which cause vasodilatation (redness and temperature) and plasma extravasation

(edema). This phenomenon is called axonal reflex, a mechanism contributing to neurogenic inflammation. The primary injury also breaks blood vessels, leading to the accumulation of white blood cells, especially the mast cell. Mast cells can also release these neuropeptides and stimulate the axonal terminals and capillaries, leading to redness (*rubor*), heat (*color*), swelling (*tumor*), pain (*dolor*), and loss of function (*functio laesa*), cardinal signs of inflammation.

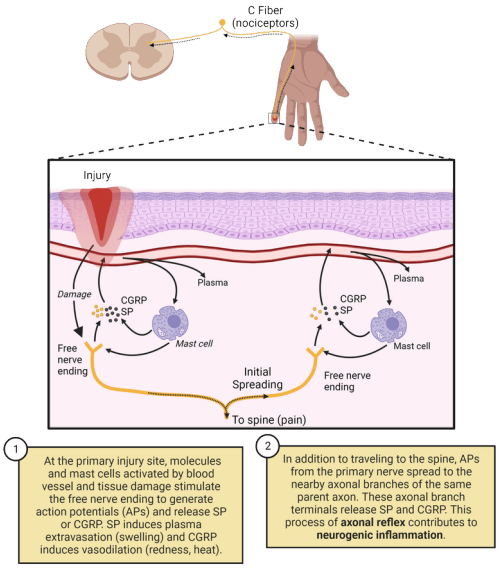


Figure 9.6 Local mechanisms of nociception

Other free nerve endings contain transient receptor potential (TRP) channels, which are temperature-sensitive mechanoreceptors. TRP channels open in response to temperature and come in a variety of types, each one sensitive to a different temperature. Figure 9.7 reviews the temperature sensitivities of several kinds of TRPs. Dr. David Julius, also pictured in Figure 9.7, shared the 2021 Nobel Prize in Physiology or Medicine for his description of these channels. Figure 9.8 shows an example of how heat causes a warm-sensing TRP channel to open, allowing in positive ions that activate the free nerve ending, which then relays signals to the brain via the spinal cord.

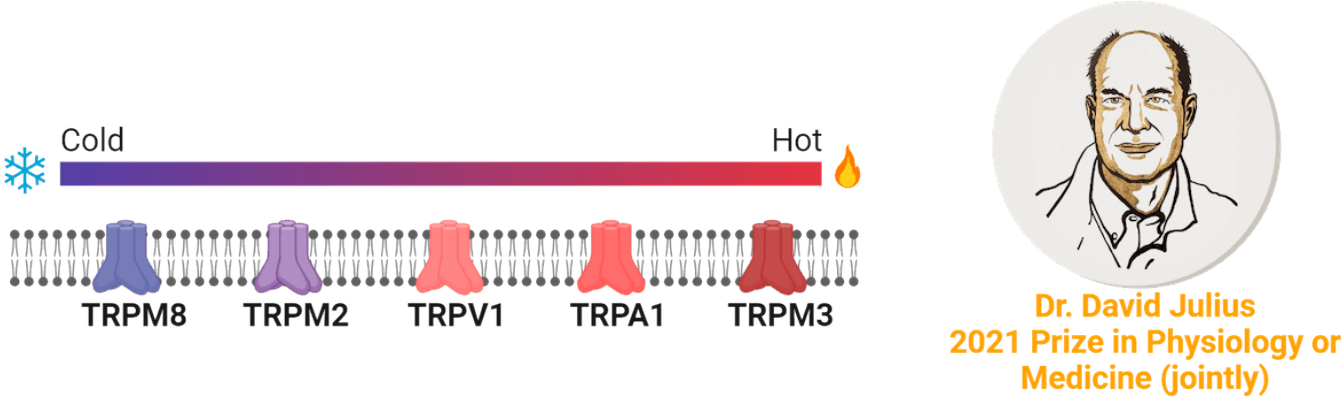


Figure 9.7 The TRP ion Channels Signals responsible for temperature and pain sensation are transmitted by transient receptor potential (TRP) channels that activate across different temperature ranges.

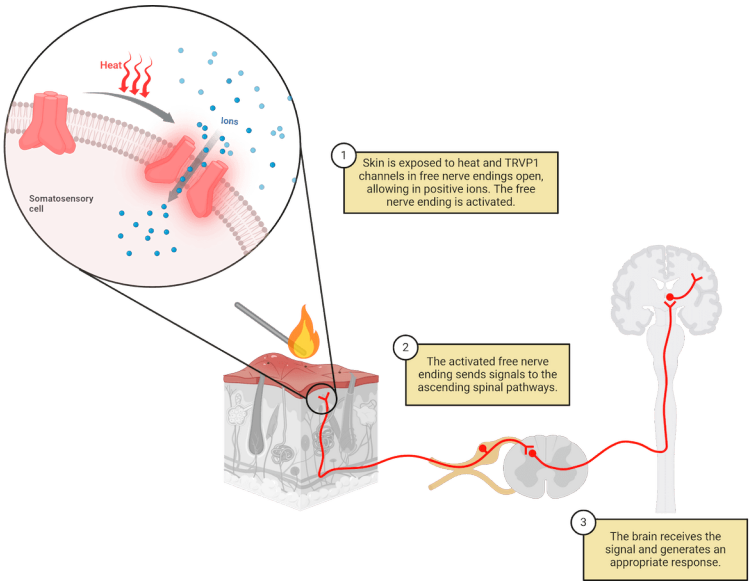


Figure 9.8 TRP channels transduce temperature information

One notable example of a TRP channel is the capsaicin receptor. Capsaicin is the key chemical ingredient in hot chili peppers. When it binds to the capsaicin receptors, it activates a TRP channel (Samanta et al., 2018) that allows calcium ions to flow into the cell, leading to depolarization (Caterina et al., 1997; Julius, 2013). This is the same channel activated by hot temperatures, which is why a spicy pepper feels hot . A similar, but separate TRP channel activates in response to cold temperatures, as well as chemicals in foods that feel cold, like mint. Activation of TRP channels, therefore, transmit information about temperature, and also are part of our experience of temperature sensations associated with a number of chemicals.

Hair follicle mechanosensation

Throughout our body, the skin can be divided into hairy and glabrous skin (mainly on the palms and soles). In the hairy skin, an axonal terminal wraps around the bottom of the hair, the hair follicle, in the dermis. The reason why we can feel a breeze blowing across our faces is that all those tiny hairs (vellus hair, or peach fuzz) are bent by the airflow. The force is transduced to the hair follicles in the skin, causing the slightest displacement (in terms of nanometers). The follicle displacement causes a stretch of the axonal membrane wrapped around the follicle. There are many mechanosensitive Na^+ channels in this wrapping axon, which open in response to this stretch. That is how we can feel the movement of hair. If the hair is pulled too hard, it can generate pain.

Proprioceptors

Imagine that in the middle of the night, you feel thirsty. Without turning on the light, you extend your arm to reach for a bottle of water. Even though there is no visual guidance, you grab the water without knocking it over or missing and grabbing air. Your ability to accurately target your hand to that water bottle with little visual or touch feedback relies on your proprioceptors. These specialized receptors exist in various muscles, tendons, and joint capsules, providing information about body position and movement. The muscle spindle and Golgi tendon organ are two of the most prominent proprioceptors that you use every day (Proske, 1979; Boyd, 1980; Hulliger, 1984). The muscle spindle is a specialized muscle fiber that is activated by muscle stretch; whereas the Golgi tendon organ is located in the tendon to sense the tension during muscle contraction. These receptors are connected to large diameter, A-alpha fibers. Together, they give you constant information about the location and trajectory of your limbs through space.

Primary afferents

As mentioned throughout the previous section, the different types of somatosensory receptors are connected to specialized axons with different diameters and myelination (Aβ, Aδ, C fibers, for example). Figure 9.9 shows the pathways these fibers take from the receptors (e.g., in the skin) into the spinal cord. These first-order axons are also called primary afferents (Crawford and Caterina, 2020). The cell body of the primary afferent fiber is located in the dorsal root ganglion (DRG), from which a pseudo-unipolar

neuron sends out a parent axon that splits off into a peripheral branch and a central branch (Lin and Chen, 2018; Haberberger et al., 2019). The peripheral branch is long and projects to the skin where it receives signals from a specific receptor, whereas the central branch is short and enters the nearby spinal cord through the dorsal root. The short branch ends with synapses onto the spinal cord dorsal horn neurons where neurotransmitters are released, or projects directly up the dorsal column of the spinal cord toward the brain. The spinal cord neurons also project up to various levels in the brain.

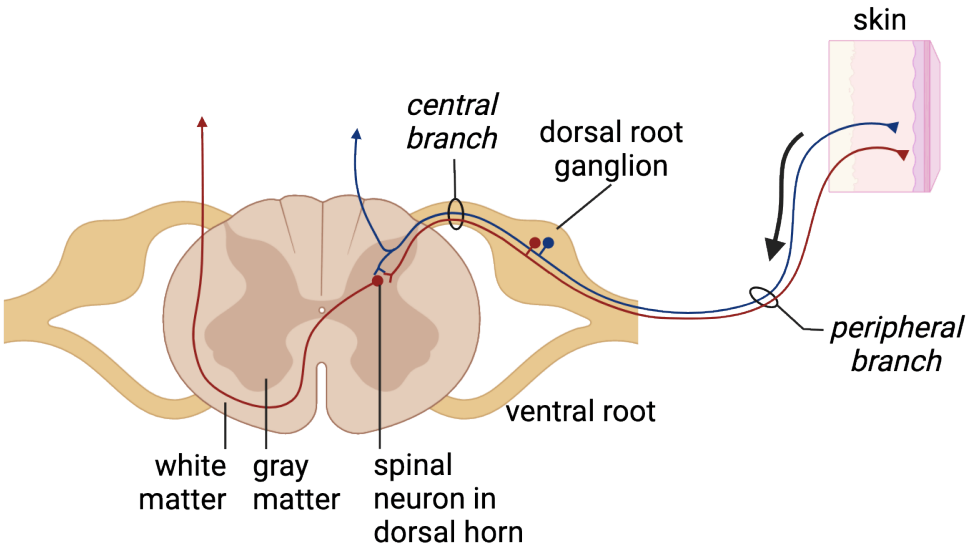


Figure 9.9 Primary sensory afferent anatomy Primary sensory afferents have cell bodies in the dorsal root ganglion. Their unipolar process splits into the peripheral branch, which goes to the sensory receptor and the central branch goes into the dorsal horn to synapse on spinal cord neurons.

While the primary afferents all follow a similar path to the spinal cord, they each propagate electrical signals along that path at different speeds. The A-fibers are a family of myelinated axons with different axonal diameters and extent of myelination. The larger the diameter, the faster the conduction of the action potential. Figure 9.10 provides a visualization of how these afferents compare in myelination and conduction speed. From large to small, they follow the order: Aα (12-20μm, 72-120 m/s), Aβ(6-12μm, 36-72 m/s), Aδ (1-6μm, 4-36 m/s), and unmyelinated C-fibers (0.2-1.5μm, 0.4-2 m/s). It is the difference of a racing car (120 m/s = 268 miles/hr) versus a fast walking (2 m/s = 4.5 miles/hr). Due to the difference in electrical signal conduction speed, even though both C-fibers and Aδ-fibers contribute to pain perception, Aδ-fibers are involved in fast and pricking pain, whereas C-fibers are involved in more slow and dull pain (Hunt and Mantyh, 2001; Julius and Basbaum, 2001).

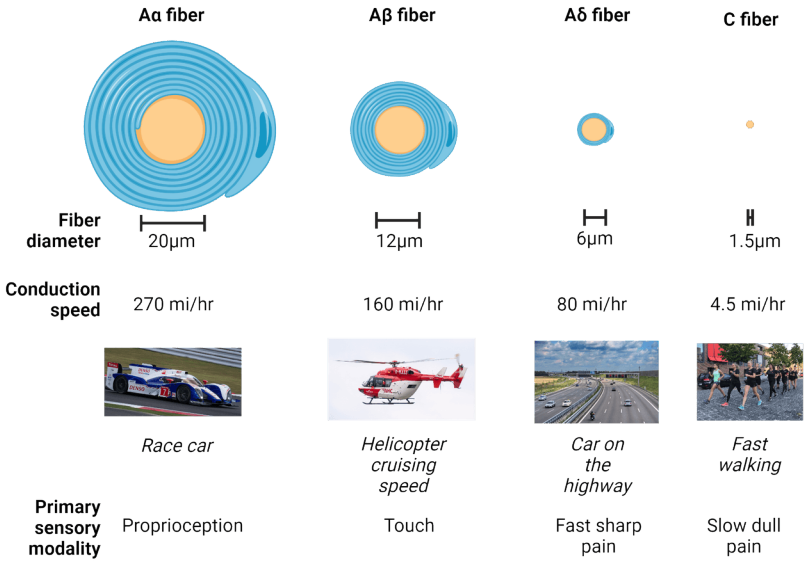


Figure 9.10 Sensory fibers Image credit: Race car image by Morio, CC BY-SA 3.0, https://commons.wikimedia.org/w/inde...curid=22169642 Helicopter image by Sebastian Koppehel, CC BY 4.0, https://commons.wikimedia.org/w/inde...curid=91350504 Highway image by Rl91, CC BY-SA 3.0, https://commons.wikimedia.org/w/inde...?curid=4591786 Walkers by Powerwalkingclub, CC BY-SA 4.0, https://commons.wikimedia.org/w/inde...curid=95373352

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6.4.2: Somatosensation in the Central Nervous System

Learning Objectives

By the end of this section, you should be able to

- Describe the anatomy of the spinal cord, thalamus, and somatosensory cortices.
- Define the ascending and descending pathways that are involved in transmitting somatosensory information.
- Explain the Gate Control theory.
- Describe how information flow to the limbic system contributes to the emotional response to pain.

From the cutaneous sensory receptors, action potentials travel through the dorsal horn to reach the lowest part of the central nervous system, the spinal cord. Axons with various levels of myelination and diameter synapse on the spinal cord dorsal horn or dorsal medulla neurons, then ascend to other levels in the brain, including the major relay station in the thalamus, and finally reach the primary somatosensory cortex where sensory perception happens. In this section, we will explain how sensory information is organized and processed from the dorsal horn of the spinal cord up to the brain, where we consciously perceive it.

Spinal Cord

The spinal cord is the lowest component of the central nervous system. It facilitates the transmission of body sensory information to the brain, as well as transmission of motor commands and autonomic nervous system modulation of internal organs from the brain to the body.

Anatomy of the spinal cord and dermatomes

The spinal cord has 31 segments, divided along the rostral-caudal axis into cervical (8), thoracic (12), lumbar (5), sacral (5), and coccygeal (1) segments. The spinal cord can also be divided into the dorsal versus ventral parts. While the ventral part is mainly involved in the processing of the motor system, the dorsal part is mainly sensory input. In the spinal cord, the central part (shaped like a butterfly) is composed of neuronal cell bodies and dendrites (gray matter), which are surrounded by axons (white matter). Each segment of the spinal cord has two pairs of nerve bundles, the dorsal roots for sensory input and the ventral roots for motor output, as well as for sympathetic output. Because of this unique organization, the body surface is represented by different segments of the spinal cord, each of which is called a dermatome (Figure 9.11) (Joseph and Loukas, 2015). In the spinal cord, the primary afferent axons synapse on the spinal cord neurons, or head straight up to the brain. The dorsal horn neurons can be subdivided into several laminae (or layers), each of which relays specific aspects of touch (laminae III-V) or pain (laminae I&II).

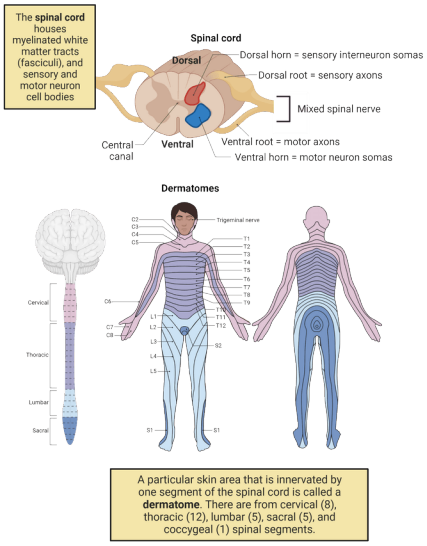


Figure 9.11 Spinal cord organization

Neurotransmitters and receptors in the spinal cord

A variety of neurotransmitters serve somatosensation in the spinal cord. Though we often represent touch information as traveling directly from the receptors on through to the brain, in reality, multiple types of neurons are involved in a complex communication within the spinal cord, helping to determine what sensory information is conveyed to higher centers in the brain or to local reflex circuits. The participating neurons include the primary afferent terminals we already discussed, along with descending fibers coming from the supraspinal origin, and intrinsic neurons inside the spinal cord. Neurotransmitters from each of these classes of neurons work in combinations to maintain the excitability of the spinal sensory neurons. In general, all primary afferent fibers use glutamate as the major excitatory neurotransmitter; Aδ fiber and C fibers also contain CGRP and SP, respectively. CGRP and SP can also be released in peripheral tissue by primary afferents, which we discussed earlier when we learned about their role in axonal reflex and neurogenic inflammation (Figure 9.6). Descending fibers and spinal interneurons can release a variety of neurotransmitters, many of which will sound familiar from other chapters, such as glutamate, GABA, neurokinins, nerve growth factor, ATP, neuropeptides (e.g., substance P), CGRP, bradykinin, cannabinoids, endorphins, cytokines, nitric oxide, ATP. These neurotransmitters interact with a variety of different types of receptors resulting in excitation, inhibition, or neuromodulation. The end result is a complex network of regulation within the spinal cord to determine what sensory signals pass to the brain and what signals do not.

Gate control theory

Gate control theory provides an example of the kind of communication that can occur within the spinal cord to determine what information is passed on to the brain. This theory was proposed by Ronald Melzack and Patrick D. Wall in 1965 (Melzack and Wall, 1965). It indicates that somehow in the spinal cord there is a gate that only allows so much information to flow forward to the brain at any given point in time. In this theory, a gate for pain information is controlled by two different types of inputs, neurons carrying primary sensory information (touch or pain), and an inhibitory interneuron, both of which combine to influence whether a projection neuron sends pain information towards the brain.

Figure 9.12 diagrams this theory. In this model, activity of a pain projection neuron is controlled by a nociceptive C fiber, as well as a non-nociceptive A-fiber and an inhibitory interneuron. In response to a painful stimulus, the unmyelinated C-fiber that is responsible for pain activates the projection neuron and inhibits the inhibitory interneuron in the spinal cord. Both of these activities open the gate to increase pain (Figure 9.12). The gate can be closed by the large myelinated A-fiber. The A-fiber, which transmits touch and vibration sensation, has 2 connections in this circuit: it excites the projection neuron weakly and it excites the inhibitory interneuron strongly. Strong A-fiber activation net inhibits the pain projection neuron through activation of more inhibitory interneuron activity in the spinal cord. This inhibition shuts down the gate, relieving the pain.

If you happen to hammer your finger, almost immediately you will shake your hand or rub or blow air to your injured finger to reduce pain. When you do this, you are using the “Gate Control Theory”. While shaking or rubbing, Aα/Aβ fibers are activated.

Although there is an increased input from C-fibers as the result of injury for increased pain, activation of Aα/Aβ fibers will excite more inhibitory interneurons that will release GABA to the projection neurons to counteract or inhibit the injury-elicited pain. Though there are some aspects of pain sensation that have been found to contradict the Gate Control theory since its proposal in 1965, it remains the single most critical model of pain sensation processes.

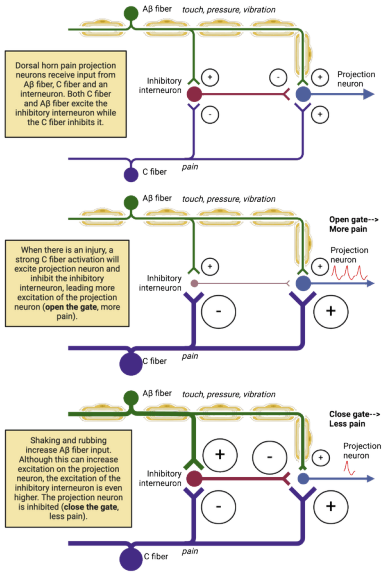


Figure 9.12 Gate control theory of nociception

Ascending pathways and their roles: from the spinal cord to the thalamus

As the sensory information comes to the spinal cord from the periphery, it will be processed inside the spinal cord first, then it will take two major systems to reach the brain. The first one is the dorsal column-medial lemniscal pathway for touch and pressure sensation and proprioception as shown in Figure 9.14. In this pathway, the primary afferent fibers ascend in the dorsal column ipsilaterally all the way to the medulla. They then synapse on the dorsal column nuclei in the medulla (i.e., nucleus gracilis and nucleus cuneatus). The axons from these dorsal column neurons in the medulla (2nd order neurons) project to the contralateral side to form a bundle, the medial lemniscus, which synapse on third-order neurons in the thalamus. From there, the thalamocortical projections from these thalamic neurons go to the primary somatosensory cortex (S1).

The second major pathway for somatosensation to the brain is the anterolateral system (i.e., located at the anterior and lateral part of the spinal cord), which originates in the spinal cord cells receiving pain and temperature input. The anterolateral system projects to the supraspinal areas through five main pathways (Willis, 1985; Willis and Westlund, 1997). The spinothalamic tract (STT) is the most prominent pain and temperature pathway (Figure 9.15). It originates from nociceptive-specific and wide dynamic range neurons in the dorsal horn of the spinal cord, and ends at the contralateral ventral posterolateral nucleus of the thalamus. Unlike the touch pathway, the STT crosses the midline in the spinal cord, at the same spinal level where primary afferents entered through the dorsal horn. In the STT, the projections from the spinal neurons proceed up the contralateral spinal column, to the thalamus.

Figure 9.13 provides a side-by-side comparison of this major difference in where each of these major pathways crosses the midline. Note how ascending touch information is in the ipsilateral spinal cord, while pain and temperature information is in the contralateral spinal cord to where the sensory information originated. For an interesting clinical implication of this difference between pain and touch pathways, try to do internet research on Brown-Sequard Syndrome and see if you can explain the clinical symptoms and signs.

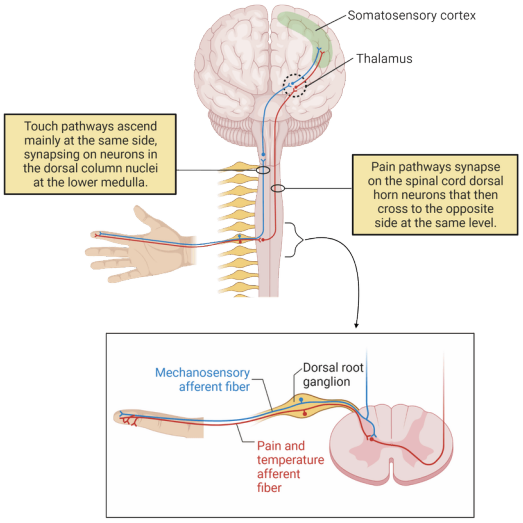


Figure 9.13 Pain versus touch pathways

The remaining four pathways of the anterolateral system deal mostly with emotional and autonomic aspects of pain, and frequently project bilaterally in the brain. They are the spinoreticular tract (arousal), the spinomesencephalic tract (affective components of pain), the spinohypothalamic tract (to the autonomic control centers for fight or flight), and the cervicothalamic tract (playing a minor role).

Because of these different tracts that contribute to the sensory information propagation from the periphery to the brain, we will be able to not only sense the location and the intensity of somatosensory input but also generate emotional responses. Imagine that you are hiking in the late afternoon. It is getting dark, and you are tired. Every step you have is almost automatic. Then you step into a pothole, and sprain your ankle... The C-fiber or Aδ-fibers around your ankle constantly send action potentials to your spinal cord, activating the dorsal horn neurons. Through STT system, your brain knows where the pain is coming from and how strong it is. Activation of the spinoreticular system will boost your arousal level, whereas activation of the spinohypothalamic system will raise your sympathetic activity to increase your heart rate and blood pressure. Finally, if you are lucky and have a strong network of descending inhibitory systems (see below), through the spinomesencephalic tract, brainstem structures will be activated and send inhibitory signals to the lumbar spinal cord to reduce the spinal cord dorsal horn neuron activity, a self-built “closed-loop feedback” system that helps the individual to cope with pain.

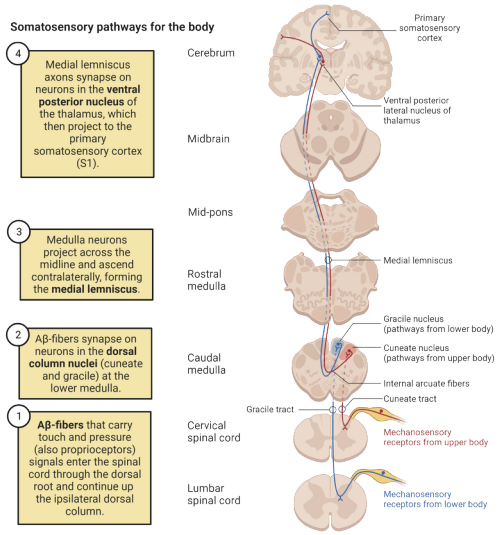


Figure 9.14 Somatosensory pathways for touch and pressure

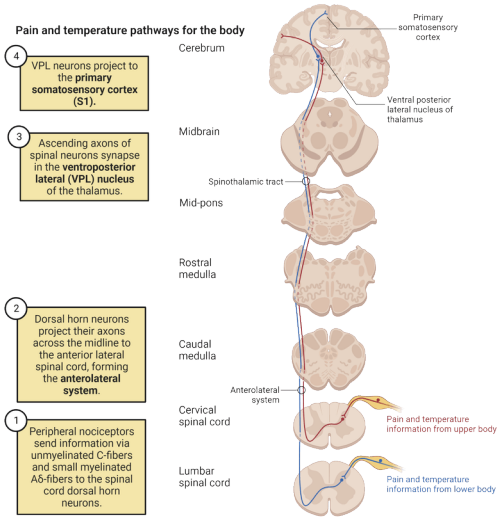


Figure 9.15 Pain and temperature pathways

Descending inhibitory pathways

As we mentioned in our earlier discussion of the neurons that control spinal-level transmission of sensory information, our brain is organized in a way to not only receive ascending input from the periphery, but also to manage inputs through a descending system sending projections downward at different levels (Sandkuhler et al., 1987; Jones and Gebhart, 1988; Millan, 2002). This protective measure enables the individual's ongoing performance without being distracted by pain. For example, when injuries happen to soldiers on the battlefield or athletes in sports competitions, they do not feel that much pain due to the strong activation of the descending inhibition. It is believed that the center controlling the descending inhibition is located in the periaqueductal gray (PAG) in the midbrain (Figure 9.16).

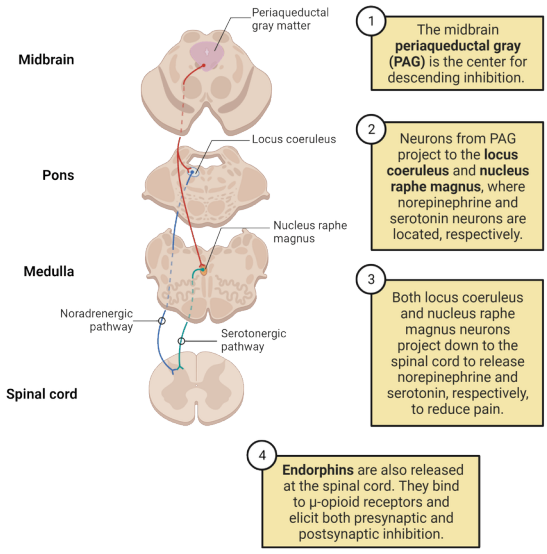


Figure 9.16 Descending pain modulation

Three major inhibitory systems contribute to the descending inhibitory system that originates in the PAG. The first one is the endogenous opioid system that releases endorphins, which can inhibit the activities of the spinal cord dorsal horn pain projection neurons to reduce or block signals to the brain. The second one is the serotonergic system, with the cell bodies located in the nucleus raphe magnus (NRM) in the brainstem, which projects their axons to the spinal cord at different levels to release serotonin. When serotonin binds to their receptors in the spinal cord projection neurons, it suppresses their activity. The third system is the noradrenergic system. The cell bodies are located in the locus coeruleus (LC), or 'blue spot', a structure in the

brainstem. The axons of the LC project down to the spinal cord and release neurotransmitter, norepinephrine/noradrenaline, which suppresses the activity of the spinal projection neurons. With the contribution of these three major descending inhibitory systems, a closed-loop of pain coping mechanism is established. However, it may vary from person to person. See more in emotional components of pain in the next main section.

Thalamus and other projections

The thalamus is the major gateway in our brain that processes not only somatosensory information but also auditory, visual, as well as gustatory information. There are several major subdivisions of the thalamus. It also contributes to modulating motor activities by communicating with the basal ganglion and the cerebellum. The major subgroup that relays the somatosensory information is the ventral posterior lateral (VPL) and ventral posterior medial (VPM) nuclei. The VPL is responsible for relaying signals coming from the trunk and extremities and is shown as the major relay in Figure 9.15. The VPM is just medial to the VPL and receives information from the head area. Neurons in either VPL or VPM are the third-order neurons that project to the primary somatosensory cortex (S1) for the perception of the sensory information in the body.

Cortical process of touch and pain

Somatosensory information first reaches the cortex in the primary somatosensory cortex (S1), in the postcentral gyrus in the anterior part of the parietal lobe. The sensory receptive areas of the body are represented on S1 as an inverted little person lying along the sulci and gyri of the cortical surface, shown in Figure 9.17. This person, known as a homunculus, is a distorted representation of a human body with the size of each body part proportionate to that area's amount of sensory innervation. For example, the hand requires more cortical resources, and it, therefore, gets more surface area (and more neurons) dedicated to its representation. S1 sends most of its projections to the secondary somatosensory cortex (S2) for further sensory processing, though there is also a communication between S1 and the motor cortices in the frontal lobe for sensory-guided motor function.

The mainstream of information after S1 and S2 flows posteriorly to reach the posterior parietal cortex, then to the temporal association cortex, parahippocampal cortex, and the cingulate cortex. The posterior parietal area receives information not only from the somatosensory cortex but also from auditory, and visual cortices. Information can therefore be integrated here from multiple modalities and then project to the prefrontal area where the integrated information can be analyzed, a decision can be made, and the motor response can be planned. Projections to the limbic system also play a critical role in processing our emotional response to somatosensory information, particularly pain or itch (Bushnell et al., 2013). The contribution of the combination of limbic system activities enables the individual to experience and integrate their emotion (e.g., anger, fear, anxiety, depression) in response to peripheral input (e.g., visual, sound, pain) or retrieval from the past experience (memory), to generate physiological responses (heart rate and blood pressure) or psychological experiences (Gilam et al., 2020). We will discuss this limbic component of pain more in the next section.

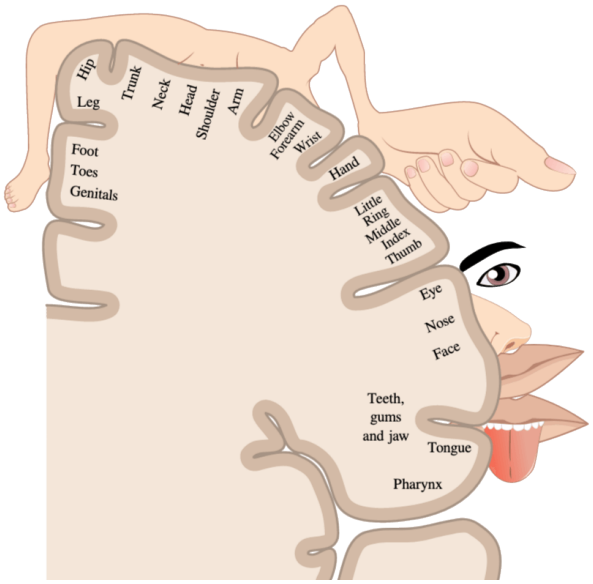


Figure 9.17 The sensory homunculus The sensory homunculus shows a map of where in the body sensory information is represented and processed in the primary somatosensory cortex. Image credit: OpenStax CC BY 4.0

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6.4.3: Pain and Itch

Learning Objectives

By the end of this section, you should be able to

- Define pain.
- Identify the different types of pain.
- Describe the neural structures involved in emotional pain.
- Describe the overlapping nature of brain areas that contribute to both pain and depression.
- Explain the cause of itch and the difference from pain.

Pain and itch are specialized somatosensory experiences that are both transmitted by shared neural pathways that start with C- and Aδ fibers in the periphery. While pain can happen in the cutaneous as well as deep tissues, itch predominantly occurs in the superficial tissue, such as the skin. However, there are some unique aspects of pain and itch that require separate consideration, which we will discuss here. Pain, in particular, comes with a strong emotional component. In our example of getting stepped on while on the bus, a core part of the response to the pain is our feelings of anger. This emotional component of pain gives it relevance to a variety of diseases and disorders of the brain, as we will learn in this section.

Pain definition and types

Pain is defined as: “An unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage (Raja et al., 2020).” Some of the key points included in this definition include that pain is always a personal subjective experience that is influenced to varying degrees by biological, psychological, and social factors. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being. Verbal description is only one of several behaviors to express pain; the inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Pain can be subdivided into several categories depending on the duration (acute or chronic), location (e.g., lower back pain, migraine), and causes (nociceptive, inflammatory, or neuropathic). Nociceptive pain results from the direct activation of nociceptors in the skin or soft tissue in response to tissue injury and usually arises from accompanying inflammation. Neuropathic pain results from direct injury to nerves in the peripheral or central nervous systems and often involves a burning or electric sensation (reflex sympathetic dystrophy, postherpetic neuralgia, phantom limb, and anesthesia dolorosa). Although acute pain is usually protective, chronic pain serves no purpose but only makes patients miserable. Please see details for pain treatment in 9.4 Pain Relief.

Congenital insensitivity to pain

There is one genetically determined condition in which patients do not experience pain but do experience the normal sensation of light touch and deep tendon reflexes. It comes in two forms: congenital insensitivity to pain (CIP), or congenital insensitivity to pain with anhidrosis (CIPA). Insensitivity to pain in CIP is caused by mutation of the voltage-gated sodium channel α-subtypes Nav1.7, which are used heavily by pain fibers (Goodwin and McMahon, 2021; MacDonald et al., 2021). Because of the loss of protective mechanism provided by pain, children with CIP usually suffer multiple injuries on the body surface, joint damage, and bone fractures. In CIPA patients, in addition to the symptoms described above, they also experience anhidrosis (no sweat) as the result of sensory and autonomic neuropathy, leading to death within the first 3 years of life because of hyperpyrexia (high body temperature) (Rosemberg et al., 1994; Gong et al., 2021). The example of CIP is instructive for the adaptive value of pain. Though the subsequent sections will describe maladaptive aspects of pain, the root value of pain as a survival signal should not be forgotten.

Psychological contribution to pain

Pain involves not only physiological processes but also emotional responses, cognitive evaluations, and behavioral responses.

Both physiological and psychological factors are integrated into the experience of pain and our emotional, cognitive, and behavioral responses to it (Gamsa, 1994; Baliki et al., 2006; Borsook and Becerra, 2009; Linton and Shaw, 2011; Bushnell et al., 2013; Gilam et al., 2020). These two factors are so intertwined that pain in the absence of injury, which is assumed to be purely psychological, activates similar brain pathways as pain originating in bodily damage. The feedback between psychological responses to pain and subsequent perception of pain is complex and extensive.

Pain disorders demonstrate the complex interchange between psychological responses and pain perception. Both physical pain from injury and pain that is psychological in origin can lead to pain disorders, or the experience of severe stress due to chronic, debilitating pain. The American Psychiatric Association (2022) recognizes this with two psychiatric diagnoses associated with pain in the Diagnostic and Statistical Manual of Mental Disorders V-TR: pain disorder associated with psychological factors either with or without a diagnosed medical condition (medical conditions such as rheumatoid arthritis, appendicitis, fractures, sprained ankle, infections, cancer, etc.). As these diagnostic categories imply, both psychological factors and a general medical condition have important roles in the onset, severity, exacerbation, and maintenance of pain. As an example, it has been found that pain (such as that from an injury or physical illness) attracts attention and that increased attention to pain also enhances the painfulness of nociceptive stimulation. This positive feedback loop (pain begets attention, which begets more pain) is attributed to the reduction of activation in key regions of the pain matrix, including the thalamus, insula, and parts of the anterior cingulate. Of course, psychological processes (such as distraction) can also reduce pain perception. The areas involved in distraction during the processing of nociceptive stimulation seem to be mediated by a prefrontal–cingulate top-down modulation of the brainstem structures. The inhibition of ascending nociceptive input comes from the powerful descending pain modulatory pathways originating in structures such as the amygdala, hypothalamus, insula, anterior cingulate cortex, periaqueductal grey, and rostroventral medulla. Projections from these higher structures contribute to descending inhibition of spinal cord dorsal horn neurons, reducing incoming transmission of pain information.

Limbic system contribution to emotional aspects of pain

The limbic system forms a rim (Latin limbus) in the medial wall of the hemispheres (Rolls, 2015). It includes the various cortical areas that make up the limbic lobe (especially medial areas of the temporal and frontal lobes) and the subcortical regions connected with these cortical areas, such as the amygdala and hypothalamus. Somatosensory system input to the limbic system is what makes things like itch or pain feel unpleasant and causes people to feel agitated, angry, or depressed. Figure 9.18 shows one example of how sensory information such as pain can influence limbic structures, which in turn help create subjective feelings and coordinate bodily responses. – Do you still recall the hypothetical situation if someone steps on your toe twice (at the beginning of this section)? Activation of your limbic system is a key step in creating your emotional response to the painful toe steps.

This connection between pain and emotion-associated brain regions may be relevant to psychiatric disorders. For example, there is quite an extensive overlap between the neural circuitry active in chronic pain and the network of some psychiatric disorders. Both circuitries for chronic pain and depression, for instance, can show similar activation patterns. On the other hand, reduced prefrontal activity often observed in schizophrenia patients can suppress the experience of pain.

Sex as a biological variable: Sex Differences in Pain Process

In addition to factors such as medical conditions and psychiatric disorders, there is another important factor that affects pain perception and processing: genetic/hormonal sex. In humans, several clinical pain conditions are more prevalent in women than men, such as pain conditions involving the head and neck, of musculoskeletal or visceral origin, and of autoimmune cause. The greater rates of these disorders in women suggests potential sex differences in pain systems, something which experimental studies of pain perception have confirmed. Specifically, in studies where people are exposed to the same painful stimulus (such as dunking your hand in ice water), women are on average more sensitive to pain, and report pain more frequently, for longer duration and of greater severity than men (i.e., lower threshold and tolerance in some modalities of pain). The average greater sensitivity of women to painful stimuli occurs across modalities: women report more sensitivity to thermal, pressure, electrical, and chemical stimuli than men. These findings imply sex differences in pain perception do not rely on a single sensory pathway.

Sex differences are also evident in pain experience in animal models of nociception, suggesting that at least some of the differences in humans are not about gendered human socialization but have evolutionarily conserved roots across species (Sorge & Strath, 2018). A common way pain is tested in animal models is a simple reflex withdrawal behavior. In these kinds of tasks, animals are exposed to something that could become painful, such as an increasingly hot surface or an increasingly sharp and strong poke on the paw. Researchers start with a low level of the potentially painful stimulus and then increase

it over trials to see when the animal starts to withdraw (pulling its paw away, for example). When withdrawal happens, the interpretation is that the stimulus has reached a level of being painful. Interestingly, in tasks like reflex withdrawal, rodents do not show sex differences under normal circumstances. However, in models where the animals show preexisting inflammation or nerve injury, females show greater reflex withdrawal responses to the same level of stimulus (Cook & Nickerson, 2005; Dance, 2019; Dominguez et al., 2009; Gaumond et al., 2002; Kim et al., 1999; LaCroix-Fralish et al., 2005; Lu et al., 2009; Mogil, 2020; Presto et al., 2022; Wang et al., 2006). Many biological factors have been found to contribute to these kinds of sex differences in nociceptive behavior, such as genetics or gonadal hormone differences and experimental variables (e.g., type of test and tissue tested). In humans, sex differences in pain probably stem both from the types of differences in immune and hormonal systems (e.g., menstrual cycle) that we can model in animals, as well as from biopsychosocial factors that are more unique to humans (Fillingim et al., 2009; Greenspan et al., 2011; Hoffmann et al., 2022; Racine et al., 2012a, 2012b; Ruau et al., 2012).

Chronic pain and depression

While brief pain may help us in many situations, chronic pain is almost always detrimental. Based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, chronic pain can be associated with broad categories of other clinical conditions (co-morbidity), including affective disorders, anxiety disorders, post-traumatic stress disorder, substance dependence, sleep disorders, cognitive disorders, malingering, personality disorders, suicidality, fatigue, obesity, etc. Here, we will further discuss the link between chronic pain and depression, which is prevalent and well-established.

Chronic pain and depression are intertwined with each other. About 8% of the U.S. population is depressed. In contrast, of those with chronic pain, 18–35% have been reported to be depressed and 6.3% have a major depressive disorder (MDD). Conversely, when surveying people with MDD, painful physical symptoms have been reported to occur in 50–66.3% of patients, a rate which is much higher than in the general population. Research into the connection between chronic pain and depression has revealed numerous clinically important facets to their interdependence: 1) depression is associated with chronic pain; 2) chronic pain can exacerbate depression; 3) in predisposed individuals, pain may be etiologically related to the onset of depression; 4) depression can affect pain perception; 5) treatment of depression can improve disability, and 6) improving pain can improve depression.

The intertwining of depression and chronic pain seems to be rooted in shared monoamine neurocircuitry. For example, it has been found that the dysfunction of the brain's serotonin system is related to both pain and depression (Bair et al., 2003; Hilderink et al., 2012; IsHak et al., 2018; Zhou et al., 2019). Serotonergic system dysfunction is associated with depression and many mainstream treatments of depression target serotonin. Coincident with this role in depression, the serotonergic neurons of the dorsal raphe nucleus send serotonergic afferents to and receive input from limbic structures involved in cognitive and emotional functions. However, dorsal raphe serotonergic neurons also send projections to the spinal cord via descending pathways, resulting in inhibition of spinal nociceptive processing. Serotonergic activity can therefore not only regulate mood states, but also reduce pain perception. There is likely a similar role for norepinephrine systems as well. As evidence of the role of serotonin and norepinephrine in chronic pain, venlafaxine and duloxetine, both selective serotonin and norepinephrine reuptake inhibitor antidepressants, have demonstrated efficacy in reducing pain in patients with diabetic neuropathy. These findings are a good reminder how important it is to always keep in mind the role of the limbic system in regulating not just psychological or psychiatric disorders but also our perception of pain (Figure 9.18).

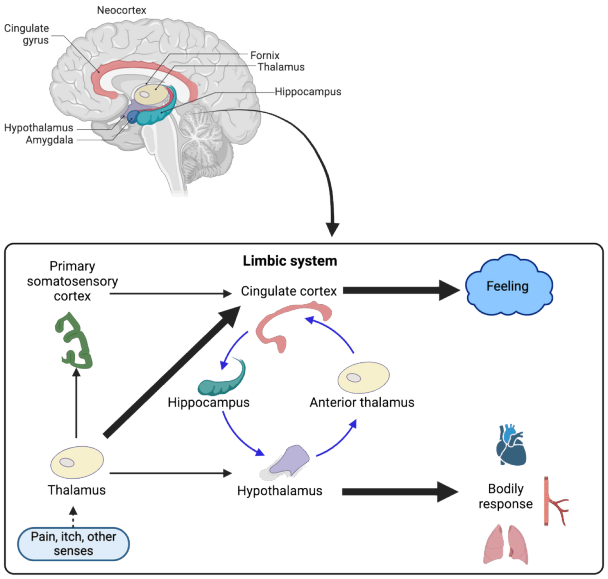


Figure 9.18 Limbic system response to somatosensation Areas in the temporal and frontal lobes contribute to the limbic system, which is critical to emotional responses to somatosensory stimuli, especially pain. Image credit: Image inspired by work of Dalgleish, T. The emotional brain. (2004). Nature Reviews Neuroscience, 5, 583–589.

Itch mechanisms and treatment

Itch sensation (also known as pruritus) plays an important protective role for an individual just like pain. Itch lets us know there is something unexpected and possibly dangerous on our skin, such as a parasite or foreign plant matter. Itch is thus useful because it directs you to scratch the itchy area and remove whatever is irritating your skin. However, as with chronic pain, chronic itch can disable an individual. The neural mechanisms for itch sensation are not fully understood. As a mechanism for the itch, some neurotransmitters or peptides (such as histamine and cowhage spicules) are suggested to bind to their specific receptors on free nerve terminals underneath the skin, thereby stimulating C-fiber and Aδ-fibers (Ikoma et al., 2006; Potenzieri and Undem, 2012; Bautista et al., 2014; Lamotte et al., 2014). But transmission from there to the spinal cord, as well as to the brain, is unclear.

Let's use a mosquito bite as an example of what we do understand about itch (Figure 9.19). The mosquito saliva contains proteins that are immunogenic to humans. By triggering a local immune response, mast cells are aggregated around the biting site and release histamine. Histamine increases the permeability of the capillaries, leading to bumps, and increases vasodilatation, leading to redness. It also binds to histamine receptors (especially the H1 subtype) to activate a G-protein, in turn causing depolarization of primary C-fiber and Aδ-fibers afferent terminals, leading to the sensation of itching.

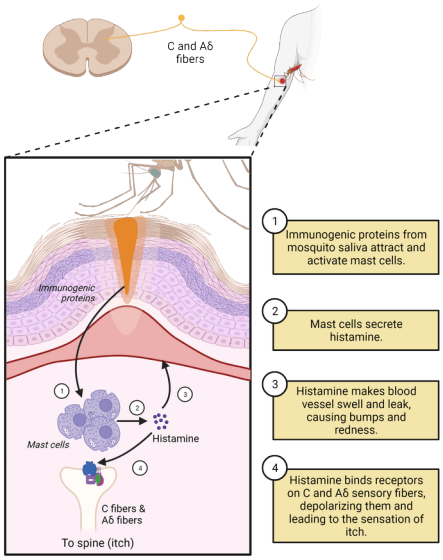


Figure 9.19 Local mechanisms of itch

Cowhage is a bean-like plant that provides another example of itch-inducing stimuli. The tiny needle-like spicules on the pods are the ones that cause itch from cowhage. Insertion of cowhage spicule(s) into the superficial skin is frequently applied as an itch model in research. The active component of cowhage, termed mucunain, is a novel cysteine protease (Reddy et al., 2008). By binding to the protease-activated receptors (PAR) a member of the G-protein coupled receptor family, it mobilizes Ca^{2+} ions and excites the C-fibers and Aδ-fibers nerve terminals. Both of these examples demonstrate our understanding of major itch mechanisms at the level of skin receptors.

How itch transmits and is processed within the central nervous system is unclear. The sensation of the itch is transmitted much slower than the sensation of touch and, though itch appears to use C-fibers (pruriceptors) and Aδ-fibers, it does not seem to be a subclassification of pain. There exist two lines of evidence that itch is different from pain. (1) Vigorous scratching produces mild pain and pain inhibits itch. (2) Opiates reduce pain and increase itch. This inhibitory relationship between pain and itch is evidence that itch is not a type of pain. In addition, molecules that induce pain do not elicit an itch sensation or vice versa (Lamotte et al., 2014). When primary afferent activity relaying itch reaches the spinal cord, it has been suggested that the spinal parabrachial pathway plays a critical role in itch processing that leads to itch-induced scratching behaviors (Bautista et al., 2014; Mu et al., 2017; Dong and Dong, 2018). Yet, we still understand very little about how it signals centrally.

The treatment of minor itch includes: Applying cold compresses, using moisturizing lotions, taking lukewarm or oatmeal baths, using over-the-counter hydrocortisone cream or antihistamines, and avoiding scratching, wearing irritating fabrics, and exposure to high heat and humidity. For severe or chronic itch, prescribed medication, including antihistamines and topical steroids, or more rarely steroid pills and antibiotics, may also be needed.

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7: SENSORIMOTOR SYSTEMS

7.1: Organization of the Sensorimotor System
7.2:Prefrontal Cortex and Sensorimotor Planning
7.3: Premotor and Supplementary Motor Cortices
7.4: Basal Ganglia
7.5: The Cerebellum
7.6: Primary Motor Cortex and Descending Motor Pathways

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7.1: Organization of the Sensorimotor System

Learning Objectives

By the end of this chapter, you should be able to

- Compile a descriptive story regarding how the following UMN brain structures collaborate with distinct contributions to movement formulation and engagement: Prefrontal and premotor cortices; Cerebellum; Basal ganglia; and Primary Motor cortex (M1)
- Enumerate the regions of control within the homunculus of M1 anatomically along the precentral gyrus.
- Differentiate the complimentary contributions to background motor control from the basal ganglia and cerebellum in terms of muscle contribution selection and the smooth stopping and starting.
- Understand the source, related circuitry, and outward expressions of the following disease states: Cerebellar Ataxia; Huntington's disease; and Parkinson's disease.
- Describe how final movement selections are made in M1 according to the findings of Apostolos Georgopoulos and how that translates into a sort of democracy of movement trajectory determination.

In this section, we will explore the contributions of UMN systems to voluntary movements. Progressively, we will discuss ascending signals providing critical decision-making information to UMN areas, and descending implementation signals to the lower areas (brainstem and spinal cord). We'll address three major cortical areas:

1. The prefrontal cortices, the most anterior of movement-related cortices where major executive decisions are made.
2. The collection of regions referred to as the premotor cortices (dorsal, ventral, cingulate, supplementary). These coordinate which muscles should be activated when new game plans are formulated, and receive feeds from posterior sensory cortices, the basal ganglia, and the cerebellum through the thalamic way station.
3. Finally, we will discuss the primary motor cortex, or M1. We will find that this area continues to compile inputs and formulate final detailed movement decisions prior to sending commands to the LMNs in the brainstem and spinal cord.

Our lower motor systems clearly need guidance if we are ever going to move how we want. In this section, we will learn how the upper motor structures are poised to deliberate, compose, compile, and then direct the lower motor neurons.

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7.2:Prefrontal Cortex and Sensorimotor Planning

The Prefrontal Cortex – Integrating our wants and needs with circumstances

Within the most anterior portions of the cerebral cortex behind our foreheads and over the orbits of our eyes, prefrontal cortices begin the earliest portions of conscious decision-making and are included as motor regions for this reason (see Figure 10.12). Willed movements depend on both decisions and integration of emotions and desires within internal representations concerning our circumstances in the world. We need to understand problems we face prior to acting and speaking in response to them, lest our actions be thoughtless or wildly inappropriate. For example, prefrontal lobotomy patients are unable to plan for their futures, and fail to self-monitor as actions occur (Milner & Petrides, 1984; Malloy et al., 1993; Chirchiglia et al., 2019). This clearly defines these cortical regions as the locus of deciding what to do. As indicated in Figure 10.12, this area receives necessary decision-making information from many other areas. After processing, it sends this information to multiple regions, providing both the feeling of the decision and the action chosen.

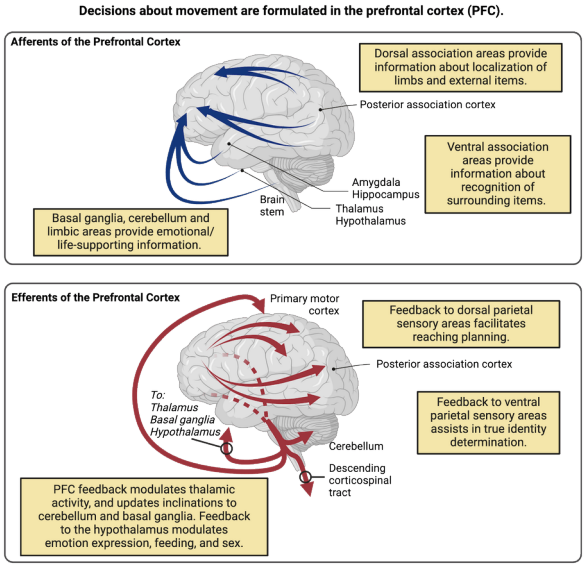


Figure 10.12 Image credit: Image inspired by Fuster, J. 2015. The Prefrontal Cortex. 5th Ed. eBook ISBN: 9780124080607

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7.3: Premotor and Supplementary Motor Cortices

Premotor cortices

Once an executive decision about a desired movement has been made in the PFC, the conscious compilation of movements into useful patterns occurs in the premotor cortices. These cortices reside in the lateral and dorsal regions of the frontal lobe, behind the prefrontal areas. This general region compiles movements by combining multiple muscle sets across space (different simultaneous contractions combining, adjusting movement trajectory) and time (different movements in sequence). See Figure 10.13 for an example of these functions, as gymnast Simone Biles plans a complex flip. Her premotor cortex will be essential for planning force and distance while her supplementary motor area stitches together the order of movements she will need.

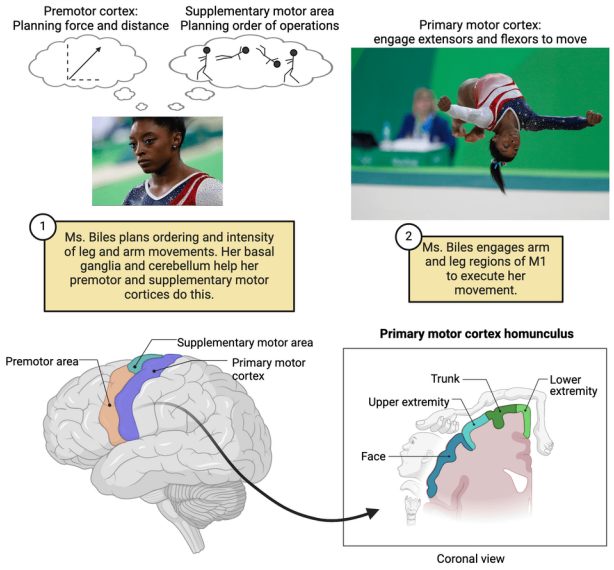


Figure 10.13 Premotor versus motor processing Image credit: Thinking Simone Biles: By Agência Brasil Fotografias - EUA levam ouro na ginástica artística feminina; Brasil fica em 8° lugar, CC BY 2.0, https://commons.wikimedia.org/w/inde...curid=50584958; Flipping Simone Biles: By Agência Brasil Fotografias - EUA levam ouro na ginástica artística feminina; Brasil fica em 8° lugar, CC BY 2.0, https://commons.wikimedia.org/w/inde...curid=50584654

Of course, Simone Biles has done these flips many times. Her repeated practice has made much of her motor planning subconscious. This process of honing motor movements into habitual, subconscious patterns relies strongly on interactions of premotor cortices with other cortical structures such as the striatum (basal ganglia), and cerebellum. These two areas become involved more heavily during acquisition (where movement skills are packaged), consolidation (where movement skills are honed into quickly accessible repertoire habits or motor programs), and retention (where established repertoire movements are stored so they can be accessed quickly in response to key circumstances). Both primates and rats suffer deficits in learning formal, visually directed motor tasks after the removal of premotor cortices – further evidence of this region's critical role in retaining learned skill and movement adaptation for future endeavors.

The premotor areas' primary output is regulation of M1 neurons, which connect extensively to LMNs. For many years, the premotor cortices were believed to influence motor movement exclusively via their regulation of the primary motor cortex. However, more recent evidence shows stimulation of the premotor cortices yielding combinations of motor responses in harmony across both sides of the body. Thus premotor cortex engages built-in and learned complex combinations of actions, within an organism's more sophisticated repertoire (Geyer et al., 2000). Premotor cortices send descending axons into the spinal cord, meaning that M1 is not the only direct regulator of LMNs. This is important to keep in mind.

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7.4: Basal Ganglia

The basal ganglia

This cluster of subcortical nuclei includes the main input regions, caudate and putamen nuclei, with circuit components extending into the external and internal globus pallidus, subthalamic nucleus, and substantia nigra reticulata. Importantly, in most animal species, the caudate and putamen nuclei are not distinct. Therefore, they have been largely treated as a similar pair and frequently referred to together as the striatum. There appear to be several parallel "loops" traversing the basal ganglia, beginning with afferents from various areas of the cortex entering and stimulating the main input cells of the striatum. The final output nuclei of the motor loops of the basal ganglia send inhibitory inputs into the movement area of the thalamus, the ventral anterior/ventrolateral (VA/VL) complex (ventral anterior and ventrolateral thalamic nuclei).

Here, we will focus on the role of the basal ganglia in the conscious support of body movement. Recall that conscious actions are guided by plans formulated and relayed by the frontal cortex. Therefore, structures involved in the motoric basal ganglia loops start with afferents from most of the cortex, including sensory and motor areas converging on neurons throughout the caudate and putamen (as stated, usually understood as a group). The subsequent pathways through the basal ganglia can be divided into a direct pathway and an indirect pathway, both of which end up affecting firing of neurons in the VA/VL thalamic complex. The VA/VL complex represents a distinct waystation that specifically targets movement control areas in the cortex, primarily premotor areas. The net effect of activity in the direct pathway is to promote VA/VL firing and therefore planned movement. The net effect of the indirect pathway is to inhibit VA/VL firing and thereby suppress unwanted movement (Figure 10.14). Balance of activity in each of these pathways helps us move how we want, while preventing undesired movements. We will see later how specific diseases impacting each pathway can lead to different symptoms.

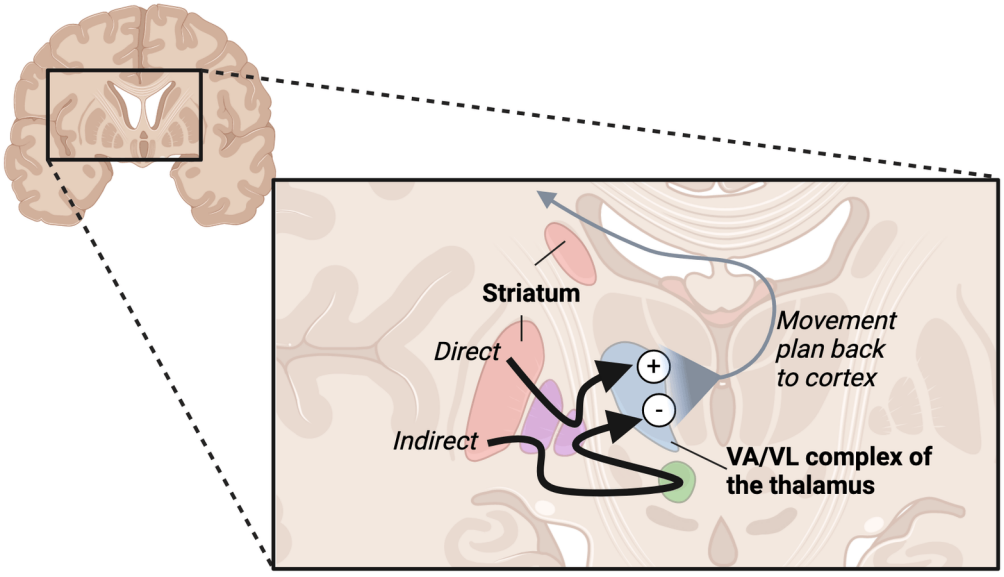


Figure 10.14 Direct vs indirect motor pathways The direct pathway of the basal ganglia promotes planned movements, while the indirect pathway inhibits unwanted movements. **Purple** = GPe/GPi and **Green** = subthalamic nucleus.

Both the indirect and direct pathway use disinhibition as an important part of how their circuit activity is controlled. To better understand disinhibition, we will look more closely at the direct pathway (see Figure 10.15).

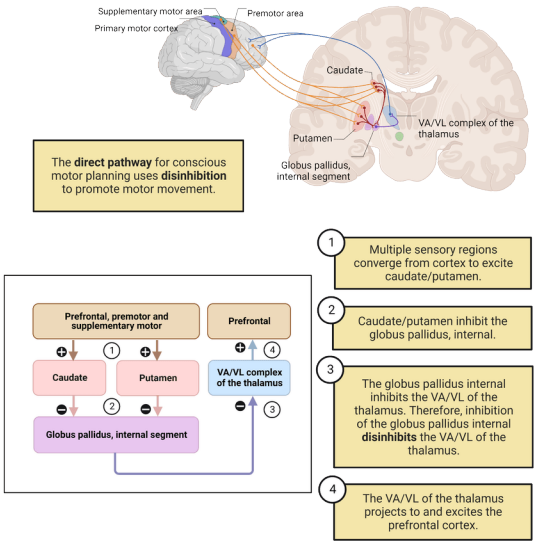


Figure 10.15 Basal ganglia circuits

In the direct pathway, the excitatory input from the frontal cortex areas synapses on inhibitory efferent neurons within the striatum. Those inhibitory striatal neurons then send afferents to the globus pallidus internal (GPi). These GPi neurons are also inhibitory and connect to the VA/VL complex of the thalamus via their own inhibitory efferent neurons. In Figure 10.15, a simplified conscious motor planning diagram for the direct pathway emphasizes the prefrontal cortex because it is where conscious decisions tend to occur, confirming your intended actions and goals along the way. Overall, this inhibition of GPi output neurons results in *disinhibition* of the movement-related thalamic nuclei in the VA/VL complex. The thalamic cells send excitatory outputs towards the premotor/supplementary motor cortices for body movement, or to the brainstem centers for eye and head movement (Groenewegen, 2003). Planned movement is thereby promoted.

The indirect pathway uses similar processes but has more complex circuitry, involving additional brain nuclei and more inhibitory/disinhibitory connections than in the direct pathway. The end result of exciting the indirect pathway is inhibition of the VA/VL and prevention of overactivation of cortical motor areas or the diminishment of *unwanted* movements. One structure within the indirect pathway, the subthalamic nucleus, adds an excitation to the equation which increases how much suppression takes place. Malfunctioning here can lead to ballistic thrusting movements and is often blamed for the inappropriate tremors occurring in diseases of the basal ganglia.

Establishing habits and motor sequences

While we've described conscious involvement, the basal ganglia does also maintain heavy involvement in subconscious skill learning and movement control. Sometimes, we have an explicit or conscious desire to repeatedly produce a specific movement sequence that is learned and established via consolidation as an accessible circuit coordinating multiple muscles in a sequence or ensemble. A motor sequence represents a timed pattern of muscle activation sequentially, like finger movements on a piano in a Beethoven concerto. A muscle ensemble represents a group of muscles activated simultaneously to either create a specific movement trajectory or ensure other parts of the body remain stiff while limbs maneuver, like a wrestler using arms, legs, and back contractions to pin an opponent. The basal ganglia are essential for using motor sequences and muscle ensembles in habitual or learned movements. Specifically, the basal ganglia help to select cooperative muscle ensembles and inhibit unhelpful muscles when executing a learned motor skill.

To understand the role of motor system learning, imagine how we might learn to draw cartoon characters like Snoopy or Garfield. Our first tries are often embarrassing. To create these drawings free-handed, we must coordinate the actions of many muscles in our arms and hand. When should we select "this" muscle, or "that," or combinations of both? The basal ganglia circuitry focuses on proper selection of either individual muscles or groups that *can* produce the desired line in the right direction (drawing Snoopy's rounded snout, or Garfield's stripes or whiskers; see Zham et al., 2017). If the wrong muscles are selected, or the groups of muscles compete rather than cooperate, the drawing will look shaky and wobbly, and we might be likely to discard it rather than showing our friends. After learning to select the right muscle groups for each part, we can proudly show our friends the results. The basal ganglia can *select* which muscle groups to activate in sequence, so muscle ensembles combine with motor sequences. The package becomes a learned habit, re-played as circumstances demand (piano playing, wrestling).

Some disease states may result from inappropriate activation of motor sequences in basal ganglia circuitry. For example, some researchers suggest that Tourette's syndrome sudden-onset expressions ("tics" or bursts of uncontrolled movement), and dystonia (writhing movements and awkward postures), stem from over-reactive sensitivities at the level of the caudate and putamen, making "chunks" of unintended movements essentially habitual (Mink, 2018; Graybiel and Mink, 2009; Albin and Mink, 2006). The circuitries controlling habitual learned movements are substantially more complex than the conscious motor circuits, involving more sub-structures within the basal ganglia. While we will not describe those complexities here, your author hopes that you will pursue more advanced classes where these circuits are covered, as they are exciting, and hotly debated.

Disorders of the basal ganglia

We shall now describe two devastating diseases, Huntington's and Parkinson's, to emphasize functions that rely on the basal ganglia. Some readers may know people who suffer from various stages of movement control deterioration in these disorders. Neither Huntington's nor Parkinson's patients can engage proper motor sequences on demand while suffering their deficits (Moisello et al., 2011). Both diseases involve basal ganglia dysfunction, but result in different symptoms due to loss of different parts of the basal ganglia circuitry.

Patients with Parkinson's disease experience severe, progressive loss of motor control. This includes (1) shakes or tremors; (2) "cogwheel" rigidity, a special kind labeled to emphasize the interspersion of stiffness with short releases, much like clock minute hands clicking into place; and (3) postural instability appearing to derive mostly from insensitivity to vestibular and muscular cues (Sveinbjornsdottir, 2016). While the tremors appear outwardly like other basal ganglia diseases such as Huntington's, they often manifest more at rest when no effort to engage movement exists (resting tremor), compared to action tremor associated with cerebellar ataxia, discussed later.

Parkinson's disease is caused by cell death of the dopaminergic neurons originating in the midbrain substantia nigra pars compacta, projecting into the caudate and putamen (Figure 10.16; Fahn 2008).

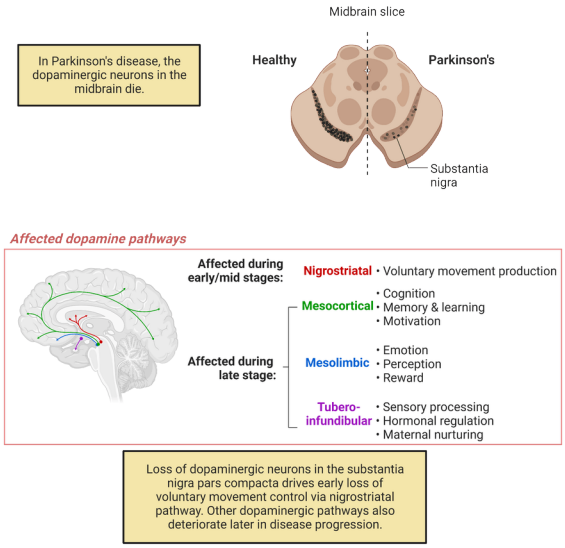


Figure 10.16 Parkinson's disease anatomical pathology

Dopamine contributions to basal ganglia function are complex. As is usually the case with a modulatory transmitter, it largely adjusts the way glutamatergic excitation engages postsynaptic cells. In this case, the postsynaptic cells are inhibitory efferent neurons in the striatum (Surmeier, 2011). The interactions of dopamine with the striatum neurons are complex but their net effect is to stimulate the parts of the caudate and putamen that promote movement behavior, i.e., the direct pathway striatum neurons (follow the circuit diagram in Figure 10.17; Wall et al., 2013, Surmeier, 2011). Its loss in Parkinson's disease makes movement much more difficult.

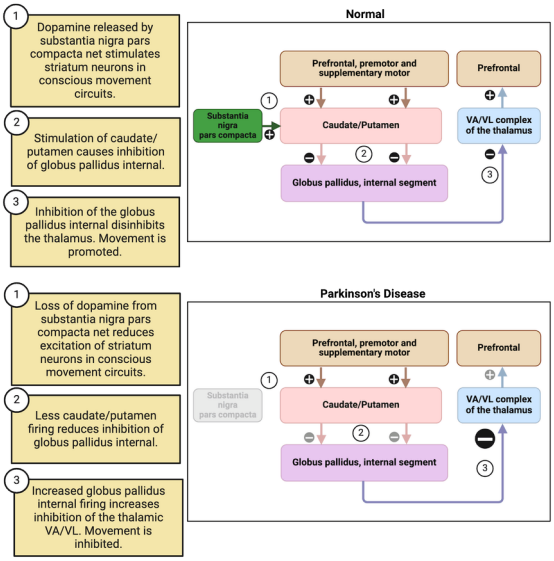


Figure 10.17 Parkinsonian state of basal ganglia

One major treatment for Parkinson's patients is Levodopa (L-DOPA). It is a precursor molecule of dopamine derived from the amino acid tyrosine and is used by the enzymes within dopaminergic neurons to produce dopamine (see Figure 10.18).

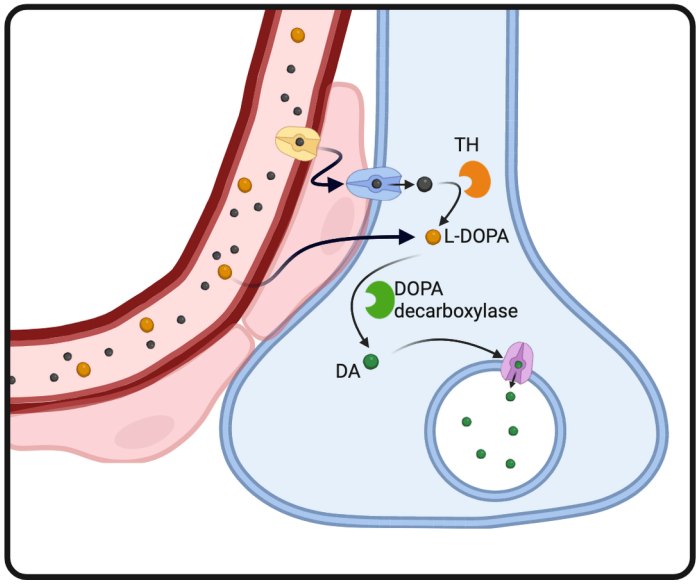


Figure 10.18 L-DOPA and Parkinson's disease treatment Reminder: L-DOPA is a precursor in dopamine synthesis.
L-DOPA is also BBB permeable, so L-DOPA in the blood can get into the dopaminergic neuron terminals and boost dopamine synthesis.

When this drug is administered, there is typically an initial surge of dopamine, yielding improved movement. However, sometimes there's a tendency to overdo. This is seen as impulsivity or a tendency to take more risks behaviorally, but that tapers off as the acute effects diminish (Voon et al., 2017). The greater propensity for movement is typically referred to as an "up, on, or acute" state by comparison to the "down, off, or long-term state" when the L-DOPA wears off (Albin & Leventhal, 2017).

The inconsistency of L-DOPA effects over time is one reason alternative treatments, like stem cell transplantation, are sought for Parkinson's, which may provide more consistent dopamine presence (Sandstrom et al., 2018). Dopaminergic replacement cell populations derived from stem cells are typically placed into patients' putamen, because this structure typically receives the highest dopaminergic input, and is most closely associated with movement control (Freed et al., 2011). Also, growth of new axons is considerably challenged across long distances in the adult brain, though strategies for guiding axon growth from the more appropriate substantia nigra pars compacta are being developed (e.g., Zang et al., 2013). Other treatments including a thalamotomy are more radical. In thalamotomy, distinct input regions of the thalamus are targeted for destruction, eliminating the supportive control provided by the compromised basal ganglia. While actors like Michael J. Fox opted for this treatment due

to its general preservation of facial expression control, it is not an ultimate cure as the movements produced are often jerky and challenged. Restoring more natural or appropriate basal ganglia activity would be preferable to eliminating its influence, but this remains a challenge to achieve.

Deep brain stimulation is another potential treatment for Parkinson's disease. In this treatment, electrodes are placed strategically into either the subthalamic nucleus, the internal globus pallidus (GPi) or select regions within the VA/VL thalamus that override the internal signaling strategy provided by the basal ganglia. Deep brain stimulation is particularly helpful in treating the resting tremors that are common in those with Parkinson's disease. The resting tremors in Parkinson's disease arise due to complex dysregulation of input to the GPi/VA/VL. Proper placement and high frequency stimulation of electrodes in these areas, supported by power coming from a battery that is typically placed under the skin around the shoulder, can significantly reduce these tremors (Figure 10.19).

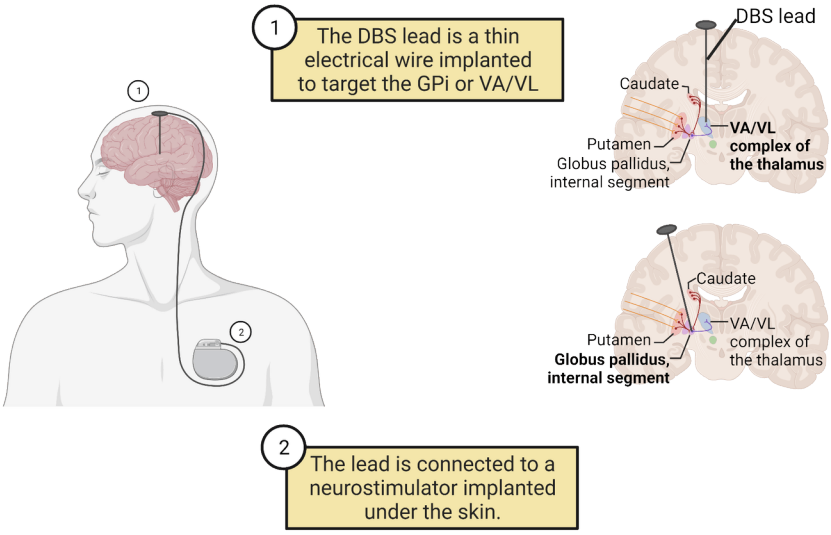


Figure 10.19 Deep brain stimulation and Parkinson's disease

Huntington's disease (HD) arises from a dominant genetic mutation on the *huntingtin* gene within the autosomal portion of chromosome four. Though the genetic mutation is present from conception, the symptoms develop over a lifetime (Walker, 2007). Being autosomal dominant means that a person only requires one copy of the huntingtin gene to develop HD and a parent with HD has a 50% chance of passing on their mutated gene to their offspring. In HD, cognitive difficulties often arise first in the chain of symptoms since the basal ganglia are involved in strategic thinking and developing capacity to adapt thinking to new circumstances, given its interaction with prefrontal and premotor cortices (Novak & Tabrizi, 2011). Typically, movement problems arising in later adulthood, usually around 50-60 years of age, elicit more profound diagnostic concerns.

HD-related movement problems include a sort of undulation of limb and facial movements as if these cannot be suppressed. Limb movements appear dance-like and are referred to as chorea, though they are far from purposefully choreographed or intended (Thompson et al., 1988). At later stages, body movements stiffen, challenging the coordination of swallowing-related pharynx and esophageal muscles (dysphagia). This leads to problems of aspiration and choking (Heemskerk & Roos, 2011).

HD symptoms occur because of the progressive death of striatal neuron cells. The loss of striatal neurons destroys basal ganglia function. The neurons that perish early and more prominently represent those striatal neurons within the indirect pathway, the pathway that primarily suppresses unwanted movement. Progressive deterioration of indirect basal ganglia pathway leaves the VA/VL of the thalamus increasingly disinhibited and yields increased and uncontrolled muscle engagement until the antagonists become overstimulated, stiffening limbs by simultaneous activation (Joel, 2001; Nair et al., 2021). This overstimulation is evidenced as increasingly intense chorea and slowed movement (bradykinesia). Harkening back to drawing Snoopy, consider either unsuppressed wild movements of muscles, or muscles getting locked into tug-of-war battles rather than smoothly guiding the pen. Snoopy's snout would either look too short, or overly long.

There are no directly targeted cures for Huntington's disease right now. The absence of a cure has made diagnosis and genetic testing for Huntington's disease ethically and emotionally complicated. Without clear treatments available, a child with a parent showing symptoms of Huntington's has a dilemma. They have a 50% chance of carrying the mutated gene. If they are tested and have the Huntington's mutation, there is little they can do, so many patients may decide they don't even want to know. Hopefully

that dilemma will be resolved in the future, as there are several treatments being actively worked out. Given the disease derives from a distinct mutation in the huntingtin gene, involving an inappropriate expansion of the genetic code, there have been some ideas about either suppressing mutated genes or targeting the mutation with gene therapy for heterozygotes. Transplantation of stem cells into Huntington's patients has also been attempted with varied success (Rosser & Bachoud-Levi, 2012). Currently, however, standard of care is pharmacological treatments, such as tetrabenazine, to reduce symptoms. Tetrabenazine is a vesicular dopamine transporter blocker that prevents the filling of dopaminergic synaptic vesicles (Bonelli, & Wenning, 2006). These drugs suppress chorea because they tend to dampen the movement initiation of the basal ganglia-based motor driving mechanisms. Dopamine net diminishes the activity in the indirect pathway, thereby promoting direct pathway initiation of planned movements. However, these drugs also tend to spread and have high cognitive side effect potential such as depression or other tensions (Paleacu, 2007). Much work is needed to improve treatment of Huntington's disease.

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7.5: The Cerebellum

The cerebellum

The cerebellum sits behind and below the cerebrum, atop the brainstem. Its folia look like two lateral bunches of curled-up spaghetti. Its main function is to smooth-out our behavioral efforts. It does this by either pre-processing movement intentions building in the premotor cortical areas, or via upper-level imagined anticipation. For example, if you contemplated a large rock in front of you in the middle of a creek, and whether you *might* be able to land on it to cross the creek. Alternatively, to improve attempted actions, we process the differences between *intended* and *actual movements*, and adjusting signal durations/ intensities until proprioception from afferent spinocerebellar tracts says we "nailed it" (Stecina, et al., 2013; Therrien & Bastian, 2019). You might compliment someone with "you have an efficient cerebellum" as a *neuroscientist exclusive* way of implying they move with sophistication.

How the basal ganglia and cerebellum divide their supportive roles in movement has intrigued neuroscientists for years. The functions of the two different regions are difficult to disentangle (Proville, et al., 2014). To simplify, coordinating necessary muscle *selection* seems to be the specialization of the basal ganglia, while coordinating contraction *timing and degree* requires the cerebellum. Analogous smooth and elegant line production while drawing Snoopy requires sophisticated starting and stopping, and smooth transitions of pen direction, to avoid jerky images (see Fujisawa & Okayama, 2015). Another way to think about it is that the basal ganglia "chunk" flexors here and extensors there, while the cerebellum smooths out their actions. Such responsibilities are emphasized more strongly in either structure, though in any one effort we *will* utilize both structures.

The cerebellum provides its smoothing functions (while you are drawing Snoopy or doing any number of other tasks) through extensive error correction. A motor error occurs when the way we actually move does not match where we intended to move. Detecting errors therefore requires at least 2 streams of information: one about action and the other about intention. Intention comes to the cerebellum from the brain via projections from the pontine nuclei in the brainstem, or from spinal cord regions where descending UMN tracts depict what we *intend* to do (either consciously or implicitly) to *anticipate* goals which also ascend the spine into the cerebellum. The cerebellar input about movement derives from proprioception feedback (largely muscle stretch), which depicts *moves that happened,* ascending from the spinal cord via spinocerebellar tracts (or trigeminal that monitors head/face movement). Progressively, the cerebellum compares these two components and adjusts the prompting UMN signals until we nail it (*intended = actual*).

The role of the cerebellum in providing smooth integration of motor effort timing and intensity can be appreciated when it is impaired, as happens in cerebellar ataxia or when someone consumes alcohol (Sokolov et al., 2017; Spencer et al., 2005; Bareš et al., 2009). Cerebellar damage (cerebellar ataxia) causes dysmetria, where one exhibits a "drunken gait" because foot placement can't be error-corrected or smoothed, and intention tremor where movements overshoot stopping points and oscillate around target destinations (Schwartze et al., 2016). It is important not to conflate alcohol effects with cerebellar damage. Drunkenness derives from the way alcohol enhances the effects of GABA across wide regions of both motor control and decision-making circuits. Cerebellar damage specifically eliminates the controlled-targeted landing of limbs to the right place. Cerebellar ataxia is analogous to rendering smooth limousine driving into two choices: full throttle or slamming on breaks. Yet visually, walking while drunk and walking with cerebellar ataxia appear outwardly similar. The cerebellum constantly contributes to posture alignment behind the scenes (subconsciously) so removing these contributions causes loose and wavy lack of balance. People can experience ataxic gait for multiple reasons. Any ataxic walking (caused by cerebellar damage or any other source) looks like feet land where they do by accident, rather than on purpose. Cerebellar ataxic gait occurs because the cerebellum can't correct the extent of movements properly, emphasizing approximations (see this video on Ataxia).

Corrective actions incorporated with ongoing movement, not after we perceive movement

Just like the basal ganglia, the cerebellum supports movement control by tweaking the thalamic VA/VL complex, though synapsing through distinct circuits. The cerebellum is inspired into action in relation to initial learning, and later provides anticipatory adjustment signals that integrate into ongoing movement but are sent prior to or in conjunction with the UMN signals that descend to initiate LMN actions. Most cerebellum contributions are made subconsciously and become integrated into movements we *subsequently* produce (the lack of sufficient adjustment is shown when errors occur, such as ataxia). Success in generating desired smooth movements, ending without jerky shakes, requires error corrections to be incorporated before movement begins.

If we had to wait for proprioceptive feedback before correcting, there would always be a “jerk-back” effect due to delays inherent in sensory systems. This can result from conscious movement monitoring. Conscious proprioception (cortical) is slower than ongoing movements, so modifications come post-movement, making it jerky and uncoordinated. Damaged cerebellum patients are limited to this, so when their conscious stream is distracted, they produce more movement errors because their cortex cannot multitask well (Brunamonti, et al., 2014). Thus, a well-primed (skill consolidated) healthy cerebellum recognizes the need, then delivers its adjustments along with *subsequent* UMN-driven movement efforts rather than correcting errors after the fact. It learns while we do behind the scenes to determine how much boosting or tapering is necessary, and subsequently contributes these adjustments to future movements. Imagine these contributions behind the scenes of established Olympic floor moves, or the slight-of-hand demonstrated by a seasoned magician (Dahms et al., 2020).

Practicing and imagining success

It’s important for new behavior to start off slowly, allowing sufficient time for proprioceptive sensory feedback to reach the CNS and become conscious perception. We do this all the time when we are learning how to move in specific ways. For example, choreographed fight moves à la Jackie Chan are typically rehearsed slowly before filming so actors can anticipate blows and pull back to “act” hit. By going slowly, we have time to consciously perceive motor errors and use our cerebellar processes to correct them. Through this slow practice, the cerebellum helps us learn how to execute movements faster and faster, with less conscious perception of proprioception needed to keep our bodies on track. Notably, even imagined movements can play a role in this learning—a mental rehearsal without physical engagement (Decety & Ingvar, 1990, Jackson et al., 2003). Actors, dancers, skaters, and sports professionals do this *all the time*. The performance improvements from imagined practice are real, not illusory, as they entrain the cerebellar circuitry support of cerebral movement control via the same circuitry that adapts to actual movement.

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7.6: Primary Motor Cortex and Descending Motor Pathways

Primary motor cortex

The primary motor cortex (M1) region receives our “upper-level” synaptic progression last. This progression collects and coordinates movement intentions before sending those UMN compilations down to the brainstem and spinal cord for movement generation by the LMNs. M1 is also the first cortical area with full lateralization of limb and face movement control: M1 neurons on the right side of the brain all target LMNs for the left limbs and facial area, while M1 neurons on the left side of the brain all target LMNs for the right limbs and facial areas. This lateralization contrasts with the premotor regions we discussed so far, which engage bilateral control. M1 lateralization is restricted to limbs and facial lateral areas, not the trunk, which is generally ipsilaterally controlled.

Primary Precentral Gyrus Organization

The posterior frontal cortex has a major crease, the central sulcus, dividing the precentral (green in Figure 10.20) and postcentral gyri.

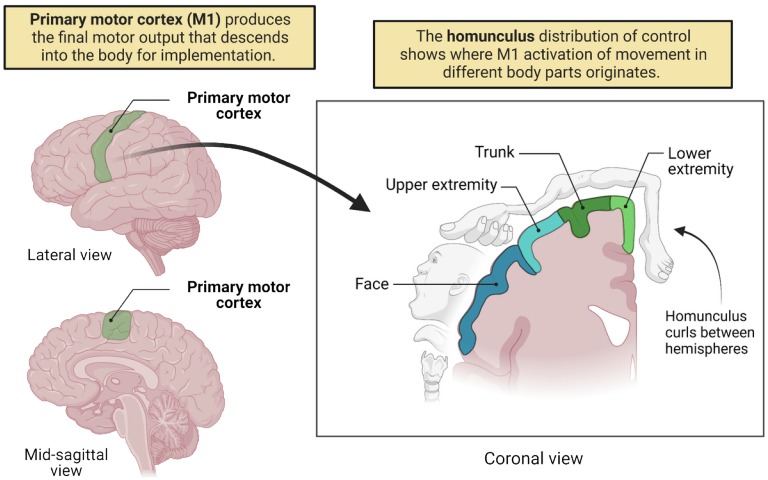


Figure 10.20 Primary motor cortex

This strip, from between the hemispheres out laterally, ending just above the lateral fissure (defining the top of the temporal lobe), contains the primary drivers of voluntarily organized/coordinated movement known collectively as the primary motor cortex. The neurons of the primary motor cortex are arranged in a homunculus. This arrangement is essentially a map of a little person lying across the precentral gyrus, so toe control is buried between the hemispheres. This map was famously created by neurosurgeon Wilder Penfield, who assessed movements when brain regions were stimulated during surgeries correcting epilepsy and made direct recordings during movements (Penfield and Rasmussen, 1950). The idea of a homunculus depicts the “person” as a distorted image made up of enlarged areas where more neuronal space engages with specific moveable body parts. The complexity or subtlety of movement of any body part tends to engage larger numbers of neurons as this attribute goes up, so the eventual map of a person has a large tongue, huge lips, prominent face around the forehead, huge hands and feet, with a smaller torso, limbs, and joints, according to the degree of movement sophistication possible. The motor homunculus is to movement sophistication as the somatosensory homunculus is to somatosensory density.

Descending motor projections

The primary motor cortex neurons send their axons out to the brainstem and spinal cord via three tracts (see Figure 10.21).

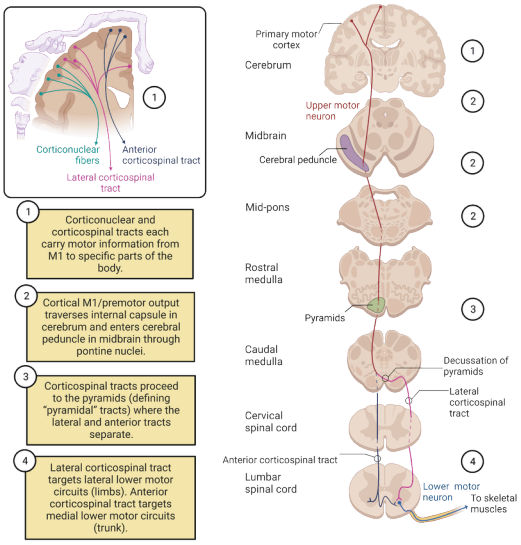


Figure 10.21 Corticospinal motor pathways for the body

- The corticobulbar (or corticonuclear) tract, carries descending efferents from the cortex, synapsing on brainstem nuclei serving regions of the jaw, face, ear mechanisms, for gagging or swallowing, or crinkling our noses. Corticobulbar tracts largely provide bilateral support, where each side directly serves ipsilaterally, and crosses over at the level of various nuclei to the contralateral side. The exception to this rule would be the descending tracts subserving the facial nucleus, specifically the lower part of the face, which is exclusively contralateral (Patestas & Gartner, 2016). We're overlooking autonomic patterning aspects of this projection to focus on controlled movement.
- The lateral corticospinal tract is the major descending tract for body limbs. It crosses almost entirely to the other side of the body to control the contralateral (opposite side from originating hemisphere) limbs, mostly the arm/hand/fingers and leg/foot/toes.
- The anterior corticospinal tract is a smaller but important tract responsible for controlling trunk muscles and more medial aspects. While some of this tract decussates (crosses over) at the level of the spinal cord in the ventral white matter as shown in Figure 10.21, a majority subserves the ipsilateral side.

The upper part of our body (head) is largely controlled via cranial nerves derived from the brainstem and therefore the corticobulbar tract. The two corticospinal tracts descend to different levels of the spinal cord. Within the spinal cord, these tracts interact with LMNs and the circuitry making up the reflex architecture (also used to engage the knee-jerk, or withdrawal reflexes, utilizing local spinal circuitry described above) to control the lower parts of our bodies such as limbs and trunk.

Why do some descending UMNs control need to cross over to operate the opposite side of the body? One simple explanation may be that visual information passing through lenses of your eyes is flipped. Events occurring to our left pass to the right sides of our retinae. The right sides of each retina connect with the right hemisphere, while the left connects with the left. However, the information they process is relevant to the opposite sides of our bodies. This probably created pressure for natural selection to derive a map of limb control so each hemisphere could control the opposite side.

People behind the science: Vector Trajectories

Apostolos Georgopoulos MD, Ph.D. currently heads a Brain Center at The University of Minnesota where he is Regents Professor of Neuroscience. His work brought important insights to the way motor cortex activates limb movement. To appreciate his findings, it's important to understand the concept of a vector, a force directing movement encompassing both *speed and direction*.

When we kick a ball softly, its path forms a vector with little *speed*. Kicking the ball harder in the same *direction* maintains this vector with greater *speed*. A different *direction* would elicit a different vector. Similarly with moving our arms.

The key to Georgopoulos' findings is, across the population of M1 neurons, each neuron's activity seems to be associated with a vector of limb movement. Or, as each M1 motoneuron fires action potentials, their frequencies intensify in relation to the limb movement's direction and trajectory range (Georgopoulos et al., 1983).

To determine this, Dr. Georgopoulos and his team recorded from hundreds of individual M1 neurons within the brains of monkeys while the monkeys moved a specialized apparatus (Georgopoulos et al., 1992). It was set up like a large lever-shift which picked up movement direction, and could be adjusted to provide back-pressure along certain trajectories.

Think of this as a large old-school Atari-like joystick, shifting rather than simply angling in different directions. When the animal pushed the lever in one direction, a distinct neuron population appearing to "prefer" that direction elicited strong bursts of activity, while other populations "preferring" other directions diminished responses. If the vector of an M1 neuron's preference required extra force, that MI neuron increased its firing rate (Georgopoulos et al., 1982). The key to the developing hypothesis was at each motion of the arm, larger populations of neurons contributed their "vote" for arm vectors into the descending feed. At each moment key populations "won" the vote to over-ride alternative movement preferences. Brain democracy!

At first, these experiments were performed with only two-dimensional movement directions across a flat surface (1983). Eventually, more exciting results were obtained from monkey arm movement tracked three-dimensionally. Based on the same premise, a more complex division of "preferences" yielded similar results (Georgopoulos et al., 1988). It is fascinating to consider the wider implications of this. Guiding one's arm or hand towards a target follows calculations of vector trajectories in regions like the posterior parietal cortex and the cerebellum, to be sent forward toward the premotor cortex.

It's now clearer how this guidance appears to help reinforce individual neurons contributing "votes" or preference activations in concert with needed directions through increasingly selective intensities of stimulation of select M1 cortical neurons (e.g., Georgopoulos et al., 1992; Taira et al., 1990). Since these preference activations persist across a population, this also seems to provide greater stability in the capacity to elicit distinct movements, diminishing the probability of select damage eliminating specific movement trajectory capacities. This would be incredibly helpful in restoring post-stroke movement, for example. To draw Snoopy, many hand muscles need to be selected individually or simultaneously and this neuronal "voting" is also supported by basal ganglia contributions along the way when we draw him again, and again (necessary for moving pictures).

Moving Beyond Vector Trajectories into Controlling Robot Arms

In the previous section, we discussed how the pioneering work of Georgopoulos pointed towards this key cortical element of “voting populations.” More recently, new and fascinating cutting-edge things have been happening to build off his work. By studying consensus of neuronal activities and how they link to vector trajectories, researchers have begun to be able to predict where limbs might go based on neuronal activity! Once you can predict what neuronal activity does, it becomes possible to tap in to those neurons to recreate movements. This basic idea is what underpins many modern efforts to link robot prosthetics to the human brain.

Many forms of brain or spinal cord damage can render a person unable to move any limbs despite owning an active and intact brain (quadriplegic). Neuroscientists such as Andrew Schwartz and others have been working to turn that remaining ability to direct movements in the brain into real movements of robotic prosthetic devices. This work is all based in the original concepts derived from Georgopoulos and has now yielded robotic arms that can respond to recordings from a patient’s brain and engage complex arm and hand type movements to select, grasp, and move objects! The details of how two human subjects with quadriplegia were implanted with specialized electrodes over the arm-related region of their M1 homunculi and subsequently gained considerable control over an attached robot arm are originally described in Lancet (Collinger et al., 2013). Since this initial proof-of-principle, improvements have been made. For example, a patient in 2015 received a version of this system that was not just unidirectional—taking motor commands and linking them to the prosthetic. This newer version also incorporated input from sensory information. Remember back to our example of a monkey swinging through the trees. To swing, grasp and release well, the monkey integrated several sources of touch information. Grasping without feeling the grasp would make branch swinging a far greater challenge for the monkey. The same applies to patients with prosthetic limbs. Adding touch feedback greatly improved the ability of the patient to use their limb. These devices, adjusted for circumstances, are moving outside of a theoretical possibility into a distinct therapeutic option reality! If movement practice feedback could also be incorporated, it is conceivable that practiced learning could get such patients back to cooking in the kitchen!

A Special inspiration from your author

It has been a pleasure sharing a neuroscientist's view of movement with you all. All the complexity ensures our capacity to *do what we want to do*. Considerable control has evolved at both lower implementation levels and higher formulation levels. Collaborations between brain, spine, and muscles above help us repeatedly *do what we want* without having to re-invent every motion from scratch. Background processing and delegation promotes the feeling of quick shifts from thinking to doing. Now you should have a better sense of the complexity. On several occasions, this chapter has used expressions like 'apparently,' 'it seems like,' or 'seems to.' Such expressions demonstrate there's a lot neuroscientists still need to learn about body movement mechanisms. The author hopes that future neuroscientists or readers with related intentions may see clarifying this as a challenge. Also, this author wishes to thank the editor Dr. Elizabeth Kirby, his father (Dr. Harald M. Sandstrom), his brother (Jonathan R. Sandstrom), and his colleague Dr. Gary L. Dunbar for their extraordinary editorial support that substantially improved this chapter's clarity and focus.

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8: DEVELOPMENT OF THE NERVOUS SYSTEM

8.1: Embryonic Stage
8.2: Stages of Neuronal Development
8.3: Synapse Formation and Maturation
8.4: Neuroplasticity
8.5: Sensitive and Critical Periods of Development
8.6: Trade-off between Plasticity and Efficiency
8.7: Characterizing Brain Development from Infancy through Young Adulthood

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8.1: Embryonic Stage

The **embryo** is initially formed through fertilization, which occurs when a sperm cell and an egg cell unite into a single cell. This fertilized egg cell, or **zygote**, starts dividing through the process of mitosis to generate the cells that make up an entire organism. Sixteen days after fertilization, embryonic cells form three layers that develop into different body tissues (Betts et al., 2022). The **endoderm**, or inner tissue, is responsible for generating the lining tissues of various spaces within the body, such as the mucosae of the digestive and respiratory systems. The **mesoderm**, or middle tissue, gives rise to most of the muscle and connective tissues. Finally the **ectoderm**, or outer tissue, develops into the body's outer layer of skin, hair, nails, as well as the nervous system. It is probably easy to see that the outer tissue of the embryo becomes the outer covering of the body, but how is it responsible for the nervous system?[1]

Neural Tube

Two weeks into embryonic development, the human nervous system begins to form. As the embryo develops, a portion of the ectoderm differentiates into the precursor for the tissue of the nervous system (Betts et al., 2022). Cells in this region form a neural plate that begins to fold inward to form a **neural groove** that is lined on each side by a neural fold. These two **neural folds** eventually fuse together to form the **neural tube** (Figure 1) and set up the development of the brain and spinal cord. Cells from the neural folds then separate from the ectoderm to form a cluster of cells referred to as the **neural crest**, which runs lateral to the neural tube. These neural crest cells migrate away from the nascent **central nervous system** (CNS) that will form along the neural groove and develop into several parts of the **peripheral nervous system** (PNS) including the enteric nervous system that governs the function of the gastrointestinal tract.

Cross section drawing of the early embryonic development of nervous system.

Figure 1: During the embryonic stage of development, the neuroectoderm folds inward to form the neural groove. As the two sides of the neural groove fuse together, they form the neural tube. The anterior end of the neural tube will develop into the brain, and the posterior portion will develop into the spinal cord.

During the third week of embryonic development, the anterior end of the neural tube begins developing into the brain, and the posterior portion begins developing into the spinal cord. This basic arrangement of tissue in the nervous system gives rise to more complex structures by the fourth week of development.[2]

Primary Vesicles

As the anterior end of the neural tube starts to develop into the brain, it generates three **primary vesicles**: the forebrain (**prosencephalon**), the midbrain (**mesencephalon**), and the hindbrain (**rhombencephalon**) (Betts et al., 2022). The forebrain is the upper-most vesicle, the midbrain is the next vesicle, and the hindbrain is the lowest vesicle. One way to think about brain organization uses these three divisions—forebrain, midbrain, and hindbrain (Figure 2).[3]

Illustration of the primary and secondary vesicle stages of development

Figure 2: During the embryonic stage of development, the neural tube evolves into three primary vesicles. These three primary vesicles then give rise to five secondary vesicles.

Secondary Vesicles

By week 5, the three primary vesicles differentiate further into five **secondary vesicles** (Betts et al., 2022) (Figure 2). The **forebrain** enlarges into two new vesicles called the **telencephalon** and the **diencephalon**. The telencephalon will become the cerebrum—the largest part of the adult brain which contains the lobes of the cerebral cortex, hippocampus, and basal ganglia. The diencephalon will give rise to several structures including the thalamus (the central relay hub for sensory signals) and hypothalamus (involved in homeostasis and regulating functions including hunger, sleep, and mood).

A third secondary vesicle, the mesencephalon or **midbrain**, is composed of the **tectum**, the **cerebral aqueduct**, the **tegmentum**, and the **cerebral peduncles**. The midbrain is an established region of the brain at the primary vesicle stage and does not further differentiate into finer divisions. The rest of the brain develops around the midbrain, which is involved in many functions including head and eye movements, motivation, and reward.

The **hindbrain** develops into the final secondary vesicles, the **metencephalon** and **myelencephalon**. The metencephalon gives rise to the **pons** and **cerebellum**. The cerebellum accounts for about 10 percent of the mass of the brain and is an important structure for coordinated movement, posture, and cognition. The cerebellum connects to the rest of the brain via the pons, because the pons and cerebellum develop out of the same vesicle. Finally, the myelencephalon gives rise to the adult structure known as the **medulla oblongata** (involved in breathing, digestion, heart rate, blood pressure, etc.). The structures that arise from the midbrain and hindbrain, except for the cerebellum, are collectively considered the **brain stem**, which specifically includes the midbrain, pons, and medulla.

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definition

A growing organism in the initial stages of development after fertilization.

×Close definition

A cell formed by the union of a female gamete (egg) with a male gamete (sperm).

×Close definition

Innermost of the three germ layers in a developing embryo.

×Close definition

Middle layer of the three germ layers in a developing embryo.

×Close definition

Outermost of the three germ layers in a developing embryo.

×Close definition

Formed when the neural plate folds inward and extends the entire length of the embryo.

×Close definition

Ridges of the ectoderm on the neural plate that form around the neural groove and fuse to form the neural tube.

×Close definition

The hollow longitudinal tube formed by the infolding of the neural plate and subsequent fusion of the neural folds. Sets the basis for development of the brain and spinal cord.

×Close definition

A temporary cluster of cells that originate from the side of the neural tube proximal to the epidermal layer. Neural crest cells give rise to diverse cell types that can support many different systems.

×Close definition

The portion of the nervous system that includes the brain and spinal cord.

×Close definition

All of the nerve cells that connect the central nervous system to all the other parts of the body.

×Close definition

The three primary vesicles include the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain).

×Close definition

One of the three primary vesicles. Also referred to as the forebrain.

×Close definition

One of the three primary vesicles. Also referred to as the midbrain.

×Close definition

One of the three primary vesicles. Also referred to as the hindbrain.

×Close definition

The five secondary vesicles include the telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon.

×Close definition

Also referred to as the prosencephalon. The forward most part of the brain. Consists of the telencephalon and diencephalon.

×Close definition

Largest portion of the central nervous system and consists of the cerebrum and related structures.

×Close definition

Neural structure located deep in the brain that includes the thalamus and hypothalamus. Connects the midbrain to the forebrain.

×Close definition

Also referred to as the mesencephalon. The top-most portion of the brain stem. Consists of the tectum, the cerebral aqueduct, the tegmentum, and the cerebral peduncles.

×Close definition

The uppermost part of the midbrain.

×Close definition

Narrow, 15mm, channel that connects the third ventricle with the fourth ventricle and facilitates the transport of cerebrospinal fluid (CSF).

×Close definition

The ventral portion of the midbrain.

×Close definition

Two bundles of nerve fibers that are located in the ventral midbrain and connect the cerebrum to the brain stem.

×Close definition

Also referred to as the rhombencephalon. The lower portion of the brain stem. Consists of the metencephalon and myelencephalon.

×Close definition

The part of the hindbrain that develops into the cerebellum and pons.

×Close definition

The part of the hindbrain that develops into the medulla oblongata.

×Close definition

Part of the hindbrain. A bridge that connects the cerebral cortex with the medulla, and reciprocally transfers information back and forth between the brain and the spinal cord.

×Close definition

The distinctive structure at the back of the brain between the cerebrum and brainstem. Important for muscle control, such as balance and movement.

×Close definition

Extension of the spinal cord that forms the lowest part of the brain stem.

×Close definition

Composed of the medulla oblongata, pons, and the midbrain. The part of the brain that connects the cerebrum to the spinal cord.

×Close definition

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8.2: Stages of Neuronal Development

The brain is made up of **neurons** and **glial cells**. Neurons, also called nerve cells, are electrically excitable cells that transmit signals called action potentials to other neurons and are considered the fundamental units of the brain and nervous system (Ludwig et al., 2022). Neurons communicate information about sensations and movement, and process information within the brain. Glial cells, or neuroglia or simply glia, are the other type of cells found in the nervous system. Glial cells are considered support cells and help neurons complete their function for communication. We discuss six main types of glial cells—four in the CNS and two in the PNS. Figure 3 depicts different glial cells and Table 1 defines their common functions.

Figure 3: Visualizing the different glial cell types.

Glial Cell Types By Location and Function

Table 1: Different types of glial cells and their basic functions [Table adapted from: Anatomy and Physiology 2e: 12.2 Nervous Tissue] CC BY 4.0.

CNS Glia	PNS Glia	Function
Astrocyte	Satellite cell	Support
Oligodendrocyte	Schwann cell	Insulation, myelination
Microglia	–	Maintenance of neural networks
Ependymal cell	–	Creating cerebrospinal fluid

Neuron Growth

Neuronal development includes several stages. Once the neural tube has closed, the first stage of neuron growth, known as **neural proliferation**, begins to occur in the ventricular zone of the neural tube. **Neurogenesis**, the process of generating new neurons, begins approximately four weeks after conception during embryonic development. This critical phase is marked by a significant proliferation of cells within the neural tube, the precursor structure to the central nervous system. Most neurons in the human telencephalon (i.e., cortex, hippocampus, basal ganglia, etc.) are generated before birth. Extensive neurogenesis does occur after birth in other brain regions like the cerebellum. But all in all, the bulk of neurogenesis (i.e., the 86 billion neurons) in the CNS occurs between the fourth week post-conception to 18 months after birth—during this early developmental period, approximately 4.6 million neurons are generated every hour (Silbereis et al., 2016)!

During neural proliferation, the cells being formed are **neural stem cells**. There are two basic types of stem cells, pluripotent and totipotent cells. Pluripotent cells can give rise to all cell types that make up the body, whereas multipotent cells are more limited than pluripotent cells. Because pluripotent stem cells can develop into any cell type in the human body, scientists are examining how they can be used in regenerative cell-based treatments for various conditions, including diabetes, spinal cord injuries, and heart disease. In CNS development, neural stem cells are special pluripotent cells that produce only radial glial cells. These radial glial cells then differentiate into neurons and glial cells, forming the central nervous system. This process of neural proliferation generates billions of cells, ultimately developing into the complex structure of the CNS.

Neuronal Migration

Newly formed neurons may remain where they are and continue to divide, or migrate to other parts of the nervous system. Neuronal migration refers to the journey of neurons from their original location to a new target location. For neurons of the central nervous system, neural migration remains within the neural tube; whereas for neurons of the peripheral nervous system, neural migration may occur across different neural regions (Purves et al., 2001). During the migration period, neurons remain immature and lack fundamental neuronal characteristics such as **axons** and **dendrites**. Ultimately, neuronal migration is supported by sophisticated molecular and cellular signaling that results in pulling and pushing the immature neuron to its target location.

In general, migration tends to follow an inside-out pattern, where neurons travel from the inside of the neural tube outwards toward their target location. This migration can be classified into two modes: 1) **radial migration**, and 2) **tangential migration**.

Radial migration, long seen as the primary mode of neuronal movement in the cortex, occurs when neurons are guided by radial glial cells to migrate toward the surface of the brain following the radial pattern of the neural tube and ultimately establish the layered organization of the neocortex (Marin et al., 2003; Wong, 2002). The second mode of neuronal movement, tangential migration, occurs when neurons move to the surface of the central nervous system (or orthogonal to the direction of radial migration). Of note, these two migration methods are not mutually exclusive, as some neurons may alternate from radial to tangential movement along the course of their migration to their target location (Marin et al., 2010).

Neuronal migration occurs through two main mechanisms. Somal translocation involves an extension reaching out from the immature neuron's soma to lead it to its target; this is used in both radial and tangential migration. Glial-mediated migration, specific to radial migration, involves immature neurons "climbing" along extended glial cells to reach their target locations.

Upon reaching their target locations, immature neurons develop distinct neuronal structures like dendrites and axons, which enable communication with other neurons. This neuronal communication leads to the formation of functional neural circuits.

Aggregation

After migrating, neurons must align and integrate with other neurons to create neural circuits. This is called **aggregation**. Aggregation is supported by two key mechanisms. **Cell-adhesion molecules** on cell surfaces recognize and bind to molecules on other cells, enabling cell-to-cell interactions and tissue stabilization (Jaffe et al., 1990; Takeichi, 1988). Additionally, **gap junctions** form communication channels between adjacent cells, allowing exchange of ions and metabolites such as glucose, which promotes biochemical coupling between the two cells (Mese et al., 2007). These mechanisms facilitate neuronal interactions and integration, ultimately giving rise to the neural circuitry of the human nervous system.

Neuron Death

Neuronal cell death, which refers to the elimination of neurons in the nervous system, occurs extensively during development and actually supports brain development. Neuron death is typically categorized as either apoptosis or necrosis. **Apoptosis** refers to active, programmed cell death to maintain appropriate development, whereas **necrosis** refers to passive, accidental cell death resulting from environmental perturbations, such as trauma, toxins, or oxygen depletion (Khalid & Azimpouran, 2023). Apoptosis occurs after neuronal proliferation, selectively eliminating excess and immature neurons to enable proper neuronal connectivity and maturation of functional networks (Hollville et al., 2019). Unlike apoptosis, necrosis is characterized by swelling and rupturing of the cell membrane, as well as leakage of the cellular contents (Rock & Kono, 2008). Necrosis leaves behind disruptive cellular debris, whereas apoptosis efficiently dismantles and "cleans up" the dead neuron, minimizing disruption to surrounding brain tissue. One example of necrosis occurs after a stroke, where disruption of blood flow may lead to accidental cell death. Excessive necrosis is detrimental and is associated with pathologies such as Alzheimer's and Parkinson's diseases (Boka et al., 1994; Goel et al., 2022; Tuo et al., 2022). Much work remains to understand and regulate cell death to preserve brain function.

Adult Neurogenesis

Until about 25 years ago, the prevailing view was that new neurons could not be generated in the human brain after birth. However, a landmark study showed that regions of the adult brain, such as the hippocampus, can generate new neurons throughout adulthood (Eriksson et al., 1997). Generating new neurons in the adult brain is referred to as **adult neurogenesis**. However, adult neurogenesis does not appear to take place in all parts of the brain. Neurogenesis has been most consistently observed in two regions: 1) the subventricular zone of the lateral ventricles and; 2) the subgranular zone in the dentate gyrus of the hippocampus (Ribeiro & Xapelli 2021). Additionally, many neurons generated during adulthood do not survive and cannot integrate into existing neural circuits. While multiple studies have demonstrated evidence of adult neurogenesis, the topic remains fairly controversial. Some studies suggest that 700 new neurons are generated in the adult hippocampus every day, while other studies suggest that adult hippocampal neurogenesis is undetectable or may not exist at all (Sorrel et al., 2018; Spalding et al., 2013). Nonetheless, given the potential clinical implications of new neurons and their possible role in preserving cognitive function, future research will continue exploring the mechanisms that support adult neurogenesis.

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definition

The fundamental units in the brain that transfer information from the brain to the rest of the body.

×Close definition

Non-neuronal cells that support and insulate neurons. Important for supporting typical brain function and protecting neurons.

×Close definition

The mass production of cells. Most prominent during early embryonic development.

×Close definition

The process by which new neurons are formed in the brain.

×Close definition

Self-renewing cells that ultimately generate neurons or glial cells, which give rise to the entire nervous system.

×Close definition

A long threadlike part of a neuron that carries electrical impulses away from the cell body and to other neurons

×Close definition

A branch-like structure of the neuron that extends from the cell body.

×Close definition

The most common mode of neuronal migration in which neurons migrate in a radial pattern to ultimately establish the different layers of the cortex.

×Close definition

Another mode of neuronal migration in which neurons migrate tangentially and may emerge as a result of interactions with axons, astrocytes, or independent of interactions with other cells. Does not rely on glial cells for migration.

×Close definition

The stage of neuronal development after migration where different classes of neurons coalesce to form different nervous system structures.

×Close definition

A subset of cell surface molecules that are involved in the binding of cells with other cells.

×Close definition

A type of cell junction in which neighboring cells are connected through intercellular channels. Also facilitates the transfer of molecules directly from the cytoplasm of one cell to another cell.

×Close definition

The process of programmed cell death to eliminate unwanted cells.

×Close definition

A form of cell injury which results in premature, unprogrammed cell death due to environmental factors such as injury or disease.

×Close definition

The process in which new neurons are generated in the adult brain.

×Close definition

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8.3: Synapse Formation and Maturation

Learning Objectives

By the end of this section, you should be able to

- Explain neurite outgrowth and the structural components of a growth cone.
- Describe polyneuronal innervation and experience related innervation modifications.

The creation of neurons and glia is only the first step in creating a functional brain. For neurons to function in meaningful ways, they have to connect to each other. Making (and keeping) these connections requires several steps. Here, we will discuss the formation of the growing axon (neurite) and major influences guiding final contact and synapse formation. We will end by describing polyneuronal innervation, our first window of opportunity to observe the potential for synaptic plasticity.

Communication by electrical impulse

The anatomist Santiago Ramón y Cajal was the first to describe fibers radiating from individual neurons (Cajal, 1995). He postulated that neurons were separate entities and used long fibers and connections to communicate. How the brain communicates through synapses was discussed in an earlier chapter. Here we will provide a short review of this process because it is integral to the formation of synaptic connections early in development. Neurons communicate with each other via the synapse which can be seen in Figure 5.16.

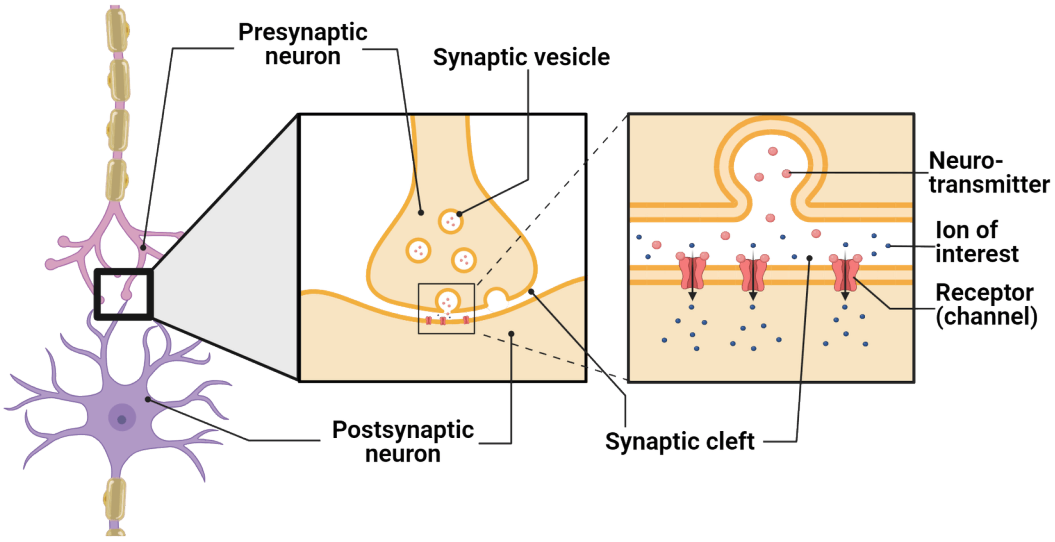


Figure 5.16 Reminder of synaptic transmission

The presynaptic neuron (sending the signal) is in close proximity with the postsynaptic neuron (receiving the signal) and can use signaling molecules and neurotransmitters to either increase or decrease the probability that the postsynaptic neuron fires an action potential. This communication occurs at the synaptic cleft (Figure 5.16). Complex mechanisms are required to ensure that the correct presynaptic neuron pairs with the appropriate postsynaptic neuron/tissue during development. Neurons extend and grow their axon using multiple cues and once they encounter their partner, they will test their match using temporary junctions, cell signaling and adhesion molecules, combined with electrical activity. Such signals, if positive, will then promote formation of a mature synapse.

During development, neurons extend a specialized structure from the tip of a growing axon or dendrite. This structure was first described by Ramon y Cajal and was coined the growth cone (Figure 5.17). Growth cones are dynamic, in that they sense and respond to the environment in search of a target tissue to innervate (connect to via a synapse). Growth cones change shape

by extending outward a leading edge (Figure 5.17), which interacts with the environment. The leading edge of the growth cone appears as a hand with fingertips. The outstretched fingertips are called filopodia (plural). Each filopodium (singular) samples the environment for attractive and repulsive signals that help to determine the direction of growth. In between each filopodium is a flat structure called the lamellipodium (Figure 5.17). Growth cones express various molecules on their surface that interact with the environment. Therefore, two unique growth cones may respond differently to the same environment.

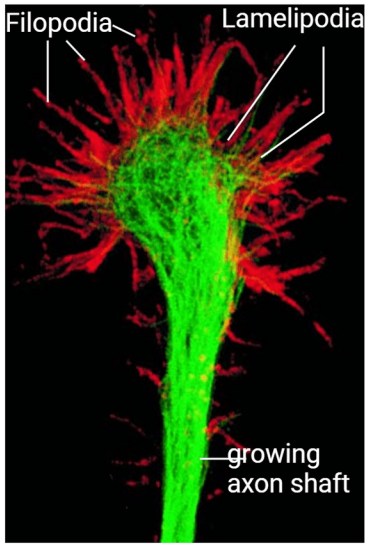


Figure 5.17 Growth cones Image credit: Microscopy image Public Domain, https://commons.wikimedia.org/w/inde...?curid=1321398. Labels added.

The growth cone is dynamic, and when it meets attractive cues, a structural protein inside the budding growth cone called actin facilitates changes in the direction of the growth cone. Actin subunits can come together in a process called polymerization to move the growth cone. Actin filaments are primarily located in the filopodia.If a repulsive signal is detected, in contrast, actin subunits detach from each other, which is commonly referred to as depolymerization. Actin subunits are essential for growth cone movements, but the axon itself is not made of actin. It is produced from a more rigid protein called tubulin. Tubulin subunits come together at the opposite end of the leading edge of the growth cone to elongate the axon.

Types of receptors expressed on the growth cone

There are several different classes of molecules expressed on the surface of a growth cone. Figure 5.18 shows three of these major classes.

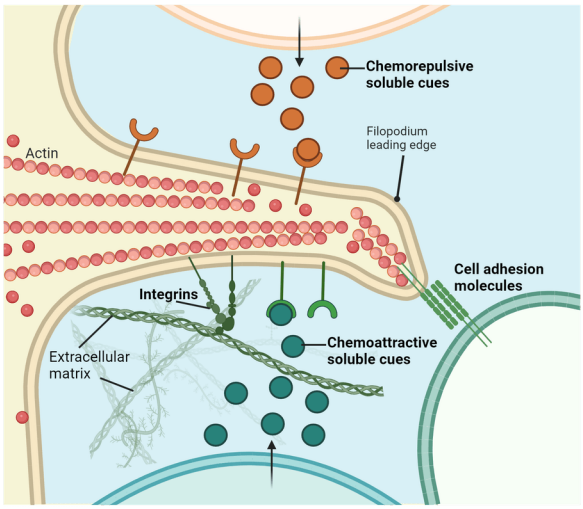


Figure 5.18 Signals guiding the growth cone

Cell adhesion molecules (CAMs) such as neural cell adhesion molecule (NCAM) bind to other CAMs on neighboring cells. These molecules can bind to each other in a process called homophilic binding (bind to the same receptor on another cell) or can bind to other CAMs through heterophilic binding (binding to a different receptor on another cell). CAMs are unique from calcium dependent cell adhesion molecules (cadherins) because cadherins require calcium for an interaction and bind via homophilic binding. Cadherins are similar to CAMs because they are receptors present on adjacent cells which interact. Both CAMs and cadherins are unique from a third class of membrane bound receptors called integrins. Integrins bind and interact with components of the extracellular matrix. These components include laminin, fibronectin, and collagen.

Additional cues can be received through ephrins, semaphorins, and netrin. Ephrins bind to Eph receptors while semaphorins bind to plexin or neuropilin receptors. Netrins are secreted factors that bind to the Unc-5/DCC receptor. Semaphorins are mostly inhibitory but under some circumstances can present attractive signals to the growing axon. There are two classes of ephrins, A and B, class A ephrins are anchored into the membrane and class B are transmembrane receptors that have an intracellular and extracellular domain. In vertebrates, netrin binds to the receptor DCC, which is expressed on the growth cone. The interaction between DCC and netrin is an attractive signal for the growth cone. Interestingly, netrin can also bind to the UNC5 receptor and when it does, it provides a repulsive cue. Thus, netrin can provide both attractive and repulsive cues.

Mechanisms of axon guidance at the midline: lessons from invertebrates

Much knowledge has been gained by studying axon guidance in the spinal cord of invertebrates. One particular piece of development that has revealed many insights into how axons find their way through the developing nervous system is how developing spinal axons in the neural tube decide whether to cross the midline in flies (Drosophila, specifically). Interneurons of the spinal cord are produced at the dorsal side of the neural tube. The growing axons of these cells are observed to first extend ventrally, toward the floor plate on the most ventral side of the developing spinal cord (Figure 5.19). Once at the floor plate, the axons must make a choice: some must stay on that side of the midline (ipsilateral) while others must cross the midline to the opposite side. Axons that cross the midline form a commissure and we refer to them as the commissural neurons. Both types of axons are needed for proper circuit formation and the balance between them is critical to later function.

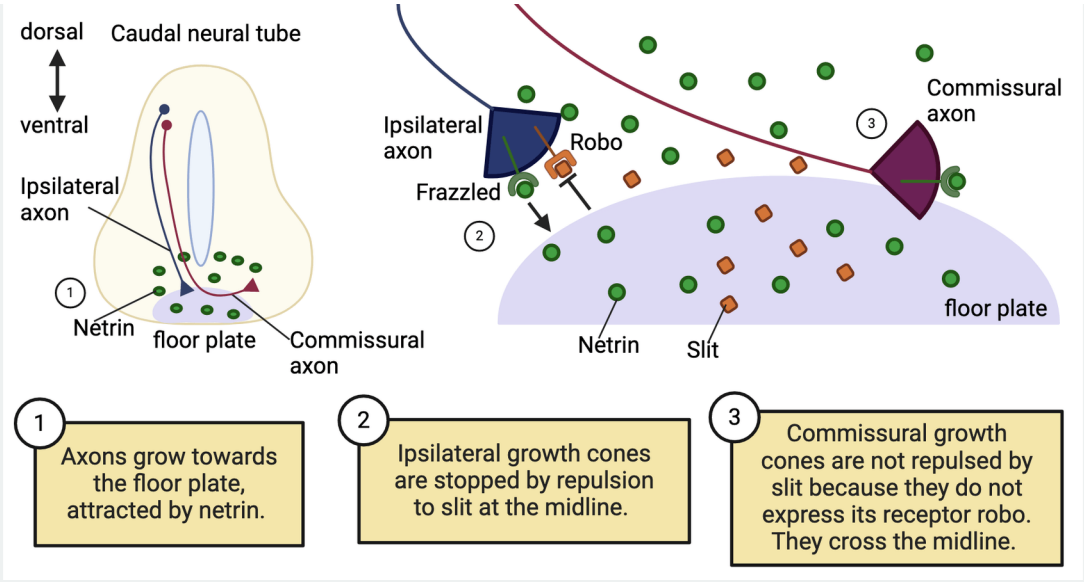


Figure 5.19 Growth cone signaling in the developing fly neural tube

Studies in Drosophila, the fruit fly, have helped us understand the signals that guide these movements of the spinal interneuron axons. First, researchers found that growth cones grow towards the floor plate through interactions between netrin and frazzled receptors. Frazzled receptors are the fruit fly equivalent to vertebrate DCC. The expression of frazzled attracts axons to the midline. However, this interaction alone does not fully describe the decision of an axon to cross the midline.

In Drosophila, the floor plate in the midline also secretes another protein, called slit. Slit provides a repulsive signal. Slit binds to the receptor robo, which is expressed on the growth cone. When slit binds to robo, axons that arrive at the floor plate due to their attraction to netrin are repelled from the midline and will not cross the midline. Mutations in slit or robo lead to an abnormal number of crossings. But if slit-robo interactions repel the growth cone, how do any axons cross-the midline? Robo expression at the growth cone must be suppressed in order for an axon to cross the midline. In the fruit fly, a protein called comm regulates the expression of robo at the surface of the growth cone. Comm suppresses robo just long enough for axons to cross the midline. A very analogous process occurs in higher vertebrates except that the Robo-like receptor Rig1, when expressed in the proper form, will allow crossing of the midline.

Synaptogenesis

Ultimately, the growth cone is directed by those attractive and repulsive signals to a putative target cell to form a mature synapse. The mature synapse has basic structural components that facilitate neuronal activity. The mature synapse contains vesicles of neurotransmitters, ionic channels (calcium channels), components to release neurotransmitters, a synaptic cleft, and a postsynaptic density (PSD) (Figure 5.16). These are all features that develop as a result of the pre- and postsynaptic cells interacting to help each other mature. When the presynaptic cell first meets the postsynaptic target, the synapse has immature characteristics, exemplified in Figure 5.20.

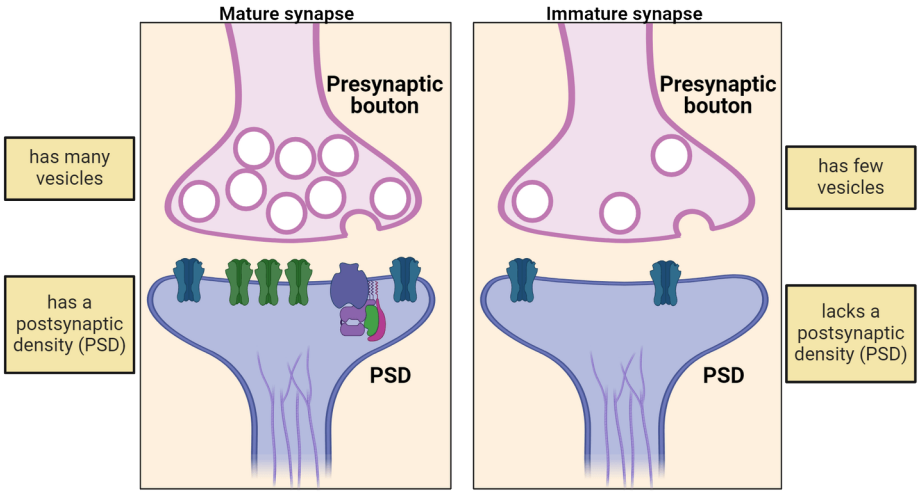


Figure 5.20 Immature v. mature synapses

There are two major classes of synapses: electrical and chemical. Chemical synapses communicate through the release of neurotransmitters, which are located in vesicles within the presynaptic neuron. The early immature chemical synapse lacks a PSD and has only very few vesicles in the presynaptic neuron. This immature chemical synapse has the ability to signal via neurotransmitter release, though it is not as robust as a mature synapse will eventually be (Figure 5.20). Rudimentary neurotransmitter release is required for chemical synapse maturation. Electrical synapses are fewer in number relative to chemical synapses and function through gap junctions that allow the electrical current to move from one cell to the next. Recent studies have shown that the components of an electrical synapse (i.e. gap junctions) are required for the development of chemical synapses (Todd et al., 2010). Thus, there is evidence that neurons first form transient electrical synapses before chemical synapses develop.

Developing a synapse entails 3 main steps. The growing axon must 1) detect a postsynaptic target and defasciculate, 2) form temporary contact with the target cells, and 3) undergo matching between the neurotransmitters of the presynaptic cell with the receptors on the target postsynaptic cell. During axon outgrowth, like-minded axons, those with similar growth trajectories, form bundles called fascicles (Stoeckli and Landmesser, 1995). Therefore, when an axon recognizes a potential postsynaptic match, the axon must undergo defasciculation. Defasciculation is when the axon breaks away from the bundle of axons to encounter its target cell. After detachment, the axon will undergo a matchmaking process that relies on cell adhesion. Cell adhesion is a process of connecting to neighboring cells in the environment using cell surface receptors. Cell contacts between the pre and postsynaptic neuron hold the two cells together long enough to initiate synaptogenesis. Subsequent signaling between the two cells ensures that the presynaptic cell synthesizes, packages, and releases an appropriate neurotransmitter that the postsynaptic cell can respond to via expression of appropriate receptors in its PSD.

Neuronal survival and cell death

The developing brain undergoes significant expansion of neural stem cells, which are required for the development of neurons and glia. Interestingly, the developing brain initially produces too many neurons, meaning that the number of cells produced is more than what is needed for adult function. How does the brain compensate for this overproduction of neurons? As it turns out, the developing brain undergoes a process called programmed cell death, or apoptosis. Through apoptosis, excess neurons die, and the developing brain is refined.

Neuronal survival is regulated by multiple mechanisms, one of which is the size of the target tissue which a neuron will innervate. In 1909, Marian Lydia Shorey first demonstrated that there was a correlation between target tissue size and the number of surviving neurons (Shorey, 1909). Removal of the budding limb from chick embryos led to a decrease in the total number of neurons innervating the tissue whereas adding an extra limb tissue increased the total number of neurons. Subsequent experiments by Viktor Hamburger (1934) later revealed that neurons underwent cell death after the target tissue was removed (Hamburger, 1934). Figure 5.21 shows an example of this kind of experiment and the resulting loss of motor neurons in the lumbar spine of developing chicks.

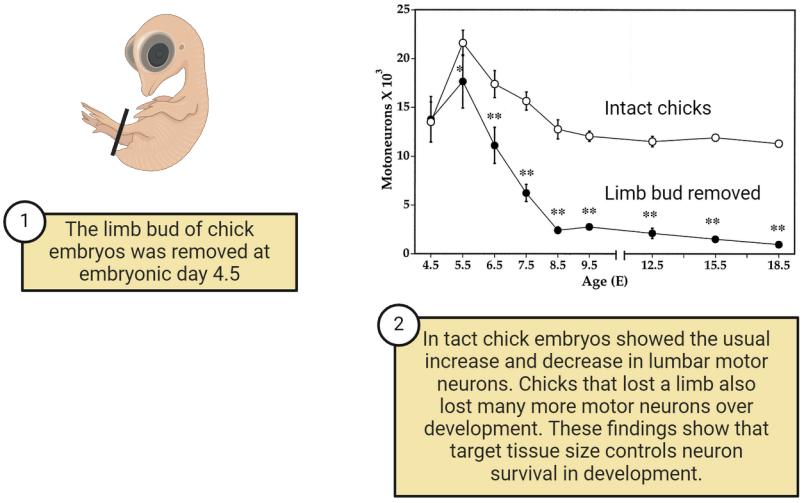


Figure 5.21 Tissue size and neuronal survival in development Data from: Peripheral Target Regulation of the Development and Survival of Spinal Sensory and Motor Neurons in the Chick Embryo. Jordi Calderó, David Prevette, Xun Mei, Robert A. Oakley, Ling Li, Carol Milligan, Lucien Houenou, Michael Burek, Ronald W. Oppenheim. Journal of Neuroscience 1 January 1998, 18 (1) 356-370; DOI: 10.1523/JNEUROSCI.18-01-00356.1998 (c) Journal of Neuroscience

These studies show that neuronal survival is not a random process and is influenced by the ability of tissues to form connections. How might the embryo decide which neurons die and which should survive? Neuronal survival is mediated by a class of molecules called neurotrophins that bind to a family of cell surface receptors called Trk receptors. Neurons that have inadequate signaling between neurotrophins and Trk receptors ultimately undergo apoptosis. Neurons have to compete with each other for access to these neurotrophins (Figure 5.22). Tissues producing less neurotrophins will support the survival of fewer neurons. This competition will also favor the survival of neurons that start to make better connections with sources of neurotrophin. In the chick limb bud removal experiments, the loss of the limb bud tissue removed a major source of neurotrophins, causing motor neurons headed towards that tissue to die off while others that found more neurotrophin-abundant targets in other tissues survived. This selection is one of the reasons we refer to this step as part of nervous system refinement. It is not random which neurons die and which survive, but rather driven by the connections the neurons are starting to form.

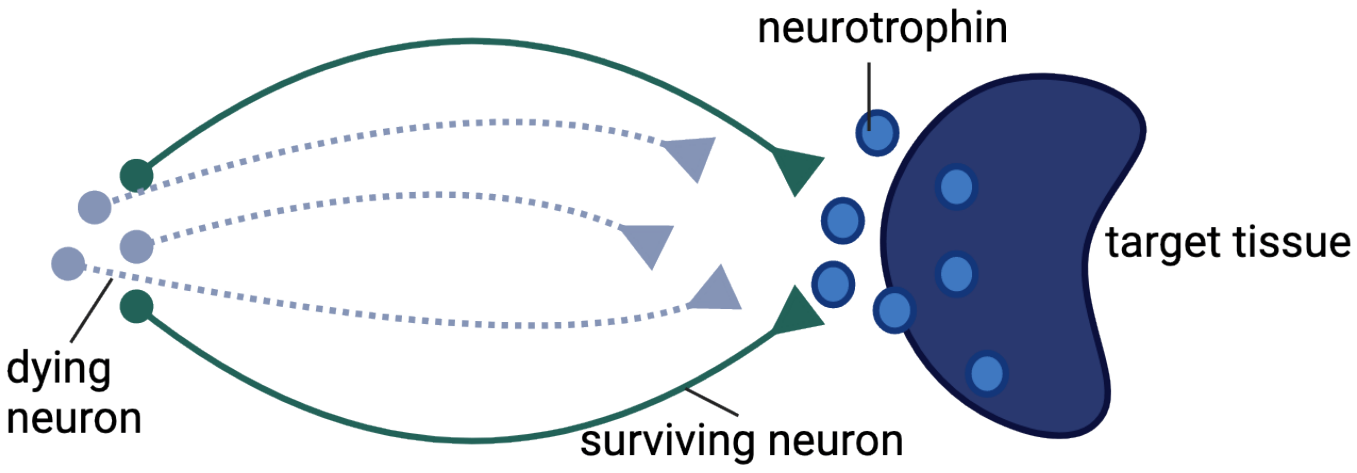


Figure 5.22 Neurotrophin and cell survival Neurons that make the strongest connections get best access to neurotrophins and survive. Others with poorer connections die.

People behind the science: Discovery of nerve growth factor (NGF)

In the 1940s, studies from the laboratory of Viktor Hamburger began exploring the use of tumor transplants in the chick embryo as a means of identifying and characterizing the factors that promote neuronal survival. As part of these studies, Rita Levi-Montalcini (Figure 5.23), a research associate in the Hamburger lab, transplanted tumor cells on one side of the body wall of the chick embryo. When comparing the transplanted side with the non-transplanted side of the embryo, Dr. Levi-Montalcini found that the presence of the tumor increased the number of nerve fibers innervating the tumor and the size of the adjacent dorsal root ganglia. Dorsal root ganglia are clusters of cell bodies found at the base of a spinal nerve. Thus, the tumor secreted a factor that promoted survival of the nerve fibers. Subsequent experiments ultimately used ganglion explants that were cultured at a distance from the tumor. She used various types of tumors and tissue to find that sarcoma tumors could promote neurite outgrowth.



Figure 5.23 Rita Levi Montalchini "Image credit: Photo by Diario de Madrid - Diario de Madrid - La científica y premio Nobel Rita Levi, vista por su sobrina nieta, CC BY 4.0, https://commons.wikimedia.org/w/inde...curid=99838777

The experiments performed ultimately paved the way for the discovery of nerve growth factor, a protein that we now know binds to TrkA receptor. Dr. Levi-Montalcini was awarded the Nobel Prize in 1986 alongside her colleague Stanley Cohen. Her story is particularly inspiring because in 1938 laws against those of Jewish descent prevented her from working in university laboratories. She spent her early career conducting experiments in her bedroom, which she later published, providing her the opportunity to work in the laboratory of Dr. Hamburger. She worked in the Hamburger lab for many years before establishing her own laboratory.

Synapse refinement

Early prenatal brain development combines coordinated control of various signals to produce an elaborate foundational unit capable of precise control of the human body. However, it is important to note that this unit represents only a foundation and is subject to refinement. We discussed refinement above in terms of which neurons survive. Synapse refinement is also a prominent feature of the developing nervous system. Synapse refinement is the process by which the early synapses are modified or eliminated because of specific signaling events.

The neuromuscular junction (NMJ) is a well-defined example of synapse refinement after birth (Bishop et al., 2004). We have learned a great deal about the capacity for refinement by studying the NMJ. The NMJ represents the synapse between the axon of a motor neuron and a muscle fiber. Muscle fibers are regulated by a single motor neuron in adults, but it has been established that in newborn rats, muscle fibers are innervated by a minimum of 2 different motor neurons. This type of innervation is called polyneuronal innervation. After birth, motor neuron innervations are reduced, but not because of neuronal cell death. Rather, the branches are eliminated or refined to target only a single muscle fiber (Figure 5.24) (Brown et al., 1976).

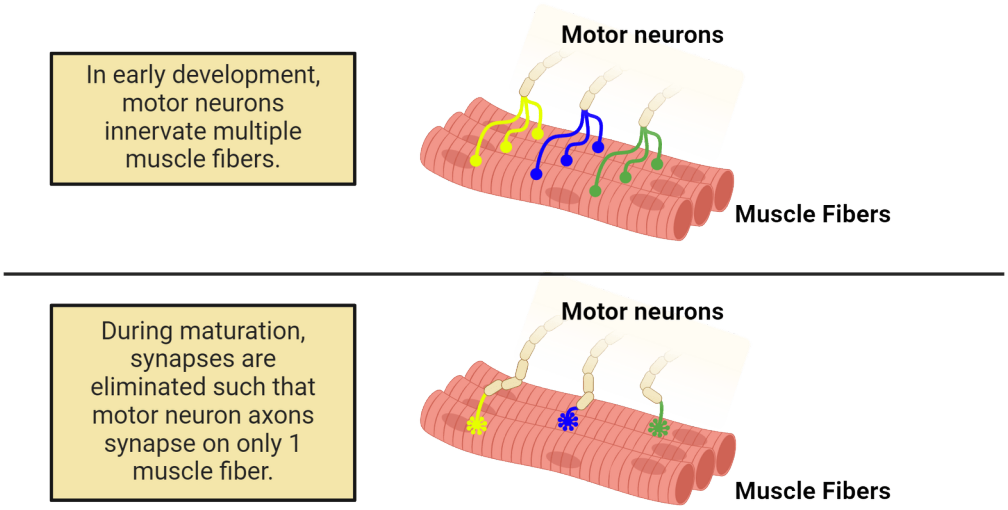


Figure 5.24 Muscle innervation development

The process of transitioning from polyneuronal innervation to mono-neuronal innervation is dependent on electrical activity and competition between two innervating neurons. It is critical for the precise recruitment of the motor unit during force and contraction generation (Lee, 2020). Should it be dysfunctional, more than one neuron would control the activity of a muscle cell. This phenomenon is not limited to the NMJ and has been demonstrated in the CNS. For example, Purkinje cells of the cerebellum that are innervated by climbing fiber inputs of the inferior olive are poly-innervated at birth, but by 2 weeks of age, the synapses are refined to a single innervation per Purkinje cell (Mariani and Changeux, 1981).

Synapse refinement in the CNS

We have discussed synapse refinement at the NMJ as a model for how synaptic connections are reorganized postnatally. Similar processes are occurring in the CNS, but what drives this process in the CNS? It turns out that, similar to how neurons must compete for neurotrophin survival cues, competition is also critical to synapse survival.In short, synapses that get used more get strengthened and those that are not used are lost. The most effective synapses are those that have a strong association between presynaptic neurotransmitter release and postsynaptic firing. Presynaptic neurons that fire in unison are especially effective at competing as a team to maintain strong connections that cause the postsynaptic neuron to fire. Figure 5.25 shows a representation of this principle. Early in development, a postsynaptic neuron may receive multiple inputs (# 1), some of which fire together (# 2) and others of which do not (# 3). The correlated inputs are much more likely to cause the postsynaptic cell to fire, because they are working together. As development proceeds, those correlated connections get stronger (# 5) and uncorrelated ones get weaker.

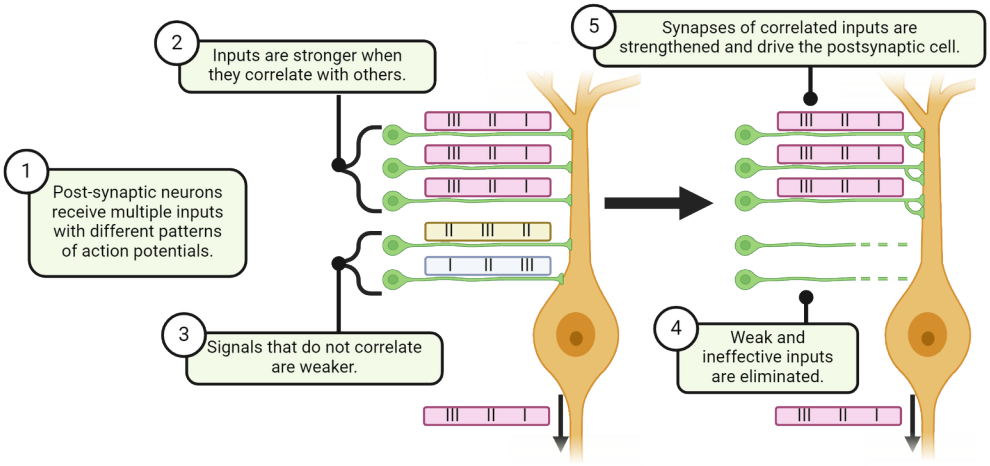


Figure 5.25 Synaptic correlation

What happens to those “weaker” synapses? Rival synapses that cannot fire synchronously with a neuron or a target cell and receive little input eventually lose synaptic connection and are eliminated through pruning (# 4 in Figure 5.25). Why do we need to eliminate synapses? Consider it like how tree roots compete for water in the rainforest. To survive and strengthen, the roots that branch out towards areas which fortify the livelihood of the tree will grow stronger, and those that fail in this sense weaken and die. Synapse numbers tend to peak during childhood in humans, with pruning then extending from late childhood through adolescence (Figure 5.26).

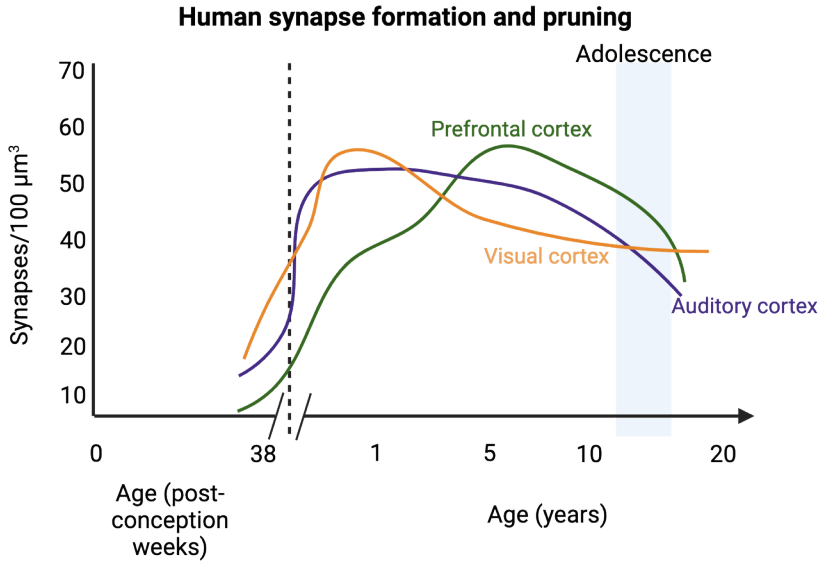


Figure 5.26 Synapse formation and pruning Synapses are over-produced and then pruned. Less active synapses are pruned while active synapses are preserved.

Pruning requires a balance; too little or too much can reduce the efficiency of brain function. Aberrant pruning can result in cognitive disorders due to faulty wiring in early life stages (Johnston, 2004; Sakai, 2020). For example, patients diagnosed with schizophrenia, a debilitating psychiatric illness with a myriad of hallucinogenic symptoms, show fewer synapses (over pruning) in brain scans relative to healthy individuals. The loss of synaptic connections is pronounced in the prefrontal cortex, a region where pruning peaks during adolescence, an active period of synapse elimination, coinciding with the onset of the disorder. In contrast, disorders such as autism have shown an excess in connections, suggesting failure to eliminate synapses. Findings like these suggest that CNS disorders can result from excessive or insufficient pruning during childhood and adolescence.

Myelination and plasticity

Myelin is a sheath that surrounds axons to promote the rate of electrical signaling. It is made of proteins and lipids and deposition of myelin on axons begins 1-2 months before birth. This makes myelination one of the later steps in nervous system development (Figure 5.27).

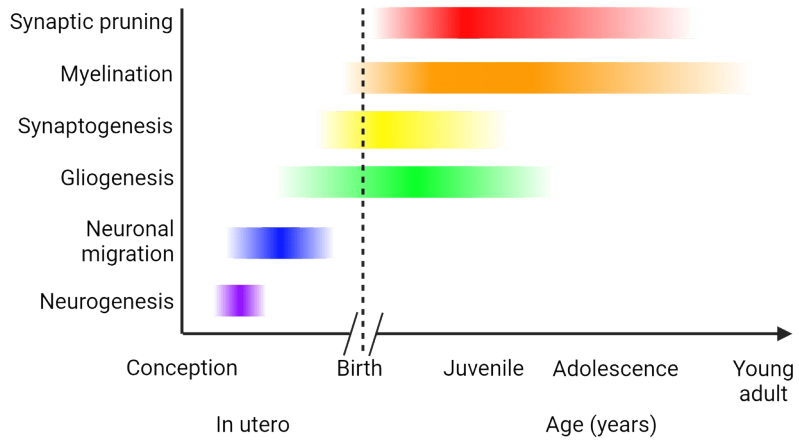


Figure 5.27 Primate neurodevelopment

Myelin is produced by oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system. Both of these are glial cells produced during gliogenesis. Myelination does not occur all at once, but rather in a progression. Generally, axons in the peripheral nervous system are myelinated first, followed by spinal cord axons and finally axons in the brain. Figure 5.28 shows MRI images of the brain during the first year of life, showing rapid accumulation of myelin (pseudocolored red) in the brain. This first year is when the peak of myelination occurs in humans. A parallel in the first month of life in rodents can also be seen in the bottom panel of Figure 5.28, where myelin has been stained dark in brains from rats aged postnatal day 7 to 35.

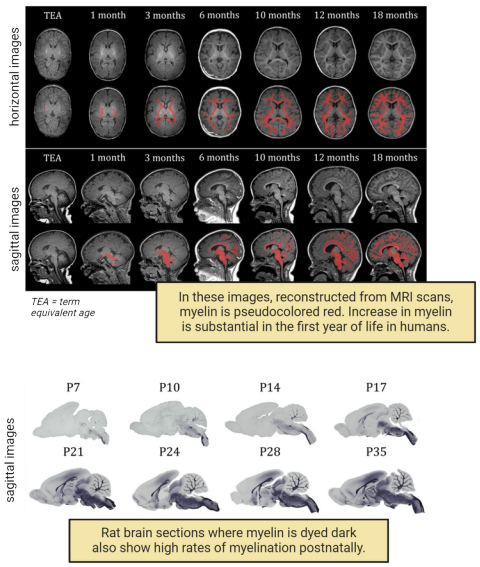


Figure 5.28 Myelination in the developing brain Images from: Erik van Tilborg , Caroline G M de Theije, Maurik van Hal, Nienke Wagenaar, Linda S de Vries, Manon J Benders, David H Rowitch, Cora H Nijboer. 2018. Origin and dynamics of oligodendrocytes in the developing brain: Implications for perinatal white matter injury. Glia, 66(2): 221-238, doi: 10.1002/glia.23256. CC BY 4.0

Though the first year is when most myelination happens in humans, myelination continues in the forebrain well into childhood and adolescence and accounts for some degree of plasticity during these time periods. Interestingly, extensive piano playing

is associated with increased myelination (Fields, 2005). In adolescence, increased risk-taking behavior can be the result of incomplete development of the forebrain, which includes reduced white matter (myelination) development (Beckman, 2004). But how does the environment affect myelin deposition? For the CNS, the answer probably lies in how sensitive developing oligodendrocytes are to environmental stimuli. Oligodendrocytes are glial cells of the CNS that produce and deposit myelin. For example, when rats were raised in an enriching environment, with toys and other rats to play with, the number of oligodendrocytes in their cortex actually increased (Szeligo and Leblond, 1977). Consistent with the increase in the number of oligodendrocytes, an enriching environment is also associated with an increase in the number of myelinated axons (Juraska, 1988). These studies were performed in rats, but there is also evidence for white matter developmental plasticity in humans. For example, neglect during childhood has been shown to decrease white matter by 17% in the corpus callosum (Teicher et al., 2004). We will discuss more about experience-dependent plasticity in neurodevelopment, but these examples help to highlight how development is not a simple series of steps but a constant interplay between developing systems and their environment.

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8.4: Neuroplasticity

Anytime you learn something new, the structure of your brain physically changes. The brain's ability to reorganize or "rewire" its connections in response to intrinsic or extrinsic experiences is called neuroplasticity.

Learning depends on the plasticity of the circuits in the brain and the ability to make lasting changes in synaptic transmission (Clark et al., 2018; "The Brain from Top to Bottom", n.d.). The brain can thus store information in networks of modified synapses, the arrangement of which constitutes the information. By activating these synaptic networks, the brain is able to retrieve the stored information.

Our understanding of the rules that govern the networking of neurons goes back to the groundbreaking work by Donald Hebb over 70 years ago. Hebb proposed that if two neurons are active at the same time, the synapses between them are strengthened—this is captured in the famous phrase "Neurons that fire together, wire together." Inspired by this hypothesis, researchers discovered long-term potentiation (LTP) in the early 1970s, providing the first supporting mechanism.

Long-term potentiation (LTP) is a persistent strengthening of a synaptic connection (Clark et al., 2018). LTP is based on the Hebbian principle: cells that fire together wire together. While not fully understood, one key mechanism of synaptic strengthening involves postsynaptic glutamate receptors called NMDA receptors (Figure 4). These receptors, normally blocked by magnesium ions, open when rapid successive presynaptic inputs depolarize the postsynaptic neuron. This allows calcium (Ca^{2+}) ions to enter the cell, triggering a signaling cascade that causes AMPA receptors to migrate from within the postsynaptic cell and insert into the postsynaptic membrane. These newly available AMPA receptors allow positive ions to enter the cell. So the next time glutamate is released from the presynaptic neuron, it will have a larger excitatory effect (EPSP) because glutamate binding to AMPA receptors will allow more positive ions into the cell. In sum, after being activated simultaneously, the increased presence of AMPA receptors strengthens the synapse and makes the postsynaptic neuron more likely to fire in response to presynaptic neurotransmitter release. Some drugs of abuse co-opt the LTP pathway, and this synaptic strengthening can lead to addiction.

In addition to LTP *strengthening* synaptic connections, neuroplasticity also requires *weakening* some connections. One well-studied process underlying the weakening of synaptic connections is **Long-Term Depression (LTD)**. Long-term depression is essentially the reverse of LTP. Similar to long-term potentiation, long-term depression also involves AMPA receptors. In this situation, calcium that enters through NMDA receptors initiates a different signaling cascade, which results in the removal of AMPA receptors from the postsynaptic membrane **(Figure 4)**. Fewer AMPA receptors in the membrane make the postsynaptic neuron less responsive to glutamate released from the presynaptic neuron. While it may seem counterintuitive, LTD may be just as important as LTP for learning and memory. The weakening and pruning of unused synapses allows for unimportant connections to be lost and makes the synapses that have undergone LTP much stronger by comparison.

Illustration showing calcium entry through postsynaptic NMDA receptors can initiate two different forms of synaptic plasticity: long-term potentiation (LTP) and long-term depression (LTD).

Figure 4. Calcium entry through postsynaptic NMDA receptors can initiate two different forms of synaptic plasticity: long-term potentiation (LTP) and long-term depression (LTD). LTP arises when a single synapse is repeatedly stimulated. This stimulation causes a calcium- and CaMKII-dependent cellular cascade, which results in the insertion of more AMPA receptors into the postsynaptic membrane. The next time glutamate is released from the presynaptic cell, it will bind to both NMDA and the newly inserted AMPA receptors, thus depolarizing the membrane more efficiently. LTD occurs when few glutamate molecules bind to NMDA receptors at a synapse (due to a low firing rate of the presynaptic neuron). The calcium that does flow through NMDA receptors initiates a different calcineurin and protein phosphatase 1-dependent cascade, which results in the endocytosis of AMPA receptors. This makes the postsynaptic neuron less responsive to glutamate released from the presynaptic neuron.

Even today, Hebb's rule, as it is often known, remains one of the primary factors for predicting which synapses will be strengthened in a network of neurons. More recent research has uncovered other characteristics of the networking of groups of neurons. For example, the LTP that leads to synaptic strengthening is very specific to neurons that are activated simultaneously, and only to such neurons.

Text Attributions

This section contains material adapted from:

Clark, M. A., Douglas, M., & Choi, J. (2018). 35.2 How Neurons Communicate. In Biology 2e. OpenStax. Access for free at

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Duboc, B. (2002). The Brain From Top To Bottom: Memory and the Brain: Plasticity in Neural Networks. Access for free at https://thebrain.mcgill.ca/ License: CC (Copyleft).

definition

A persistent strengthening of synaptic connections based on recent patterns of activity. A mechanism underlying “neurons that fire together, wire together.”

×Close definition

A long lasting decrease in the strength of synaptic connection based on recent patterns of activity.

×Close definition

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8.5: Sensitive and Critical Periods of Development

Life experiences impact brain development and subsequent behavior. Sensitive and critical periods are developmental periods that are especially pertinent in shaping neural and behavioral outcomes. **Sensitive periods** refer to developmental time windows during which experiences have an especially strong impact on brain organization. While similar experiences can still affect the brain outside of these sensitive periods, the consequences for brain reorganization will not be as strong. **Critical periods** refer to the limited time windows during which experiences, or lack thereof, have lasting effects on brain function and behavior (Knudsen, 2004). Disruptions during critical periods due to atypical experiences or adversity may lead to irreversible changes to brain structure. Sensitive and critical periods both involve heightened neuroplasticity. Sensitive periods offer broad windows for experience to shape neural circuitry, while critical periods are a subset that can result in irreversible changes to the brain (Knudsen, 2004).

Sensitive Periods of Development

The brain is especially malleable and adaptive to environmental inputs during childhood. Early life experiences profoundly impact how brain networks organize and develop. For example, language acquisition occurs during early childhood. Research shows a close relationship between the age of exposure to a language and proficiency in that language—peak proficiency is far more likely for those exposed to that language in early childhood (Newport et al., 2001). This is especially pertinent for learning a second language. A seminal study examined second language acquisition in native Chinese or Korean speakers who moved to the United States and learned English at different ages (Johnson & Newport, 1989). Results indicated that children who began learning the second language (English) before age 7 were able to reach proficiency akin to native English speakers; children arriving between age 7 and puberty were less proficient; and after puberty, an individual's second language proficiency is likely to remain low (Figure 5). These findings support a brain-maturation account, such that the ability to learn languages gradually declines and ultimately flattens as the brain matures. Importantly, this is not to say that learning a second language is impossible after brain maturation; but lower neuroplasticity after this sensitive period contributes to slower second language learning. The ability to learn second languages throughout life, albeit more slowly with age, demonstrates that second language acquisition reflects a sensitive rather than critical developmental period. In summary, children may be better equipped to learn a second language during this sensitive period due to the heightened neuroplasticity.

Figure 5: The relationship between age of learning a second language and total correct responses on an assessment of grammar for a second language [Image adapted from: Johnson, J. S., & Newport, E. L. (1989). Critical period effects in second language learning: The influence of maturational state on the acquisition of English as a second language. Cognitive Psychology, 21(1), 60-99.]

Critical Periods of Development

Early childhood also features critical periods when environmental input irreversibly shapes brain function and structure. Critical periods can be exemplified in sensory development and first language learning. Past experiments with animals have shown that sensory deprivation during infancy (e.g., an animal is deprived of sight or sound) can have lasting and irreversible consequences on their brain development (Hubel & Wiesel, 1970). For instance, animal studies show that depriving one eye of visual input during a critical period permanently impairs vision by reducing cortical neuron responses to that eye (Gordon & Stryker, 1996). In response to such visual deprivation, the brain reorganizes and prioritizes visual input from the non-deprived eye.

The brain's adaptive nature can also be seen in individuals who are born blind or deaf and as a result may rely on other sensory systems. For example, in humans, the occipital cortex is typically involved in visual perception. In individuals with early blindness (who become blind during the first few years of life), the occipital cortex shifts from processing visual input to other sensory-related information, such as tactile and auditory sensations (Voss, 2013). This adaptive process is known as **cross-modal plasticity**. Recent research indicates that cross-modal plasticity can persist after sensory function (e.g., vision) is restored, suggesting brain reorganization during critical periods may persist throughout adulthood (Mowad et al., 2020).

Critical periods of development occur for first language acquisition. In the early 1970s, the tragic story of Genie, an adolescent girl who for most of her childhood experienced severe isolation and neglect, caught the world by storm. When discovered, Genie was unable to communicate verbally with language. Researchers studied Genie's linguistic development over many years and concluded that, despite initial progress in speech and grammar, her language proficiency remained severely impaired (Curtiss, 1974). A more recent study found that children, who lacked language input during the first year of life due to isolation or hearing

difficulties, later had severe language-syntax impairments (Friedmann & Rusou, 2015). In sum, the absence of key environmental inputs, especially during critical periods in early childhood, may be particularly detrimental to subsequent brain development.

Adolescence as a sensitive period of development

Adolescence, the phase between childhood and adulthood (often considered ages 10-24), is marked by significant brain and behavioral changes. As a result of the ubiquitous social, cognitive, and emotional changes during adolescence, this stage of development is now widely considered a sensitive period of development.

How does brain development during adolescence shape behavior? Substantial neuroimaging research has shown that the frontal lobes, which include regions of the brain involved in executive function, such as the prefrontal cortex, are late-developing and undergo significant maturation that continues well into adolescence (Fuster et al., 2002; Casey et al., 1997; Giedd, 2004). Parallel to these brain development findings, prior work indicates that adolescence is marked by increased sensation-seeking and risk-taking behaviors (Spear, 2000). Neuroscientists have suggested that adolescent risk-taking may result from underdeveloped self-regulation, heightened sensation-seeking, and an immature executive function system unable to control reward-seeking impulses (Steinberg et al., 2004).

While the propensity for adolescents to take risks is often viewed negatively, it plays a role in adolescent development. Exploration and experimentation during this period are essential for forming personal identity, developing decision-making skills, and fostering independence. By navigating new experiences and challenges, teenagers learn to assess risks, understand consequences, and gradually develop the autonomy needed for adulthood. Some degree of risk-taking behavior in adolescence can contribute positively to cognitive, social, and emotional growth.

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definition

Time limited period of development where intrinsic and extrinsic experiences have an especially strong impact on brain development.

×Close definition

A special class of sensitive periods in which the effects of experience have lasting consequences on subsequent brain development. Absence of key experiences may lead to a disrupted course of brain development.

×Close definition

An adaptive process of the brain, such that loss of one sensory modality induces cortical reorganization that leads to enhanced sensory performance in other sensory modalities.

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8.6: Trade-off between Plasticity and Efficiency

Neuroplasticity varies across brain networks, with each developing on its own timeline (Dow-Edwards et al., 2019). The neural circuitry for basic sensory processes reaches peak plasticity in infancy and stabilizes by early childhood (thereby eliminating the need to relearn basic perception). In contrast, regions governing higher-order executive functions like self-regulation develop later and are highly plastic during adolescence. This developmental pattern illustrates the balance between neuroplasticity for development and stable and efficient processing in mature brains. A trade-off exists: high neuroplasticity and flexibility in a brain network corresponds to low stability and efficiency, and vice versa.

Neural efficiency refers to the brain's ability to meet task demands with minimal energy expenditure. It also encompasses the ease of communication between different brain regions. The efficiency of information flow across the brain accelerates in adolescence as axons gain myelin insulation, improving electrical transmission speed and reducing energy consumption (Spear, 2013).

Another factor underlying differences in neural efficiency is the formation of synapses. Early research revealed two general phases in synapse development: first a rapid overproduction of synapses, followed by programmed elimination of non-functional synapses to reach adult levels (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997; Shonkoff & Phillips, 2000). This synapse-formation pattern emerges at different timescales for different brain networks—synapse formation related to sensory processes peaks first, followed by language-related processes, and finally higher-order cognitive functions (Figure 6).

Relevant to neural efficiency, excess synapses during adolescence in frontal lobe regions may render information processing less efficient in those brain regions (Blakemore, 2012). In other words, during adolescence, the brain may require many synapses to carry out cognitive processes. However, as these neuronal connections and functional networks become refined during development, the brain may require fewer synapses to carry out the same cognitive processes. In this way, the brain could shift toward prioritizing the most efficient synapses, which may ultimately lead to more efficient cognitive processing.

Chart

Figure 6. The number of new synapses related to sensory function, language skills, and higher-order cognition across development. Synapse formation peaks early for sensory-related functioning (in the first months of life), followed by language skills (late in the first year), and finally higher-order cognitive functions (during early childhood). Green = auditory and visual cortex; Blue = Broca's area; Red = prefontal cortex. Image adapted from: The Developing Brain: https://www.ncbi.nlm.nih.gov/books/N...gure/mmm00006/

The tradeoff between neuroplasticity and stable efficient processing can be illustrated by recent research. In one study, a drug (valproate) reopened a critical period for a sensory task. When given this drug, adults could better learn to identify the names of musical pitches (termed "absolute pitch"), a skill that typically can only be acquired early in life (Gervain et al., 2013). This discovery holds exciting potential for increasing adult plasticity to learn new skills and rewire undesired established neural pathways (e.g., for treating addiction or psychiatric disorders). However, caution is needed when tampering with plasticity in the brain. For example, critical periods have evolved for a reason, and reopening critical periods might destabilize long-established neural circuits for efficiently processing things like how to see the world or understand language.

Finally, psychedelic drugs have shown potential to treat addiction and some psychological disorders. A recent study suggests that psychedelic drugs can reopen critical periods and increase neuroplasticity in mice (Nardou et al., 2023). Additionally, psychedelics may induce cellular and molecular adaptations related to neuroplasticity and these may support the clinical effects of psychedelics in humans (de Vos et al., 2021; Calder & Hassler, 2023). While more work on psychedelics and neuroplasticity is needed, the possibility of inducing neuroplasticity could lead to rich learning and brain restructuring, but it also underscores the importance of working with a trained professional when the brain is in a more malleable state in order to not destabilize desired neural circuits.

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definition

The process in which the brain spends fewer energy resources to carry out specific brain functions and subsequent behavior.

Typically indicative of a matured functional brain network.

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8.7: Characterizing Brain Development from Infancy through Young Adulthood

Adversity, especially early in childhood, has long-lasting consequences on brain development and behavioral outcomes. For instance, research has shown that experiencing poverty during early childhood is associated with lower academic performance, educational attainment, and adult earnings (Duncan et al., 1998, 2010). Relatedly, children whose families have higher family income tend to be associated with higher language, memory, social-emotional processing, and self-regulation skills (Noble et al., 2005, 2007). In terms of the brain, higher family income correlates with expanded surface area in brain regions governing language and executive function (Noble et al., 2015). While poverty clearly correlates with negative brain and behavioral outcomes, much remains unknown about how these effects on neural development emerge over time.

The Baby's First Years project is conducting the first randomized control trial of poverty reduction in early childhood, examining its impact on brain development (Noble et al., 2021). In the study, 1,000 diverse low-income mothers in four metropolitan areas in the United States were randomly assigned to receive a large ($333) or nominal ($20) monthly cash gift. By measuring infants' electrical brain activity one year into the poverty-reduction intervention, the researchers showed that infants whose mothers were randomized at the time of birth to receive a large monthly cash gift showed greater electrical brain activity in regions associated with better language, cognitive, and social-emotional outcomes in later childhood. Scientists are continuing to explore how adversity affects brain organization and its potential impact on behavior.

Given the extensive social, emotional, and cognitive changes during adolescence, the Adolescent Brain Cognitive Development (ABCD) study was launched as the largest long-term study of brain development and child health in the United States. Twenty-one U.S. research sites are tracking over 11,000 children's biological and behavioral development over a decade from age nine through early adulthood (Luciana et al., 2018). The ABCD study assesses brain structure and function, cognition, physical and mental health, social and emotional function, and culture and environment, offering insights into adolescent brain development and its behavioral impacts. The ABCD study's extensive data explores key topics, such as links between family environment, children's behavior problems, and brain structure (Gong et al., 2021), effects of cannabis use on psychopathology (Paul et al., 2021), and links between screen time, academic performance, and mental health (Paulich et al., 2021).

These ongoing large-scale studies promise to provide insights into how environmental factors shape brain development and behavior, potentially informing future interventions and policies to support healthy child and adolescent development.

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9: EVOLUTION, GENETICS, AND EXPERIENCE

9.1: Evolution of Minds and Behavior

9.2: Evolution - Mechanisms and Evidence

9.3: Human Evolution

9.4: Fundamental Genetics and Genetic Variation

9.5: DNA, Chromosomes, and Gene-Environment Correlations

9.6: The Nature-Nurture Question and Behavior Genetics

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9.1: Evolution of Minds and Behavior

Learning Objectives

1. Discuss the claim that nothing in psychology makes sense except in the light of evolution.
2. Explain the process of natural selection and provide an example.
3. Describe what is meant by adaptation and explain what is meant by a psychological adaptation.
4. Explain how evolution can be nonrandom, yet still without purpose.
5. Describe what William James meant by the term "instincts" applied to humans, according to Cosmides and Tooby.
6. Discuss how evolutionary psychologists conceptualize human nature.
7. Discuss evolution as the unifying principle for psychology, given that evolution is the unifying principle for all of biology.
8. Discuss how two types of selection (hint: one of these is kin selection) may explain the duality of human moral nature and feelings of moral conflict.
9. Describe the primary features of evolutionary psychology as an approach to the study of the mind and brain.

Overview

Why do humans and other animals move, why do they have particular mental capabilities and not others, and what laws or principles govern the organization of behavior and mental processes? In this section, the concept of evolution will be introduced and the insights it can provide regarding mind and behavior considered. When we recognize that mental activities and behavior in humans and other animals are the product of a biological organ, the brain, we can then apply principles of biological science to an understanding of psychology. This approach focuses attention on the biological functions served by mental abilities and behavior and how they contribute to adaptation to environmental change.

Evolution, Natural Selection, and Psychological Adaptation

> "In the distant future I see open fields for far more important researches. Psychology will be based on a new foundation, that of the necessary acquirement of each mental power and capacity by gradation." Charles Darwin, *On the Origin of Species* (1859/1996, p. 394)

> "Nothing in biology makes sense except in the light of evolution." Theodosius Dobzhansky (1973, p. 125)

When looking at nature, it is important to ask why things in nature have the properties that they do. This is especially important when thinking about organisms. Why do organisms possess the traits that they do? Why do birds have feathers? Why do we have emotions and why are our emotions so similar to the emotions found in a wide range of other animal species? Why do we have the capacity to think, why does our thinking take the forms that it does, and why are many of our thinking processes fundamentally similar to the thinking processes found in many other animal species? Why do we see color, while many other species don't? Why do we have the capacity to form mental images of the past and of imagined futures?

Psychology is the scientific study of mental processes and behavior. These processes are, of course, all functions of a biological organ, the brain. Like other organs, the brain and its operations have evolutionary origins. Understanding evolution can give us fresh insights about our psychology and the psychology of other species. The characteristics of organisms, including mental and behavioral traits, perform biological functions that contribute to survival and reproduction.

The minds and behavior of organisms have been shaped by evolutionary forces over millions of years, just like their anatomical and physiological features. To the trained eye, the mark of evolution is still evident in the psychology of present-day humans and other animals. And, as Darwin's principle of the continuity of species predicts, human and animal species, although diverse, show fundamental similarities in mind and behavior just as they do in their anatomy and physiology. Although there are many factors that affect evolution, the key driving force in evolution is the process of natural selection (Dawkins, 1976, 1982).

Natural Selection

Darwin was not the first to propose that species evolve, that they change over time. Darwin's brilliant insight was the discovery of the primary process which guides evolutionary change--natural selection, the survival and reproduction of the "fittest". "Fit" in this context does not mean the healthiest or the strongest, rather it is a reference to the ability to pass one's genes on to the next generation. Natural selection is similar to artificial selection, a process used by animal breeders to enhance characteristics which they deem desirable. But in natural selection it is the environment that does the selection.

Natural selection acts on natural variation within populations. One important feature of life is that individual organisms within any sexually-reproducing species vary from one another in countless ways. Natural selection works because some individuals are better suited to the environment than others; those individuals better fit to the environment have a competitive advantage and naturally survive and reproduce in greater numbers and therefore pass on their heritable (genetic) traits to succeeding generations with greater frequency. This is the essence of evolution.

Evolution by natural selection is inevitable given three factors:

- genetic variation in heritable traits in a population of reproducing organisms due to mutation and the mixing of genes during sexual reproduction;
- competition among members of the population for limited environmental resources;
- those individuals who are better suited, better "fit," to the demands and opportunities of the environment have a competitive advantage and therefore survive and reproduce in greater numbers. The result is the proliferation of the genes and traits which provide superior fitness to the environment. Fitness is measured not simply in terms of survival, but more importantly by reproductive success, the number of living offspring that are produced.

In other words, some individuals, by chance, happen to have genetic characteristics that make them better prepared to survive and reproduce, leading their genes to be selected and to persist in future generations. By this process of selection, traits which give a competitive edge in solving problems of survival and reproduction and in exploiting environmental opportunities tend to be preserved over generations, while traits less well-suited are removed. For example, those better at predator avoidance, better at obtaining energy from food, better at successful mating, or better at inventing ways to use the environment for adaptive advantage survive and reproduce more offspring. By this process of natural selection, over countless generations, species of living things evolve characteristics (including mental and behavioral traits) that are well-adapted to solve problems and to exploit opportunities in their particular environments. Gradually, over long periods of time, organisms acquire adaptive "design" by completely natural and unintentional processes. Note that as the environment changes, new traits may evolve. In a sense, evolutionary change tracks changes in the environment, creating an improving match between organism and environment over evolutionary time.

Nevertheless, relatively rapid changes in the environment may outpace the rate of evolutionary change. This means that adaptations that evolved for an earlier environment may not necessarily be well suited to the current environment. This is important in understanding some of the psychological traits of humans that were once advantageous, but which have now become non-adaptive. For example, some experts have argued that humans have an innate disposition to be territorial and to be suspicious and wary of strangers, of outsiders, and perhaps even hostile to those outside of their own group. Although this may have been an adaptive psychological trait in our ancient Pleistocene past when humans lived in small groups of hunter-gatherers, in today's world these tendencies may dispose us toward prejudice and even dangerous and wasteful wars.

Environmental Selection and Sexual Selection

The type of natural selection discussed above is environmental selection--selection by the environment of which genetic variants in a population will survive long enough to have a chance to reproduce. Note that the environment "selects" who will survive and who won't by virtue of the fact that the environment presents challenges to survival such as disease, predators, and insufficient supplies of resources such as energy (in the form of sunlight for plants, or food for animals), territory, and water. The "selection" by the environment occurs when individuals that just happen to be better suited to meet the challenges presented by the environment naturally have a competitive advantage and survive and reproduce in greater numbers than those unlucky individuals who are less well fit to the environment.

In addition to environmental selection, in sexually reproducing species, there is a second layer of selection, sexual selection--selection based on the "attractiveness" of potential sexual partners. All other factors being equal, individuals with genes that make them more attractive to the opposite sex tend to have more reproductive opportunities and, at least in times past, tend to have more offspring than those perceived to be less attractive. This effect is in part due to the fact that bodily features associated

with health and likely reproductive success tend to be perceived as sexually attractive (presumably as a result of brain evolution).

Evolution is neither random nor purposeful

It is important to note, as described above, that although evolution depends on random variations (in traits and genes) among individuals within a population, evolution is not a random process--natural selection acts on the random variation, constraining it toward successful adaptation. As Buss and Hawley (2010, p. ix) state, “Individual differences are indispensable for natural selection. Without heritable variants, natural selection—the only known process capable of creating and maintaining functional adaptations—could not occur.” In this way, evolution is not random as some who don't understand the process are apt to claim--natural selection gives it direction.

Furthermore, it is important to note that evolution is not purposeful, even though it is not random. Evolution happens automatically, without purpose, simply as a result of differential rates of reproduction in a population occurring as a consequence of the fact that individuals in a population with traits (and genes) that are more successful in a particular environment end up surviving and producing more offspring than their competitors--that's natural selection. This results in changes in gene frequencies in populations of organisms, and that is evolution. As biologist, Theodosius Dobzhansky (1964, p.449), stated: "My genes are different sequences of the same four "letters" of the "genetic alphabet" which also compose the genes of a fish or of a corn plant. Genes reproduce themselves generally with an astonishing accuracy; the sequences of the four 'letters,' the nucleotide bases, are usually identical in hundreds of billions of cells of the bodies of the parents and of their progeny. Occasionally, there occur, however, changes, "misprints," mutations. Self-reproduction plus mutation make possible natural selection. Natural selection makes possible evolution." We might even say that given these conditions, natural selection and evolution are not only possible, but inevitable.

Adaptations

The heritable features which organisms use to solve problems of survival and reproduction are called **adaptations**. These evolved adaptations can be anatomical, such as having wings or fur; physiological, such as digestive processes or having an immune system; and behavioral and mental (i.e. psychological). The evolved behavioral and mental traits of an organism are its **psychological adaptations** (e.g. having a fear response to danger; feelings of sexual attraction which draw you toward desirable potential mates; having a "sweet tooth" that drives you to seek out and ingest high caloric foods; having tender feelings toward your offspring motivating care-giving; understanding cause-effect relations and making causal inferences; having the mental ability to imagine future actions and to mentally anticipate the probable outcomes of those actions; and so on). According to psychologists who favor an evolutionary perspective, the mind can be seen as a large collection of evolved psychological adaptations (not all psychologists agree with this view; see Panksepp and Panksepp, 2000). These psychological adaptations are built by evolution into the structure of the brain and its physical operations. These psychological adaptations can be quite specific and concrete, such as the innate emotions related to pair-bonding and mating (e.g. "falling in love") or inborn human taste preferences for sweets and fats (see Cosmides and Tooby, 1997), or they can be quite general and abstract *instincts of thought* such as the innate disposition to understand the world in terms of cause-effect, to be sensitive to predictability between events, and to form categories and inferences based on similarities among things. These and other instincts of thought make up much of what we call intelligence (Koenigshofer, 2017).



Figure 9.1.2: Cultural overlays on a set of psychological adaptations. Human mating involves a number innate "instinctive" emotions and psychological needs which have evolved to foster reproduction of genes. Genetic evolution of these psychological adaptations has been accompanied by cultural evolution (selection and cultural transmission of learned behaviors via tradition, modeling, and other mechanisms of cultural transmission) of traditional practices associated with the genetically evolved psychological adaptations, the "reproductive instincts." (Image from Wikimedia Commons; File:Long Wedding Dress for Couple with Flowers.jpg; https://commons.wikimedia.org/wiki/F...th_Flowers.jpg; by epSos.de; licensed under the Creative Commons Attribution 2.0 Generic license).

In humans, psychological adaptations such as the emotions involved in mate selection, pair bonding, and mating are often associated with learned ritual behaviors that are culturally transmitted over generations and become part of the culture of particular human groups (see Figure 3.1.2). Such cultural practices are often based on commonly held "myths" that unify and help identify large groups of humans as culturally distinct from one another while facilitating cooperative effort among the members of such large groups toward common goals. According to one author (Harari, 2014), this ability to form cultural myths that imbue large numbers of strangers with a common identity, permitting them to work toward common goals, is unique to humans and accounts, in large part, for the unprecedented success of our species compared to all others. However, it is important to realize that this ability to form unifying myths depends upon features of the human brain that don't exist in sufficient degree in other animal species. Myths associated with cultural practices ranging from marriage or child birth to religious ritual or imperialism require the ability to form abstract concepts. Although research shows that non-human animal species can form concepts (Smith et al., 2010; Zentall et al., 2008), human concepts are highly abstract, apparently uniquely so, and ability for high levels of abstraction may depend upon the unique complexity of the human cerebral cortex (Koenigshofer, 2017). However, in addition, to ability to form abstract concepts, ability to learn and to transmit learned knowledge and behaviors from one generation to the next (cultural transmission) was essential to human uniqueness, and this ability to transmit learned information from generation to generation, by tradition and other non-genetic means, also depended upon particular features of the human brain. Thus, the great accomplishments of human civilization, which set us so clearly apart from other species, ultimately depended upon human brain evolution setting the stage, with human cultural evolution superimposed and critically dependent on brain evolution. One specific example may help drive the point home. Many experts believe that human tool making and tool use were extremely important in human evolution and early human adaptive success. The manufacture of stone tools by early humans was a complex and sophisticated cognitive and manual task beyond the capability of all other primates. Orban and colleagues (2006) identified a set of regions in the dorsal intraparietal sulcus (IPS) of the human cerebral cortex which they believe perform the complex visual analysis needed for the precision with which humans manipulate tools; these brain areas are not found in monkeys. Thus, a key product of human cultures was only possible because of unique features evolved in the human brain. This is only one example of a general claim: human cultural achievements that make our species so unique depend upon unique features of human brain evolution.

Individual Selection, Kin Selection, and Human Moral Conflict

From an evolutionary perspective, the minds and behavior of humans and animals, just like their anatomy and physiology, have

evolved in service of survival and reproduction, either through the reproduction of one's own genes, or indirectly through the survival and reproduction of close relatives and their genes (Dawkins, 1976). The former (individual selection) favors the self-interested side of human nature; the latter (kin selection) favors our altruistic side including prosocial behaviors such as caring, giving, sharing, and cooperation (some of the adaptive benefits of living in groups in social species such as humans, wolves, lions, chimpanzees, elephants, etc). In humans at least, self-interest and the interests of others often conflict, generating psychological tension experienced as moral dilemma. For humans, it is likely that there is an optimal balance between these two opposing behavioral dispositions; an extreme, maladaptive imbalance can lead to psychopathologies such as narcissistic and anti-social personality disorders. The duality of human moral nature may have roots in the duality of these two evolutionary processes, selection for survival and reproduction of one's own genes and kin selection, selection for survival and reproduction of the genes of close genetic relatives (Koenigshofer, 2010, 2016).

Evolutionary Psychology

Because psychological adaptations are located in the brain and its operations, these adaptations can be understood as information processing features of neural systems. On this view, the brain is a computational machine comprised of an enormous number of computational systems or modules, essentially mini-computers, made of circuits of neurons whose circuit configurations and operations have been shaped by evolutionary forces, developmental processes, and environmental experiences.

As noted in the opening quote above, Darwin recognized the relevance of evolution to psychology. Others have followed his lead. As Cosmides and Tooby (1997, p. 1) state, "In the final pages of the Origin of Species, after he had presented the theory of evolution by natural selection, Darwin made a bold prediction: 'In the distant future I see open fields for far more important researches. Psychology will be based on a new foundation, that of the necessary acquirement of each mental power and capacity by gradation.' Thirty years later, William James tried to do just that in his seminal book, Principles of Psychology, one of the founding works of experimental psychology (James, 1890). In Principles, James talked a lot of "instincts". This term was used to refer (roughly) to specialized neural circuits that are common to every member of a species and are the product of that species' evolutionary history. Taken together, such circuits constitute (in our own species) what one can think of as 'human nature.'"

Today, the influence of these early thinkers is expressed in evolutionary approaches to psychology. Cosmides and Tooby (1997, p. 1) state: "The goal of research in evolutionary psychology is to discover and understand the design of the human mind. Evolutionary psychology is an approach to psychology, in which knowledge and principles from evolutionary biology are put to use in research on the structure of the human mind. It is not an area of study, like vision, reasoning, or social behavior. It is a way of thinking about psychology that can be applied to any topic within it. In this view, the mind is a set of information-processing machines that were designed by natural selection to solve adaptive problems faced by our hunter-gatherer ancestors." Furthermore, they explain, "Psychology is that branch of biology that studies (1) brains, (2) how brains process information, and (3) how the brain's information-processing programs generate behavior. Once one realizes that psychology is a branch of biology, inferential tools developed in biology -- its theories, principles, and observations -- can be used to understand psychology" (Cosmides and Tooby, 1997 p. 3).

Evolutionary psychologists have applied this approach to emotion (Johnston, 1999; Ketelaar, 2015), intelligence and cognition (Bouchard, 2014; Koenigshofer, 2017; Pika, et al., 2020), personality (Buss and Hawley, 2010; Figueredo, et al., 2009), language (Corballis, 2010; Fitch, 2010; Pinker, 2003), social cognition (Fiddick, 2015; Vonk, et al., 2015), and a wide range of other psychological processes. Evolution by natural selection is gaining increasing acceptance among psychologists as "a strong candidate for central inclusion in a unifying meta-theory of psychology" (Marsh and Boag, 2013, p. 655; also see Goetz & Shackelford, 2006), just as evolution has become the unifying principle for all of biology. As you read about evolution and its mechanisms in the following sections, keep in mind that not only physical traits evolve, but mental and behavioral traits and capabilities (psychological traits) do as well.

In the remainder of this chapter we examine the processes of evolution in greater detail including primate and human evolution, and evolutionary theories in psychology. To emphasize the importance of evolution to an understanding of mind and behavior, recall the claim stated above: *Nothing in psychology "makes sense except in the light of evolution."*

Summary

Behavior and the information processing mechanisms that underlie behavior are biological processes (in their origin and functions), dependent upon a biological organ, the brain. Just as evolution by natural selection is the organizing principle for all of biology, it must be a key organizing principle for psychology as well. Natural selection is the primary driving force of evolution,

although other processes (examined in other sections of this chapter) are also involved. Natural selection occurs automatically without purpose or goal simply as a mechanistic consequence of two facts of life: 1) that individuals of any species vary from one another in their heritable traits, and 2) that some individuals by chance, because of the traits they possess (and the genes that underlie those traits), have a competitive advantage that favors their rates of survival and reproduction in a particular environment compared to those variants that are less fit. Therefore, the individuals (and the underlying genes) that are best fit to the environment end up leaving more surviving offspring and therefore have a disproportionately greater impact on the genes and traits of future generations. As a consequence, evolution occurs over generations, causing species to accumulate traits that are a better fit to survival and reproduction in the particular environments they occupy. For biological psychology, it is important to recognize that in addition to anatomy and physiology, psychological traits are also shaped into adaptive form by these same processes. Thus, to understand human and animal behavior, an evolutionary approach provides a biological context within which we can examine origins, functions, and organizing principles of minds and behavior. This approach does not negate or deny the influence of learning and culture but views these processes as biological phenomenon with evolutionary and neurophysiological roots in the brain.

References

Bouchard, T. J. (2014). Genes, evolution and intelligence. *Behavior genetics*, *44*(6), 549-577.

Buss, D. M., & Hawley, P. H. (Eds.). (2010). *The evolution of personality and individual differences*. Oxford University Press.

Corballis, M. C. (2010). Mirror neurons and the evolution of language. *Brain and language*, *112*(1), 25-35.

Cosmides, L., & Tooby, J. (1997, January 13). Evolutionary psychology: A Primer. Retrieved February 20, 2021, from https://www.cep.ucsb.edu/primer.html (Links to an external site.)

Darwin, C. (1859/1996). The origin of species. Oxford, UK: Oxford University Press

Dawkins, R. (1976). The selfish gene. Oxford University Press.Dawkins, R. (1976). The Selfish Gene. Oxford: Oxford University Press.

Dawkins, R. (1982). The Extended Phenotype: The Gene as the Unit of Natural Selection. San Francisco: Freeman.

Dobzhansky, T. (1964). Biology, Molecular and Organismic. *American Zoologist* 4 (4), 443-452.

Dobzhansky, T. (1973). Nothing in biology makes sense except in the light of evolution. The American Biology Teacher, 35,

125-129.

Fiddick, L. (2015). Social by Design: How Social Psychology Can Be More Cognitive Without Being Less Social. In *Evolutionary Perspectives on Social Psychology* (pp. 15-26). Springer, Cham.

Figueredo, A. J., Gladden, P., Vasquez, G., Wolf, P. S. A., & Jones, D. N. (2009). 16 Evolutionary theories of personality. *The Cambridge handbook of personality psychology*, 265.

Fitch, W. T. (2010). *The evolution of language*. Cambridge University Press.

Goetz, A. T., & Shackelford, T. K. (2006). Modern application of evolutionary theory to psychology: Key concepts and clarifications. *The American journal of psychology*, 567-584.

Grant, B. R., & Grant, P. R. (1989). Natural selection in a population of Darwin's finches. *The American Naturalist*, *133* (3), 377-393.

Grant, R. B., & Grant, P. R. (2003). What Darwin's finches can teach us about the evolutionary origin and regulation of biodiversity. *BioScience*, *53* (10), 965-975.

Harari, Y. N. (2014). *Sapiens: A brief history of humankind*. Random House.

Johnston, V. S. (1999). *Why we feel: The science of human emotions*. Perseus Publishing.

Kennair, L. E. O. (2002). Evolutionary psychology: An emerging integrative perspective within the science and practice of psychology. *Human Nature Review*, *2*, 17-61.

Ketelaar, T. (2015). Evolutionary psychology and emotion: A brief history. In *Evolutionary perspectives on social psychology* (pp. 51-67). Springer, Cham.

Koenigshofer, K. (2010). *Mind Design: The Adaptive Organization of Human Nature, Minds, and Behavior*. Pearson Educational Solutions, Boston.

Koenigshofer, K. (2016). *Mind Design: The Adaptive Organization of Human Nature, Minds, and Behavior*. Revised Edition. Amazon e-book.

Koenigshofer, K. A. (2017). General Intelligence: Adaptation to Evolutionarily Familiar Abstract Relational Invariants, Not to Environmental or Evolutionary Novelty. *The Journal of Mind and Behavior*, *38* (2), 119-153.

Marks, J. Chapter 2, Evolution, in *Explorations: An Open Invitation To Biological Anthropology*; https://pressbooks-dev.oer.hawaii.ed...r/__unknown__/; licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, except where otherwise noted.

Marsh, T., & Boag, S. (2013). Evolutionary and differential psychology: conceptual conflicts and the path to integration. *Frontiers in psychology*, *4*, 655.

Orban, G. A., Claeys, K., Nelissen, K., Smans, R., Sunaert, S., Todd, J. T., Wardak, C., Durand, J. & Vanduffel, W. (2006). Mapping the parietal cortex of human and non-human primates. *Neuropsychologia* 44 (13):2647 –67. [GAO, arKV, GV]

Panksepp, J., & Panksepp, J. B. (2000). The seven sins of evolutionary psychology. *Evolution and cognition*, *6*(2), 108-131.

Pika, S., Sima, M. J., Blum, C. R., Herrmann, E., & Mundry, R. (2020). Ravens parallel great apes in physical and social cognitive skills. *Scientific reports*, *10*(1), 1-19.

Pinker, S. (2003). *The language instinct: How the mind creates language*. Penguin UK.

Smith, J. D., Beran, M. J., Crossley, M. J., Boomer, J., & Ashby, F. G. (2010). Implicit and explicit category learning by macaques (Macaca mulatta) and humans (Homo sapiens). *Journal of Experimental Psychology: Animal Behavior Processes*, *36* (1), 54.

Vonk, J., McGuire, M., & Johnson-Ulrich, Z. (2015). The Evolution of Social Cognition. In *Evolutionary Perspectives on Social Psychology* (pp. 81-94). Springer, Cham.

Zentall, T. R., Wasserman, E. A., Lazareva, O. F., Thompson, R. K., & Rattermann, M. J. (2008). Concept learning in animals. *Comparative Cognition & Behavior Reviews*. *3,* 13–45. https://doi.org/10.3819/ccbr.2008.3000

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9.2: Evolution - Mechanisms and Evidence

Learning Objectives

1. Describe how the present-day theory of evolution was developed.
2. Explain natural selection and its role in evolution.
3. Explain convergent and divergent evolution.
4. Describe homologous and vestigial structures.
5. Discuss misconceptions about the theory of evolution.
6. Explain the categories of evidence for evolution.
7. Describe species and speciation.
8. Explain kin selection, inclusive fitness, and the evolution of altruistic behaviors such as helping, cooperation, and giving.

Overview

The theory of evolution is the unifying theory of biology, meaning it is the framework within which biologists ask questions about the living world. Its power is that it provides direction for predictions about living things that are borne out in experiment after experiment. Recall the claim by geneticist, Theodosius Dobzhansky, that “nothing makes sense in biology except in the light of evolution." He meant that the tenet that all life has evolved and diversified from a common ancestor is the foundation from which we approach all questions in biology. It is important to keep this claim in mind when we think about brain evolution and psychology. The evolutionary links among animal species help explain the similarities in their brains and behavior.

Summary of Key Points:

1. Evolution: All species of living organisms, from bacteria to baboons to blueberries, evolved at some point from a different species. Although it may seem that living things today stay much the same, that is not the case—evolution is an ongoing process.
2. Understanding Evolution: Evolution by **natural selection** describes a mechanism for how species change over time. That species change had been suggested and debated well before Darwin began to explore this idea. The view that species were static and unchanging was grounded in the writings of Plato, yet there were also ancient Greeks who expressed evolutionary ideas. Darwin was the first to describe the primary mechanism of evolutionary change--natural selection.
3. When Darwin proposed his theory of evolution, the mechanisms of inheritance were unknown. Now, we know a great deal about those mechanisms. Here are some key definitions. **Chromosomes** are long strings of genes made of the molecule, deoxyribonucleic acid (DNA). A **gene** is a segment of a chromosome coding for synthesis of a specific protein. **Alleles** are alternative forms of a gene at the same location on the chromosome (for example a blue gene for eye color and a brown gene for eye color are alleles). **Genotype** is the genetic makeup of an individual. **Phenotype** is the actual anatomical, physiological, and behavioral/psychological characteristics of an individual.



Figure 9.2.1: All organisms are products of evolution adapted to their environment. (a) Saguaro (Carnegiea gigantea) can soak up 750 liters of water in a single rain storm, enabling these cacti to survive the dry conditions of the Sonora desert in Mexico and the Southwestern United States. (b) The Andean semiaquatic lizard (Potamites montanicola) discovered in Peru in 2010 lives between 1,570 to 2,100 meters in elevation, and, unlike most lizards, is nocturnal and swims. Scientists still do not know how these cold-blood animals are able to move in the cold (10 to 15°C) temperatures of the Andean night. (credit a: modification of work by Gentry George, U.S. Fish and Wildlife Service; credit b: modification of work by Germán Chávez and Diego Vásquez, ZooKeys)

Understanding Evolution

Darwin's evolution by natural selection describes a mechanism for how species change over time. Darwin described evolution as "descent with modification."

In the eighteenth century, James Hutton, a Scottish naturalist, proposed that geological change occurred gradually by the accumulation of small changes from processes operating like they are today over long periods of time. This contrasted with the predominant view that the geology of the planet was a consequence of catastrophic events occurring during a relatively brief past. Hutton's view was popularized in the nineteenth century by the geologist Charles Lyell who became a friend to Darwin. Lyell's ideas were influential on Darwin's thinking: Lyell's notion of the greater age of Earth gave more time for gradual change in species, and the process of change provided an analogy for gradual change in species. In the early nineteenth century, Jean-Baptiste Lamarck published a book that detailed a mechanism for evolutionary change. This mechanism is now referred to as an inheritance of acquired characteristics by which modifications in an individual that are caused by its environment, or the use or disuse of a structure during its lifetime, could be inherited by its offspring and thus bring about change in a species. A simple example or two will illustrate why this is wrong--the idea suggests that if you go to the gym and get buff, then you will have buff kids, or if you lose a finger in an accident, that you will have children missing a finger, and that such changes will eventually become characteristics of the species. Today we know that if the change in characteristics does not change genes, the change cannot be passed on to future generations. While this mechanism for evolutionary change was discredited, Lamarck's ideas were an important influence on evolutionary thought.

Charles Darwin and Natural Selection

In the mid-nineteenth century, the actual mechanism for evolution was independently conceived of and described by two naturalists: Charles Darwin and Alfred Russel Wallace. Importantly, each naturalist spent time exploring the natural world on expeditions to the tropics. From 1831 to 1836, Darwin traveled around the world on *H.M.S. Beagle*, including stops in South America, Australia, and the southern tip of Africa. Wallace traveled to Brazil to collect insects in the Amazon rainforest from 1848 to 1852 and to the Malay Archipelago from 1854 to 1862. Darwin's journey, like Wallace's later journeys to the Malay Archipelago, included stops at several island chains, the last being the Galápagos Islands, west of Ecuador. On these islands, Darwin observed species of organisms on different islands that were clearly similar, yet had distinct differences. For example, the ground finches inhabiting the Galápagos Islands comprised several species with a unique beak shape. The species on the islands had a graded series of beak sizes and shapes with very small differences between the most similar. He observed that these finches closely resembled another finch species on the mainland of South America. Darwin imagined that the island species might be species modified from one of the original mainland species. Upon further study, he realized that the varied beaks of each finch helped the birds acquire a specific type of food. For example, seed-eating finches had stronger, thicker beaks for breaking seeds, and insect-eating finches had spear-like beaks for stabbing their prey.

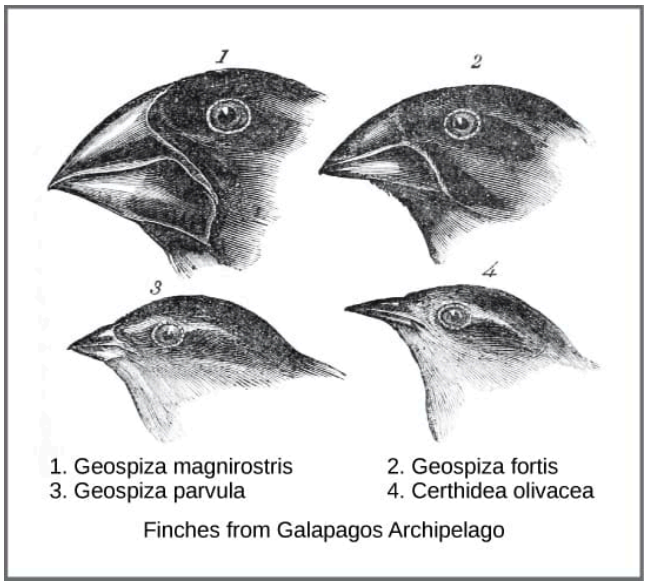


Figure 9.2.2: Darwin observed that beak shape varies among finch species. He postulated that the beak of an ancestral species had adapted over time to equip the finches to acquire different food sources.

Wallace and Darwin both observed similar patterns in other organisms and they independently developed the same explanation for how and why such changes could take place. Darwin called this mechanism natural selection. Natural selection, also known as "survival of the fittest," is more accurately described as survival and *reproduction* of the fittest. Survival alone is insufficient. Evolution involves differential rates of reproduction. Survival alone without reproduction has no effect on the genetic evolution of a species. Natural selection results in the more prolific reproduction of individuals with traits that contribute to survival and reproduction in a changing environment; this increased rate of reproduction in individuals with traits better fit to the environment compared to individuals with traits less fit leads to evolutionary change.

For example, a population of giant tortoises found in the Galapagos Archipelago was observed by Darwin to have longer necks than those that lived on other islands with dry lowlands. These tortoises were "selected" because they could reach more leaves and access more food than those with short necks. In times of drought when fewer leaves would be available, those that could reach more leaves had a better chance to eat and survive than those that couldn't reach the food source. Consequently, long-necked tortoises would be more likely to be reproductively successful and pass the long-necked trait to their offspring. Over time, only long-necked tortoises would be present in the population, as short-necked animals failed to survive and reproduce.

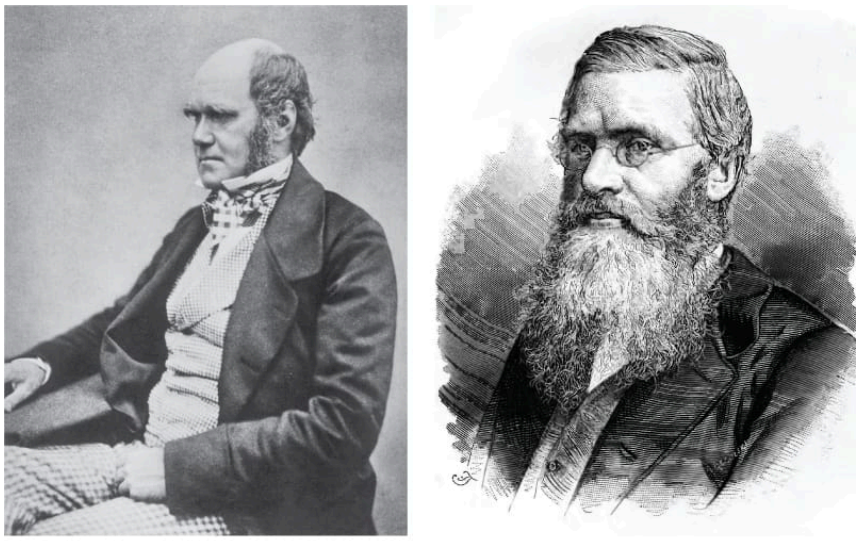
Natural selection, Darwin argued, was an **inevitable outcome of three principles** that operated in nature.

First, **most characteristics of organisms are inherited**, or passed from parent to offspring. Although no one, including Darwin and Wallace, knew how this happened at the time, it was a common understanding.

Second, more offspring are produced than are able to survive, so resources for survival and reproduction are limited. The capacity for reproduction in all organisms outstrips the availability of resources to support their numbers. Thus, there is **competition for** those **resources in each generation**. Both Darwin and Wallace's understanding of this principle came from reading an essay by the economist Thomas Malthus who discussed this principle in relation to human populations.

Third, **offspring vary** among each other in regard to their characteristics **and those variations are inherited**. Darwin and Wallace reasoned that **offspring with inherited characteristics which allow them to best compete for limited resources will survive and have more offspring than those individuals with variations that are less able to compete**. Because characteristics are inherited, these traits will be better represented in the next generation. This will lead to change in populations over generations in a process that Darwin called **descent with modification**. Ultimately, natural selection leads to greater adaptation of the population to its local environment; it is the only mechanism known for adaptive evolution.

Papers by Darwin and Wallace presenting the idea of natural selection were read together in 1858 before the Linnean Society in London. The following year Darwin's book, *On the Origin of Species*, was published. His book outlined in considerable detail his arguments for evolution by natural selection.



(a) (b)

Figure 9.2.3: Both (a) Charles Darwin and (b) Alfred Wallace wrote scientific papers on natural selection that were presented together before the Linnean Society in 1858.

Demonstrations of evolution by natural selection are time consuming and difficult to obtain. As briefly discussed in earlier in this section, one of the best examples has been demonstrated in the very birds that helped to inspire Darwin's theory: the Galápagos finches. Peter and Rosemary Grant and their colleagues have studied Galápagos finch populations every year since 1976 and have provided important demonstrations of natural selection. The Grants found changes from one generation to the next in the distribution of beak shapes in the medium ground finch on the Galápagos island of Daphne Major. The birds have inherited variation in the bill shape with some birds having wide deep bills and others having thinner bills. During a period in which rainfall was higher than normal because of an El Niño (an unusual warming of the Pacific Ocean near the West coast of the Americas), the large hard seeds that large-billed birds ate were reduced in number; however, there was an abundance of the small soft seeds which the small-billed birds ate. Therefore, survival and reproduction were much better in the following years for the small-billed birds. In the years following this El Niño, the Grants measured beak sizes in the population and found that the average bill size was smaller. Since bill size is an inherited trait, parents with smaller bills had more offspring and the size of bills had evolved to be smaller. As conditions changed and a long period of drought ensued, larger seeds became more available. The trend toward smaller average bill size ceased and selection for larger beaks and body size resulted in a lasting increase in beak size.

Another well known example of observable evolution is the peppered moth. Because of its importance as another example of natural selection in action, we review the details here. Prior to industrialization in England, the peppered moth had light colored wings that closely matched the color of the bark of the trees. This inherited trait provided camouflage for the moths helping to protect them from predator birds. Although most of the moths had light colored wings, a few each generation had darker wings, but without sufficient camouflage these darker colored moths had been easy prey and survived and reproduced with low frequency. As industrialization came to England, soot from factories began to slowly turn the bark of trees darker and darker. As this occurred, darker wings were now an advantage, helping to hide the darker moths from predators when they landed on trees, increasing their survival and reproductive rates over the lighter colored moths. As natural selection continued over decades, the light colored moths, once the predominant form, were increasingly replaced over generations by darker winged variants, until today, after no more than a hundred years of evolution, the peppered moth has dark wings (although with cleaner air, numbers of the lighter variant are increasing as the tree bark continues to lighten). This transformation of the species as a consequence of natural selection, as the environment changed, is a good example of evolution rapid enough that it can be observed.

Process and Pattern of Evolution

Natural selection can only take place if there is variation, or differences, among individuals in a population. Importantly, these differences must have some genetic basis; otherwise, the selection will not lead to change in the next generation. This is critical because variation among individuals can be caused by non-genetic reasons, such as an individual being taller because of better nutrition rather than different genes.

Genetic diversity in a population comes from two main mechanisms: mutation and sexual reproduction. **Mutation**, a change in DNA, is the ultimate source of new **alleles** (alternative forms of a gene located at the same place on a chromosome), or new

genetic variation in any population. The genetic changes caused by mutation can have one of three outcomes on the phenotype. A mutation affects the phenotype of the organism in a way that gives it reduced fitness—lower likelihood of survival or fewer offspring. A mutation may produce a phenotype with a beneficial effect on fitness. And, many mutations will also have no effect on the fitness of the phenotype; these are called neutral mutations. Mutations may also have a whole range of effect sizes on the fitness of the organism that expresses them in their phenotype, from a small effect to a great effect. Sexual reproduction also leads to genetic diversity: when two parents reproduce, unique combinations of alleles assemble to produce the unique genotypes and thus phenotypes in each of the offspring.

A heritable trait that helps the survival and reproduction of an organism in its present environment is called an **adaptation**. Scientists describe groups of organisms becoming adapted to their environment when a change in the range of genetic variation occurs over time that increases or maintains the "fit" of the population to its environment. The webbed feet of platypuses are an adaptation for swimming. The snow leopards' thick fur is an adaptation for living in the cold. The cheetahs' fast speed is an adaptation for catching prey.

Whether or not a trait is favorable depends on the environmental conditions at the time. The same traits are not always selected because environmental conditions can change. For example, consider a species of plant that grew in a moist climate and did not need to conserve water. Large leaves were selected because they allowed the plant to obtain more energy from the sun. Large leaves require more water to maintain than small leaves, and the moist environment provided favorable conditions to support large leaves. After thousands of years, the climate changed, and the area no longer had excess water. The direction of natural selection shifted so that plants with small leaves were selected because those populations were able to conserve water to survive the new environmental conditions.

Formation of New Species: Although all life on earth shares various genetic similarities, only certain organisms combine genetic information by sexual reproduction and have offspring that can then successfully reproduce. Scientists call such organisms members of the same biological species. For example, a mule is a cross between a donkey and a horse. However, since the mule cannot reproduce (donkey and horse do not have the same number of chromosomes), donkeys and horses are considered separate species. However, a cross between a Dachshund and a Norwegian Elkhound can result in offspring that can reproduce with another domestic dog, and thus all domestic dogs are considered the same species (all have the same number of chromosomes). **Speciation** (the formation of new species) occurs over a span of evolutionary time, so when a new species arises, there is a transition period during which the closely related species continue to interact.

The evolution of species has resulted in enormous variation in form and function. Sometimes, evolution gives rise to groups of organisms that become tremendously different from each other. When two species evolve in diverse directions from a common point, it is called **divergent evolution**. Such divergent evolution can be seen in the forms of the reproductive organs of flowering plants which share the same basic anatomies; however, they can look very different as a result of selection in different physical environments and adaptation to different kinds of pollinators. As you will see in the section on human evolution, human and apes lines diverged from one another millions of years ago, yet evidence of a common ancestry comes from many sources, including similarities in DNA.



Figure 9.2.4: Flowering plants evolved from a common ancestor. Notice that the (a) dense blazing star (Liatrus spicata) and the (b) purple coneflower (Echinacea purpurea) vary in appearance, yet both share a similar basic morphology. (credit a: modification of work by Drew Avery; credit b: modification of work by Cory Zanker)

In other cases, similar phenotypes evolve independently in distantly related species. For example, flight has evolved in both bats and insects, and they both have structures we refer to as wings, which are adaptations to flight. However, the wings of bats and insects have evolved from very different original structures. This phenomenon is called **convergent evolution**, where similar traits evolve independently in species that do not share a recent common ancestry. The two species came to the same function, flying, but did so separately from each other.

Natural Selection and Adaptive Evolution

Natural selection only acts on the population's heritable traits: selecting for beneficial alleles and thus increasing their frequency in the population, while selecting against deleterious alleles and thereby decreasing their frequency—a process known as **adaptive evolution**. Natural selection does not act on individual alleles, however, but on entire organisms. An individual may carry a very beneficial genotype with a resulting phenotype that, for example, increases the ability to reproduce (fecundity), but if that same individual also carries an allele that results in a fatal childhood disease, that fecundity phenotype will not be passed on to the next generation because the individual will not live to reach reproductive age. Natural selection acts at the level of the individual; it selects for individuals with greater contributions to the gene pool of the next generation, known as an organism's evolutionary (Darwinian) fitness.

Fitness is often quantifiable and is measured by scientists in the field. However, it is not the absolute fitness of an individual that counts, but rather how it compares to the other organisms in the population. This concept, called relative fitness, allows researchers to determine which individuals are contributing additional offspring to the next generation, and thus, how the population might evolve.

Evidence of Evolution

The evidence for evolution is compelling and extensive. Looking at every level of organization in living systems, biologists see the signature of past and present evolution. Darwin dedicated a large portion of his book, On the Origin of Species, to identifying patterns in nature that were consistent with evolution, and since Darwin, our understanding has become clearer and broader.

Fossils

Fossils provide solid evidence that organisms from the past are not the same as those found today, and fossils show a progression of evolution. Scientists determine the age of fossils and categorize them from all over the world to determine when the organisms lived relative to each other. The resulting fossil record tells the story of the past and shows the evolution of form over millions of years. For example, scientists have recovered highly detailed records showing the evolution of humans and horses.



(a) (b)

Figure 9.2.5: In this (a) display, fossil hominids are arranged from oldest (bottom) to newest (top). As hominids evolved, the shape of the skull changed. An artist's rendition of (b) extinct species of the genus Equus reveals that these ancient species resembled the modern horse (Equus ferus) but varied in size.

Anatomy and Embryology

Another type of evidence for evolution is the presence of structures in organisms that share the same basic form. For example, the bones in the appendages of a human, dog, bird, and whale all share the same overall construction (Figure 18.1.618.1.6) resulting from their origin in the appendages of a common ancestor. Over time, evolution led to changes in the shapes and sizes of these bones in different species, but they have maintained the same overall layout. Scientists call these synonymous parts **homologous structures.**

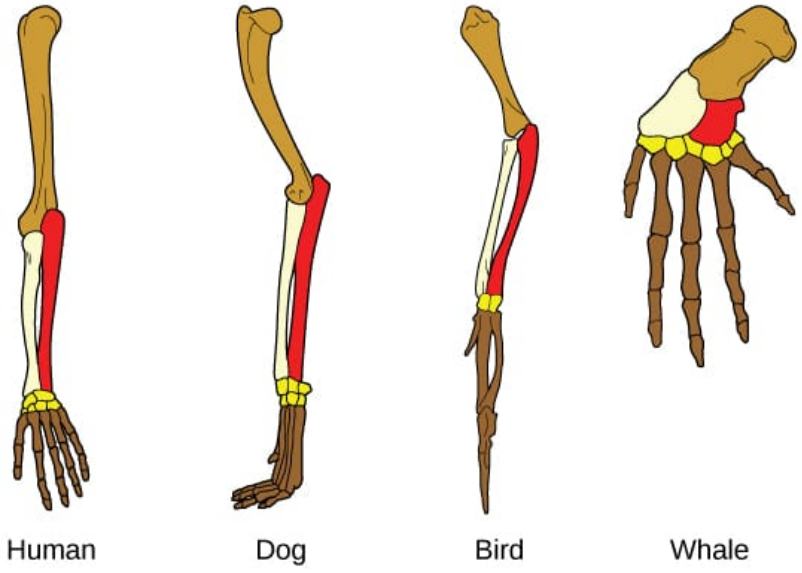


Figure 9.2.6: The similar construction of these appendages indicates that these organisms share a common ancestor.

Some structures exist in organisms that have no apparent function at all, and appear to be residual parts from a past common ancestor. These unused structures without function are called **vestigial structures**. Examples of vestigial structures are wings on flightless birds, leaves on some cacti, and hind leg bones in whales.

Link to Learning

Visit this interactive site to guess which bones structures are homologous and which are analogous, and see examples of evolutionary adaptations to illustrate these concepts.

Another evidence of evolution is the **convergence of form** in organisms that share similar environments. For example, species of unrelated animals, such as the arctic fox and ptarmigan, living in the arctic region have been selected for seasonal white phenotypes during winter to blend with the snow and ice. These similarities occur not because of common ancestry, but because of similar selection pressures—the benefits of not being seen, by prey or by predators, respectively.



(a) (b)

Figure 9.2.7: The white winter coat of the (a) arctic fox and the (b) ptarmigan's plumage are adaptations to their environments. (credit a: modification of work by Keith Morehouse)

Embryology, the study of the development of the anatomy of an organism to its adult form, also provides evidence of relatedness between now widely divergent groups of organisms. Mutational tweaking in the embryo can have such magnified consequences in the adult that embryo formation tends to be conserved. As a result, structures that are absent in some groups often appear in their embryonic forms and disappear by the time the adult or juvenile form is reached. For example, all vertebrate embryos, including humans, exhibit gill slits and tails at some point in their early development. These disappear in the adults of terrestrial groups but are maintained in adult forms of aquatic groups such as fish and some amphibians. Great ape embryos, including humans, have a tail structure during their development that is lost by the time of (their) birth.

Biogeography

The geographic distribution of organisms on the planet follows patterns that are best explained by evolution in conjunction with the movement of tectonic plates over geological time. Broad groups that evolved before the breakup of the supercontinent Pangaea (about 200 million years ago) are distributed worldwide. Groups that evolved since the breakup appear uniquely in regions of the planet, such as the unique flora and fauna of northern continents that formed from the supercontinent Laurasia and of the southern continents that formed from the supercontinent Gondwana. The presence of members of the plant family Proteaceae in Australia, southern Africa, and South America is best explained by their presence prior to the southern supercontinent Gondwana breaking up.

The great diversification of marsupials in Australia and the absence of other mammals reflect Australia's long isolation. Australia has an abundance of endemic species—species found nowhere else—which is typical of islands whose isolation by expanses of water prevents species to migrate. Over time, these species diverge evolutionarily into new species that look very different from their ancestors that may exist on the mainland. The marsupials of Australia, the finches on the Galápagos, and many species on the Hawaiian Islands are all unique to their one point of origin, yet they display distant relationships to ancestral species on mainlands.

Molecular Biology

Like anatomical structures, the structures of the molecules of life reflect Darwin's "descent with modification" (i.e. evolution). Evidence of a common ancestor for all of life is reflected in the universality of DNA as the genetic material and in the near universality of the genetic code and the machinery of DNA replication and expression. Fundamental divisions in life between the three domains (archaea--single celled organisms without a cell nucleus; bacteria; and eukaryote--including plants, animals, and fungi) are reflected in major structural differences in otherwise conservative structures such as the components of ribosomes and the structures of membranes. In general, the relatedness of groups of organisms is reflected in the similarity of their DNA sequences—exactly the pattern that would be expected from descent and diversification from a common ancestor.

DNA sequences have also shed light on some of the mechanisms of evolution. For example, it is clear that the evolution of new functions for proteins commonly occurs after gene duplication events that allow the free modification of one copy by mutation, selection, or drift (changes in a population's gene pool resulting from chance), while the second copy continues to produce a functional protein.

Misconceptions About Evolution

Although the theory of evolution generated some controversy when it was first proposed, it was almost universally accepted by biologists, particularly younger biologists, within 20 years after publication of *On the Origin of Species*. Nevertheless, the theory of evolution is a difficult concept and misconceptions about how it works abound.

Link to Learning

This site addresses some of the main misconceptions associated with the theory of evolution.

Evolution Is Just a Theory

Critics of the theory of evolution dismiss its importance by purposefully confounding the everyday usage of the word "theory" with the way scientists use the word. In science, a "theory" is understood to be a body of thoroughly tested and verified explanations for a set of observations of the natural world. Scientists have a theory of the atom, a theory of gravity, and the theory of relativity, each of which describes understood facts about the world. In the same way, the theory of evolution describes facts about the living world. As such, a theory in science has survived significant efforts to discredit it by scientists. In contrast, a "theory" in common vernacular is a word meaning a guess or suggested explanation; this meaning is more akin to the scientific concept of "hypothesis." When critics of evolution say evolution is "just a theory," they are implying that there is little evidence supporting it and that it is still in the process of being rigorously tested. This is a mischaracterization.

Individuals Evolve

Evolution is the change in genetic composition of a population over time, specifically over generations, resulting from differential reproduction of individuals with certain alleles. Individuals do change over their lifetime, obviously, but this is called development and involves changes programmed by the set of genes the individual acquired at birth in coordination with the individual's environment. When thinking about the evolution of a characteristic, it is probably best to think about the change of the average value of the characteristic in the population over time. For example, when natural selection leads to bill-size change in medium-ground finches in the Galápagos, this does not mean that individual bills on the finches are changing. If one measures the average bill size among all individuals in the population at one time and then measures the average bill size in the population several years later, this average value will be different as a result of evolution. Although some individuals may survive from the first time to the second, they will still have the same bill size; however, there will be many new individuals that contribute to the shift in average bill size.

Evolution Explains the Origin of Life

It is a common misunderstanding that evolution includes an explanation of life's origins. Conversely, some of the theory's critics believe that it cannot explain the origin of life. The theory does not try to explain the origin of life. The theory of evolution explains how populations change over time and how life diversifies the origin of species. It does not shed light on the beginnings of life

including the origins of the first cells, which is how life is defined. The mechanisms of the origin of life on Earth are a particularly difficult problem because it occurred a very long time ago, and presumably it just occurred once. Importantly, biologists believe that the presence of life on Earth precludes the possibility that the events that led to life on Earth can be repeated because the intermediate stages would immediately become food for existing living things.

However, once a mechanism of inheritance was in place in the form of a molecule like DNA, either within a cell or pre-cell, these entities would be subject to the principle of natural selection. More effective reproducers would increase in frequency at the expense of inefficient reproducers. So while evolution does not explain the origin of life, it may have something to say about some of the processes operating once pre-living entities acquired certain properties.

Organisms Evolve on Purpose

Statements such as “organisms evolve in response to a change in an environment” are quite common, but such statements can lead to two types of misunderstandings. First, the statement must not be understood to mean that individual organisms evolve. The statement is shorthand for “a population evolves in response to a changing environment.” However, a second misunderstanding may arise by interpreting the statement to mean that the evolution is somehow intentional. A changed environment results in some individuals in the population, those with particular phenotypes, benefiting and therefore producing proportionately more offspring than other phenotypes. This results in change in the population, if the characteristics are genetically determined.

It is also important to understand that the variation that natural selection works on is already in a population and does not arise in response to an environmental change. For example, applying antibiotics to a population of bacteria will, over time, select a population of bacteria that are resistant to antibiotics. The resistance, which is caused by a gene, did not arise by mutation because of the application of the antibiotic. The gene for resistance was already present in the gene pool of the bacteria, likely at a low frequency. The antibiotic, which kills the bacterial cells without the resistance gene, strongly selects individuals that are resistant, since these would be the only ones that survived and divided. Experiments have demonstrated that mutations for antibiotic resistance do not arise as a result of antibiotic.

In a larger sense, evolution is not goal directed. Species do not become “better” over time; they simply track their changing environment with adaptations that maximize their reproduction in a particular environment at a particular time. Evolution has no goal of making faster, bigger, more complex, or even smarter species, despite the commonness of this kind of language in popular discourse. What characteristics evolve in a species are a function of the variation present and the environment, both of which are constantly changing in a non-directional way. What trait is fit in one environment at one time may well be fatal at some point in the future. This holds equally well for a species of insect as it does the human species.

Population Evolution and the Modern Synthesis

The mechanisms of inheritance, or genetics, were not understood at the time Charles Darwin and Alfred Russel Wallace were developing their idea of natural selection. This lack of understanding was a stumbling block to understanding many aspects of evolution. In fact, the predominant (and incorrect) genetic theory of the time, blending inheritance, made it difficult to understand how natural selection might operate. Darwin and Wallace were unaware of the genetics work by Austrian monk Gregor Mendel, which was published in 1866, not long after publication of Darwin's book, *On the Origin of Species* (1859). Mendel’s work was rediscovered in the early twentieth century at which time geneticists were rapidly coming to an understanding of the basics of inheritance. Initially, the newly discovered particulate nature of genes made it difficult for biologists to understand how gradual evolution could occur. But over the next few decades, genetics and evolution were integrated in what became known as **the modern synthesis**—the coherent understanding of the relationship between natural selection and genetics that took shape by the 1940s and is generally accepted today. In sum, the modern synthesis describes how evolutionary processes, such as natural selection, can affect a population’s genetic makeup, and, in turn, how this can result in the gradual evolution of populations and species. The theory also connects this change of a population over time, called microevolution, with the processes of macroevolution that gave rise to new species and higher taxonomic groups with widely divergent characters.

Kin Selection

In the discussion of natural selection, the emphasis was on how natural selection works on individuals to favor the more fit and disfavor the less fit in a population. The emphasis was on the survival (mortality selection), mating success (sexual selection), or family size (fecundity selection) of **individuals**. But what of the worker honeybee who gives up her life when danger threatens

her hive? Or the mother bird who, feigning injury, flutters away from her nestful of young, thus risking death at the hands of a predator? How can evolution produce genes for such instinctive patterns of behavior when the owner of these genes risk failing the first test of fitness: survival?

A possible solution to this dilemma lies in the effect of such seemingly altruistic behavior on the overall ("inclusive") fitness of the family of the altruistic individual. Linked together by a similar genetic endowment, the altruistic member of the family enhances the chance that many of its own genes will be passed on to future generations by sacrificing itself for the welfare of its relatives. It is interesting to note that most altruistic behavior is observed where the individuals are linked by fairly close family ties. Natural selection working at the level of the family rather than the individual is called **kin selection**.

How good is the evidence for kin selection? Does the behavior of the mother bird really increase her chances of being killed? After all, it may be advantageous to take the initiative in an encounter with a predator that wanders near. But even if she does increase her risk, is this anything more than another example of maternal behavior? Her children are, indeed, her kin. But isn't natural selection simply operating in one of the ways Darwin described: to produce larger mature families?

Perhaps clearer examples of altruism and kin selection are to be found in those species of birds that employ "helpers". One example: Florida scrub jays (*Aphelocoma coerulescens coerulescens*). These birds occupy well-defined territories. When they reach maturity, many of the young birds remain for a time (one to four years) in the territory and help their parents with the raising of additional broods. How self-sacrificing! Should not natural selection have produced a genotype that leads its owners to seek mates and start raising their own families (to receive those genes)?

But the idea of kin selection suggests that the genes guiding their seemingly altruistic behavior have been selected for because they are more likely to be passed on to subsequent generations in the bodies of an increased number of younger brothers and sisters than in the bodies of their own children. To demonstrate that this is so, it is necessary to show that:

1. the "helping" behavior of these unmated birds is really a help and that
2. they have truly sacrificed opportunities to be successful parents themselves.

Thanks to the patient observations of Glen Woolfenden, the first point is established. He has shown that parents with helpers raise larger broods than those without. But the second point remains unresolved. Perhaps by waiting until they have gained experience with guarding nests and feeding young and until a suitable territory becomes available, these seemingly altruistic helpers are actually improving their chances of *eventually* raising larger families than they would have if they started right at it. If so, then once again we are simply seeing natural selection working through one of Darwin's criteria of individual fitness: ability to produce larger mature families.

The evolutionary advantage of helping ceases if the young are not actually siblings of the helper. It is well-established (e.g., by DNA analysis) that the females of many species of birds have "extramarital" affairs; that is, produce broods where the young have been sired by more than one male. Interestingly, it turns out that the more promiscuous the females of a given species, the less likely it is that they are assisted by helpers. Conversely, those species that employ helpers tend to be monogamous (however, there are a few exceptions.)

Kin Selection in Social Insects

The honeybee and other social insects provide the clearest example of kin selection. They are also particularly interesting examples because of the peculiar genetic relationships among the family members.

Male honeybees (drones) develop from the queen's unfertilized eggs and are haploid. Thus, all their sperm will contain exactly the same set of genes. This means that all their daughters will share exactly the same set of **paternal** genes, although they will share — on average — only one-half of their mother's genes. (Human sisters, in contrast, share one-half of their father's as well as one-half of their mother's genes.) So any behavior that favors honeybee sisters (75% of genes shared) will be more favorable to their genotype than behavior that favors their children (50% of genes shared).

Since that is the case, why bother with children at all? Why not have most of the sisters be sterile workers, caring for their mother as she produces more and more younger sisters, a few of whom will someday be queens? As for their brothers, worker bees share only 25% of their genes with them. Is it surprising, then, that as autumn draws near, the workers lose patience with the lazy demanding ways of their brothers and finally drive them from the hive?

No Perfect Organism

Natural selection is a driving force in evolution and can generate populations that are better adapted to survive and successfully reproduce in their environments. But natural selection cannot produce the perfect organism. Natural selection can only select on existing variation in the population; it does not create anything from scratch. Thus, it is limited by a population's existing genetic variance and whatever new alleles (genetic variants) arise through mutation and gene flow (when some organisms from one population migrate into another population).

Natural selection is also limited because it works at the level of individuals, not alleles, and some alleles are linked together due to their physical proximity in the genome, making them more likely to be passed on together (linkage disequilibrium). Any given individual may carry some beneficial alleles and some unfavorable alleles. It is the net effect of these alleles, or the organism's fitness, upon which natural selection can act. As a result, good alleles can be lost if they are carried by individuals that also have several overwhelmingly bad alleles; likewise, bad alleles can be kept if they are carried by individuals that have enough good alleles to result in an overall fitness benefit.

Finally, it is important to understand that not all evolution is adaptive. While natural selection selects the fittest individuals and often results in a more fit population overall, other forces of evolution, including genetic drift and gene flow, often do the opposite: introducing deleterious alleles to the population's gene pool. Evolution has no purpose—it is not changing a population into a preconceived ideal. It is simply the sum of the various forces described in this chapter and how they influence the genetic and phenotypic variance of a population.

Summary

Evolution is the process of adaptation through mutation and natural selection which allows better biologically fit (i.e. better adapted) characteristics to be passed to succeeding generations while less well adapted characteristics tend to be weeded out. Over time, organisms evolve characteristics that are beneficial to their survival and reproduction. For living organisms to adapt and change to environmental pressures, genetic variation must be present. With genetic variation, individuals have differences in form and function that allow some to survive environmental conditions better than others. These organisms pass their favorable traits to their offspring. Eventually, environments change, and what was once a desirable, advantageous trait may become an undesirable trait and organisms may further evolve. Evolution may be convergent with similar traits evolving in multiple species or divergent with diverse traits evolving in multiple species that came from a common ancestor. Evidence of evolution can be observed by means of DNA code and the fossil record, and also by the existence of homologous and vestigial structures.

The modern synthesis of evolutionary theory grew out of the combination of Darwin's and Wallace's formulations of evolution with Mendel's analysis of heredity, along with the more modern study of population genetics. The modern synthesis describes the evolution of populations and species, from small-scale changes among individuals to large-scale changes over paleontological time periods. To understand how organisms evolve, scientists can track populations' allele frequencies over time.

Kin selection and inclusive fitness involve selection for altruistic behaviors which benefit close genetic relatives.

References

1. Theodosius Dobzhansky. "Biology, Molecular and Organismic." *American Zoologist* 4, no. 4 (1964): 449.

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9.3: Human Evolution

Learning Objectives

1. Explain the basic trends of human evolution including bipedalism and encephalization.
2. Describe hominins and what distinguishes hominins from other members of the Primate order.
3. Describe the category of features that distinguishes proto-hominins from hominins.
4. Describe, including approximate date ranges, the evolution of the genus *Homo,* including *e*arly *Homo* species and modern humans.
5. Explain how material culture helps inform us about the psychology of ancestral *Homo sapiens* and other hominin species.

Overview

Trends: There are a number of trends in the evolution of the proto-hominins (primitive ape-like species regarded as possibly ancestral to modern humans) to modern Homo sapiens. These traits do not occur all at once, but over millions of years.

Proto-Hominins and Hominins: In determining what fossil features a specimen must have in order to be classified as a hominin (the term used for humans and their ancestors after the split with chimpanzees and bonobos), many different characteristics are examined, including those related to bipedalism and dental features related to chewing. Apes have a space between biting teeth and grinding teeth where the upper canine fits when the jaws close. Other characteristics such as brain and body size are also considered.

Homo Genus: The emergence of the genus Homo (our genus) marks the advent of larger brains, the emergence of material culture (e.g. stone tools), and the eventual colonization of the world outside of Africa.

Material Culture: The earliest evidence of material culture is in the form of stone tools found on sites which dated back to 2.4 million years ago.



Figure 9.3.1: The original complete skull (without upper teeth and mandible) of a 2.1 million years old Australopithecus africanus specimen so-called "Mrs. Ples" (catalogue number STS 5, Sterkfontein cave, hominid fossil number 5), discovered in South Africa . Collection of the Transvaal Museum, Northern Flagship Institute, Pretoria, South Africa. (CC BY-SA 4.0; José Braga; Didier Descouens).

Human and Ape Evolutionary Paths: Divergence from Common Ancestors

Before we begin our discussion of human evolution, it will be helpful to take a look at the big picture. The two figures below along with Figure 3.7.16, much further below, collectively depict 20 million years of evolution leading to our species, *Homo sapiens*. Figure 3.7.2 shows the last 10 million years of humanoid evolution. Figure 3.7.3 shows the last 20 million years of humanoid evolution and so is inclusive of Figure 3.7.2, which shows greater detail beginning with the Homininae (African hominids including humans) phylogeny, 10 Mya to present. Both of these figures show our genus Homo at the top left of each diagram. Figure 3.7.16 shows an enlarged and much more detailed depiction of the genus Homo including relationships between Homo sapiens and Neanderthals and the fact that these two species once co-existed at the same time outside of Africa about 30,000-40,000 years ago. In the first two figures immediately below, notice the great divergence into a surprisingly large number of species over millions of years. Also notice how small and how recent the genus Homo is by comparison, and how one very recent species that emerged during the Pleistocene, humans, has so quickly come to dominate the Earth, at least for now. It is hoped that by closely examining these figures, you will be better able to organize the details that follow in this section and that you will be able to understand them within the larger context of primate evolution.

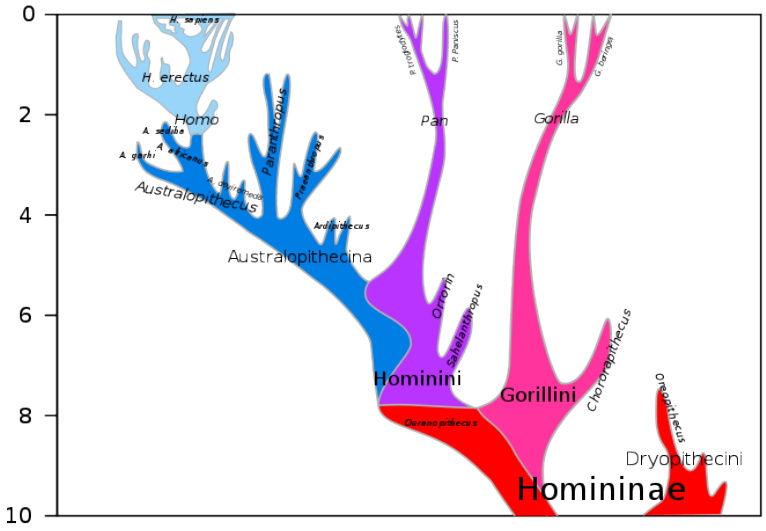


Figure 9.3.2: Hominini (includes Homo and Pan, but excludes gorillas) and Homininae (African hominids including humans) phylogeny, 10 Mya to present; the human branch beginning with Homo, top left, is enlarged and shown in greater detail in Figure 3.7.16 closer to the bottom of this page. The Hominin ancestral line (modern humans, extinct human species and all our immediate ancestors including members of the genera *Homo*, *Australopithecus*, *Paranthropus* and *Ardipithecus*) and the ape line, including gorillas, diverged from one another about 8 Mya (million years ago) and the Hominin and Pan (chimpanzee) lines diverge from one another about 6 Mya. Homo sapiens are shown at the very top left. To go back 20 Mya, see Figure 3.7.3 below. There you can see that Pongo (orangutans) diverged from the Hominin line much earlier, about 14 million years ago (Image from Wikimedia Commons; File:Hominini lineage.svg; https://commons.wikimedia.org/wiki/F...ni_lineage.svg; by Dbachmann; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

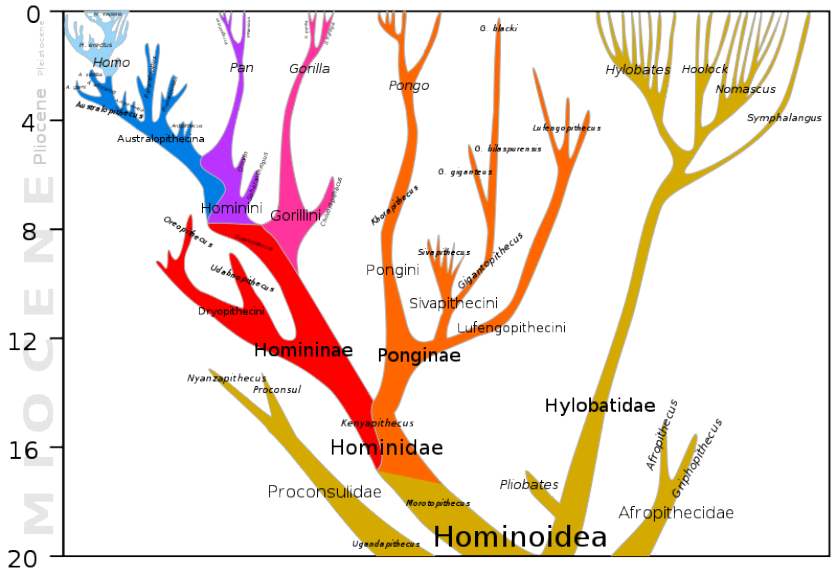


Figure 9.3.3: Hominoidea phylogeny, 20 Mya to present. A hominoid, sometimes called an ape, is a member of the superfamily Hominoidea: extant members are the gibbons (lesser apes, family Hylobatidae) and the hominids. A hominid is a member of the family Hominidae, the great apes: orangutans (Ponginae; Pongo), gorillas (Gorillini), chimpanzees (Pan) and humans. Note that the split between the Homo line, leading to humans, from the chimpanzee and gorilla lineages occurred about six million and eight million years ago, respectively. (Image from Wikimedia Commons; File:Hominoidea lineage.svg; https://commons.wikimedia.org/wiki/F...ea_lineage.svg; by Dbachmann; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Trends in Human Evolution

A number of questions about human evolution are:

- Why did our earliest ancestors stand up?
- Why did some species become extinct until only one species, *Homo sapiens*, was left?
- When, where and why did modern humans evolve?
- What was the role of the Neanderthals?
- What makes us human?

While hypotheses suggest answers, research continues to refine our understanding of human evolution.

This section provides an overview of key finds and trends in **hominin** evolution. (For additional information, see the "For Further Exploration" at the end of this page).



Figure 9.3.4: A man contemplating his evolution.

Defining Hominins

It is through our study of our hominin ancestors and relatives that we are exposed to a world of “might have beens”--of other paths not taken by our species, of other ways of being human. But in order to better understand these different evolutionary trajectories, we must first define the terms we are using. If an imaginary line were drawn between ourselves and our closest relatives, the great apes, bipedalism (habitually walking upright on two feet) is where that line would be drawn. Hominin**,** then, means everyone on “our” side of that line defined by bipedalism. Thus, hominins are humans and all of our extinct bipedal ancestors and relatives since our divergence from the last common ancestor (LCA) that we shared with chimpanzees. As shown above in Figures 3.3.2 and 3.3.3, many scientists believe that this split between human and chimpanzee lineages took place about 6 million years ago. However, data from DNA using estimated mutation rates suggests that the split between the human and ape lineages may have occurred much earlier--divergence between human and chimpanzee lines taking place about 7 to 8 million and possibly as many as 13 million years ago, while the divergence between human and gorilla lines may have occurred as long ago as 8 to 19 million years ago (Gibbons, 2012). These different estimates may be confusing to students. However, this wide range of estimates serves as a good example of how our knowledge is incomplete and sometimes changing as new discoveries and methods arise. In this context, it is best to keep in mind that "[...] when all is said and done a taxonomy is just a hypothesis; it is not written on stone tablets" (Wood, 2010, p. 8908).

Morphological Trends in Human Evolution

There are a number of trends in the evolution of the human lineage from the proto-hominins (early human ancestral species) to modern *Homo sapiens*. These traits do not occur all at once, but over millions of years. In general, the trends include:

- the forward movement of the foramen magnum (the hole at the bottom of the skull where spinal cord enters skull to connect with brain): related to upright posture
- a reduction in the size of the canines
- an increase in the size of the molars
- an increase in cranial capacity
- flattening of the face
- rounding of the skull

Again, not all of these traits occur at the same time and there is variation among the various hominin species, but all of these morphological characteristics occur in the evolutionary line of *Homo sapiens*. Two other trends are especially important in the evolution of hominins:

- bipedalism, and

- encephalization of the brain.

These are discussed in more detail next.

Bipedalism

Bipedalism, or upright walking, was the first morphological trait on the road to humanity. Human bipedalism is the primary form of moving around (this is called habitual bipedalism). Other primates practice temporary or occasional bipedal locomotion, e.g., primates like chimpanzees may walk bipedally while they carry something in their hands. Few other animals are habitual bipeds like humans, e.g., birds and kangaroos.



Figure 9.3.5: Human skeleton walking.

There are numerous anatomical changes that evolved to make hominins efficient bipedal locomotors including changes in position of foramen magnum (see above), the vertebral column of the spine, the pelvis, femur and tibia bones, knee joint, and foot structure--many of these changes being related to improved balance and shock absorption (eLucy 2007).

The morphological changes associated with bipedalism take millions of years to evolve. They first appear 6.0-7.0 million years ago (mya), but are not fully in place until around 4.0 mya. These physical changes continue to refine until we see them as we do today in modern Homo sapiens (Jurmain et al. 2013).

Hypotheses about the Evolution of Bipedalism

Several hypotheses have been proposed over the last century or so to explain the evolution of hominins. As bipedalism is the first trait on the road to modern humans, these hypotheses focus on the emergence of habitual bipedalism. Many have been refuted as new data is discovered. The first hypothesis was the hunting hypothesis proposed by Charles Darwin. The hunting hypothesis claims that the key to human evolution was the shift from an arboreal life to a terrestrial one. He predicted that the earliest hominins would be found in Africa based on the similarities he saw between humans and African apes. He suggested that bipedalism gave the first hominins an advantage in that it freed up their hands to carry weapons used to hunt animals. Darwin also suggested that larger brains preceded bipedalism as intelligence was needed to make the tools. Now we know that habitual bipedalism predates large brains so Darwin's hypothesis is no longer considered an adequate explanation. With the discovery of new data, other hypotheses have been proposed including the patchy-forest and provisioning hypotheses.

The patchy forest hypothesis suggests that the emerging mosaic environment that began at the end of the Miocene made bipedalism advantageous. The phrase mosaic environment in this case refers to an environment that had patchy forest interspersed with grasslands that eventually became the African savannas of today. This caused food resources to become spread out over the landscape. For traveling long distances, bipedalism is more energy efficient than quadrupedalism (walking on "all fours"). Traveling bipedally freed up hands for carrying provisions and the early hominins could have easily fed from both terrestrial

and arboreal resources.

The provisioning hypothesis states that having hands free to carry food allowed males to provision females and offspring. Since much of the females energy went to child-rearing, the ability of a male to provision her and her offspring would have been an attractive quality. Those males who could walk more efficiently bipedally while carrying food would have been prime mate material, allowing both the male and female to reproduce successfully. However, species such as wolves provision their females and offspring even though they are quadrupeds by consuming meat and regurgitating it to the pups.

The truth of the matter is that the origins of bipedalism are still murky. Further research will hopefully help us come closer to a determination of why bipedalism, and hence our early ancestors, evolved. In the meantime, you can explore other hypotheses on the origins of bipedalism on the NOVA web site: http://www.pbs.org/wgbh/nova/evoluti...ipedalism.html [optional].

Dental Features

Apes have a chewing complex which is good for cutting and shredding food. Over time, hominins lose this dental feature, as the canine reduces in size, and the molars increase in size (Larsen 2014).

Brain Evolution

In relation to other mammals, primates have a more expanded and elaborate brain, including expansion of the cerebral cortex. Compare the complexity of the human brain on the left to the cat brain on the right (photos are not to scale).



Figure 9.3.6: Human Brain.



Figure 9.3.7: Cat Brain.

Clearly, significant anatomical changes have taken place during the evolution of the brain in primates, in other mammals, and in animals in general. Are there generalizations that can be made about the evolution of animal brains?

Striedter (2006) has identified a number of general principles of brain evolution applicable across a wide range of species (i.e. not just primates or mammals).

1) Embryonic brains across species are more similar than adult brains, because brains tend to diversify more as they grow toward adult form;

2) relative brain size to body size in the vertebrates (animals with backbones) has tended to increase more often than decrease over evolutionary time;

3) it appears that increases in relative brain size were generally accompanied by increases in social or food foraging complexity;

4) most increases in relative brain size were accompanied by increases in absolute body size;

5) increases in absolute brain size require changes in the brain's internal connections which imply greater modularity or specialization (specialized processing modules increasing the "division of labor" as opposed to the whole brain doing all kinds of processing equally) of brain anatomy and functioning;

6) evolution generally enlarges brains by extending the period of brain development before and after birth while conserving (keeping the same) the "birth order" of different brain regions, so that big-brained animals tend to have disproportionately larger late-"born" (late-developing) regions ("late equals large"), such as cerebral cortex, leading to disproportionately more cerebral cortex (increased corticalization) in big-brained mammals (non-mammals don't have cerebral cortex); however there are exceptions to this rule, for example, at any given absolute brain size, there is more cerebral cortex in simians than in prosimians, and in parrots there is an unusually large telencephalon (forebrain) which is not accounted for by the rule;

7) changes in size proportions of brain areas, although "automatic" within the scaling (allometric) rules above, can still be adaptive and undergo natural selection;

8) as brain regions increase in absolute or proportional size, they tend to become laminated--organized into sheets of neurons--allowing point for point corresponding connections between sensory and motor maps with minimal axonal and dendritic wiring, saving space and metabolic energy;

9) as brain size increases, more regional subdivisions occur from ancestral parts subdividing into new parts, as in the dorsal thalamus (located below the cortex near the center of the brain), or, as in the case of neocortex, a new part was added onto an ancestral set of conserved (retained over evolution) brain parts;

10) a principle known as Deacon's rule is that "large equals well connected," meaning that as the relative size of a brain structure increases it tends to receive more connections and to project (send) more outputs to other structures.

Striedter (2006) adds a number of additional generalizations about the mammal and primate brains, including human brains:

11) six-layered mammalian neocortex (found only in mammals like us) probably evolved from a 3-layered reptilian precursor called dorsal cortex (something like that found in turtles) by addition of several layers of cortex;

12) aside from neocortex, the mammalian brain is similar to the reptilian brain (which also has hippocampus, for example) but even with a "fundamental scheme" of brain regions and circuitry, many minor changes in wiring can drastically change how information flows through a brain and thus how it functions--thus, the mammal brain is not just an upscale version of the reptilian brain;

13) increasing corticalization in mammals cannot be explained in terms of the above scaling (allometric) rules and involved highly specialized changes in brain anatomy presumably due to natural selection which expanded precursor sensory and motor cortical regions;

14) bird forebrains evolved along a very different path with expansion of their dorsal ventricular ridge (DVR), the major sensorimotor region of the avian telencephalon, highly similar in function to mammalian neocortex, making "many birds at least as intelligent as most mammals."

Striedter adds a number of points about the **human brain** in an attempt to identify features that make it special compared to the brains of other mammals.

15) In the six million years since bipedal apes (hominins) diverged from other apes, absolute brain size increased radically (about fourfold), not gradually, but in bursts--**from when genus *Homo* first evolved, absolute brain size doubled from 400 to 800 cubic centimeters, then remained relatively steady in *Homo erectus* during the next 1.5 million years, but then exploded again in the transition to *Homo sapien* until about 100,000 years ago, at which time absolute brain size reached its current value of about 1,200 to 1,800 cubic centimeters.** The first jump in Homo brain size was likely related to change in diet involving transition to meat and later the cooking of meat. The second leap was perhaps stimulated by competition among humans for mates and other resources;

16) the principle of "late equals large" predicts large neocortex in humans (the human neocortex to medulla ratio is twice that of chimpanzees);

17) the principle of "large equals well connected" is consistent with known expanded numbers of projections from human neocortex to motor neurons in medulla (located just above spinal cord) and spinal cord permitting greater precision of control over muscles serving hands, lips, tongue, face, jaw, respiratory muscles, and vocal folds, required for the **development of human language about 50,000 to 100,000 years ago**;

18) once human language appeared, dramatic changes in human behavior became possible without further increases in brain size;

19) increase in brain size has some disadvantages: including increased metabolic costs because the brain utilizes so much metabolic energy (20% of human metabolic energy even though it is only 2% of human body weight; being so metabolically expensive increases in brain size must be paid for by improved diet or reduction of other metabolic energy demands); decreased connectivity perhaps making the two hemispheres more independent of one another, and perhaps explaining why the two cerebral hemispheres became functionally specialized (performing different cognitive functions); and size limits of neonatal brain due to constraints imposed by size of the human mother's pelvis and birth canal. According to Striedter, these costs may explain why human brain size plateaued about 100,000 years ago;

20) within neocortex (found only in mammals), the lateral prefrontal cortex (located forward of your temples) has become relatively enlarged in the human brain, likely increasing its role in behavior some key evolutionary changes in brain structure were not caused by increases in absolute or relative brain size, such as evolution of the neocortex of mammals, but require additional explanation; comparing distantly related species on absolute brain size alone misses important factors, for example, brains of some large whales weight 5 times as much as the human brain but whale brains have poorly laminated and thin neocortex; in cases of distantly related species, comparisons of relative brain size are more useful, for example, human and some toothed whales (e.g. killer whales) have relative brain sizes significantly larger than average mammals of similar body size;

22) two general hypotheses about brain evolution are that individual brain systems evolve independently by natural selection (the mosaic hypothesis) or alternatively that components of such systems evolve together because of functional constraints (the concerted or constraint hypothesis), with a third view being that all brain evolution is simultaneously both mosaic and concerted.

One problem with Striedter's approach is that it doesn't explicate the forces of natural selection that may account for more specific features of brain evolution in specific species, including our own. He admits that evolution of the neocortex cannot be explained by evolution of bigger brains and that neocortex evolved independently of absolute brain size. However, aside from restating the theory that complex social life in ancestral humans, along with competition among humans for resources, stimulated the evolution of increases in the size and complexity of the neocortex, he offers little insight about what role natural selection played in the evolution of the neocortex of mammals, or in brain evolution in general. As Adkins-Regan (2006, p.12-13) states in her critique of Striedter's work, "There is relatively little discussion of tests of hypotheses about the selective pressures responsible for the origin and maintenance of traits . . . The author would seem to be experiencing symptoms of discomfort with the concept of adaptation. . .. Given that brain mechanisms are products of natural selection, a central strategy in neuroscience should be to use the methods of evolutionary biology, which have been so successful in helping us to understand the mechanisms and design of organisms generally."

Encephalization of the Brain

Encephalization of the brain refers to a couple of things: 1) the **increase in brain size** over time and 2) the **size of the brain in relation to total body mass**. The brain-size to body mass ratio does not change that much in the hominins in spite of presumed increases in intelligence, however increases in brain size becomes significant beginning with the early Homo species. Studies of living mammal species suggest that **increased number of neurons and increased density of neuron packing into the cranial cavity may be a key factor in the evolution of increased intelligence across species.** However, while there is gradual increase in brain size throughout the australopithecine lineage, it is not until early *Homo* that there is a significant increase in cranial capacity, approximately a 20% increase over australopithecines. More significant is the approximately 50% increase in brain size of *Homo erectus* and the earlier *Homo* species. It is not just the size of the brain that is important. During this process of encephalization, it has been speculated, without fossil evidence, that there was also a rewiring of the brain that coincides with the emergence of material culture such as stone tools. It is not until this occurs that hominins leave Africa, enabled greatly by cultural advances.

Non-human primate brains are symmetrical as are the brains of early hominins. **With the emergence of *Homo* we see the**

lateralization of the brain--it becomes asymmetrial (right brain, left brain). We know this from endocasts. Endocasts form when minerals replace brain matter inside the cranium during the fossilization process. These endocasts allow researchers to study the cortical folds of the brain and compare it to modern humans. Based on endocasts, researchers determined that three areas of the brain began to **change in *Homo*:** the **cerebellum**, which handles learned motor activities, the **limbic system**, which processes motivation, emotion and social communication, and the **cerebral cortex**, which is responsible for sensory experiences, memory, and complex mental functions such as language, cognition, planning, imagination, and intelligence. It is these changes that may have allowed the early members of our genus, *Homo*, to develop **cultural adaptations to environmental pressures**.

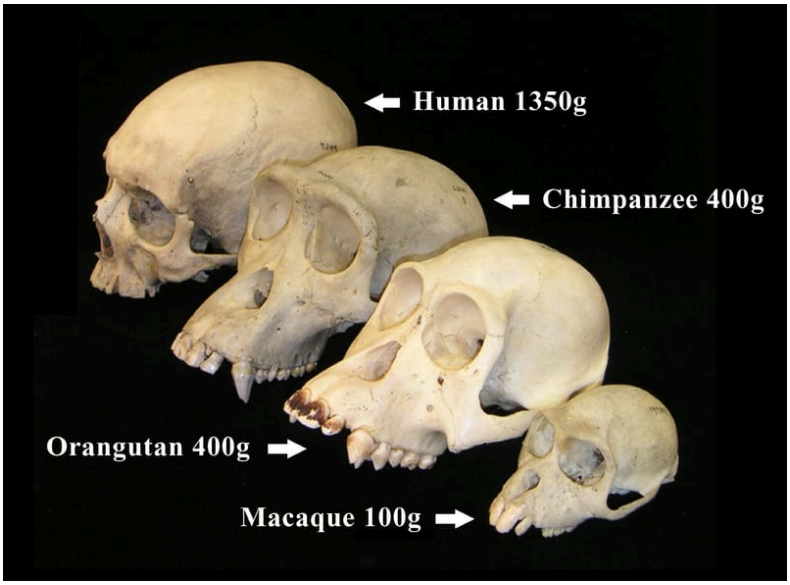


Figure 9.3.8: Comparison of cranial capacities of living primates. Primate skulls provided courtesy of the Museum of Comparative Zoology, Harvard University. (Image from Wikimedia Commons; File:Primate skull series with legend.png; https://commons.wikimedia.org/wiki/F...ith_legend.png; by Christopher Walsh, Harvard Medical School; licensed under the Creative Commons Attribution-Share Alike 2.5 Generic license).

Why did the brain change in early Homo?

The question that confronted researchers was why the brain changed. Big brains have some disadvantages:

- they require a lot of metabolic energy; approximately 25-30% of a human's metabolic energy is consumed by the brain although it comprises only 2% of total body weight
- big brains require infants to be born in an immature state with head and brain size small enough to permit birth through a relatively small birth canal, resulting in a longer period of infant dependency (the average infant brain at birth is only about 1/3 the size of an adult brain with much of brain development and behavioral and mental development occurring over a period of years after birth)
- longer infant dependency is an increased drain on maternal energy; the mother must have proper nutrition not only for herself but for the nursing infant
- it has been suggested that larger brains decrease the bipedal efficiency of females because they must have a wider pelvis and birth canal to give birth to a large brained infant

So, for large brains to become evolutionarily fixed in the *Homo* population, the advantages had to outweigh the disadvantages listed above.

One possible explanation incorporates the interaction of three different variables: group size, complex subsistence patterns (such as foraging for food or domestication of animals and plants), and the nutritional value of meat (Campbell and Loy 2000: 318). Let's address group size first.

Research suggests that brain size and size of social groups correlate positively among living primates, implying that big brains helped individuals keep track of complex social information such as dominance hierarchies, alliances, enemies, etc.

Second, a big brain allows primates to keep track of large subsistence territories and allows omnivores to develop strategies for collecting a wide variety of foods.

Third, eating meat is a relatively easy way to get the nutrition needed to run a big brain, which, as mentioned above, in modern humans takes about 1/4 to 1/3 of our daily metabolic energy. However, raw meat requires a lot of energy to digest, so the invention of cooking meat over a fire may have played a role in evolution of larger brains because cooked meat is much easier, and requires less metabolic energy, to digest. Thus, cooking of meat provided a rich source of metabolic energy, supporting evolution of larger brains.

The argument for the social brain hypothesis is laid out by Robin Dunbar (1998). Dunbar also claims that it was changes in the neocortex, the 2-4 mm thick top layer of the cerebral hemispheres, that were critical in the "homininzation" (development of human cognitive abilities) of our ancestors.

A related perspective on the evolution of the human brain emphasizes the role of culture in increasing brain size. As Geertz (2013, p. 180-181) states:

> The Australopithecine brain was approximately the same size as that of modern-day chimpanzees (some 400– 600 cm^3). The Homo sapiens brain is approximately 1200–1700 cm^3. But the expansion of the brain had begun already with the appearance of Homo habilis, the first hominine species that came out of the Australopithecine line some 2.5 million years ago (with a brain size of 500–800 cm^3) and became even more spectacular with the appearance 1.5 million years ago of the stone tool artist Homo erectus whose brain grew closer in size to modern humans at 750–1250 cm^3. It is today assumed by archeologists and paleontologists that the production and use of tools was incremental to the expansion of the brain. Because tool use is much more than simply knocking stones and bones together, and indeed, it depends very much on the recipes, rules and instructions of cultural patterns, it is widely accepted today that culture drove the expansion of the brain (along with other things, of course, such as eating meat). The causal chain, once again, however, is culture first, brain expansion afterwards. . . . 'Because tool manufacture puts a premium on manual skill and foresight, its introduction must have acted to shift selection pressures so as to favor the rapid growth of the forebrain as, in all likelihood, did the advances in social organization, communication, and moral regulation which there is reason to believe also occurred during this period of overlap between cultural and biological change. Nor were such nervous system changes merely quantitative; alterations in the interconnections among neurons and their manner of functioning may have been of greater importance than the simple increase in their number.'

The Forebrain includes the cerebral cortex (frontal, parietal, temporal, and occipital lobes) and a number of subcortical structures such as the thalamus, hypothalamus, limbic system, and basal ganglia. Different selection pressures arising from tool manufacture and use, complex social organization, communication, moral regulation, and other social and cultural factors would have likely affected different areas of the forebrain, and even different lobes of the cerebral cortex, in different ways. This follows from the fact of brain organization that different brain circuits and networks are specialized for different cognitive and behavioral functions (see Cosmides & Tooby, 2002).

Geology and Environmental Background

The Miocene period (roughly 23-5 million years ago) was geologically active in Africa. This is the period of the adaptive radiation of the apes and a period of mountain building that led to the formation of the Great Africa Rift Valley. With the emergence of the rift mountains, the rains that heretofore had moved across the continent from the Atlantic Ocean were blocked (referred to as a rain shadow), leading to the aridification of Eastern Africa. The savanna environment that evolved in Eastern Africa was and is a much more open environment than the forested environment of Western and Central Africa, leading to rise of new adaptations for plants and animals. It is in this newly emerging environment that hominin evolution takes off.

Paleoclimatic data has been correlated with speciation events in hominin evolution, but it does not seem to account for all speciation events. Nonetheless, the paleoclimatic data suggests the following:

- Grasslands spread in Africa between 10-5 million years ago during a cooling and drying phase. It is during this time frame that the common ancestor of African apes and humans lived. The common ancestor was more like a quadruped who was arboreal or at least spent a significant amount of time in the trees. In the middle of this period, approximately 7-6 million years ago, the first bipedal hominin emerged, and a few other early hominins are referred to as proto-hominins in recognition of their primitive, ape-like features.
- In the mid-Pliocene period, 3-2 million years ago, yet another cooling and drying phase is correlated with the adaptive radiation of the hominins, including the emergence of the robust australopithecines in the genus *Homo,* the same genus as

modern humans.
- Near the beginning of the Pleistocene period, also known as the Ice Age, the environment continued to get drier. Open habitats spread in East Africa. During this period, *Homo ergaster* (*Homo erectus*) emerges and finally leaves the African continent.

This data has a tendency to make us think that hominin evolution was driven by environmental changes; however, geologic, climatic, and environmental changes in Africa during the Miocene, Pliocene and Pleistocene may have had little to do with the evolution of hominins, leaving open the possibility that the hypotheses discussed above, or others yet to be proposed, may be more causally related to the evolution of hominins.

Key Transitions in Human Evolution

On the evolutionary road to modern humans, some scientists have identified several "key transitions: (1) African ape to terrestrial bipedal ape (around 4 Ma)[Ma=million years ago]; (2) terrestrial bipedal ape (australopithecine) to 'early Homo' (around 2 Ma); (3) Early Homo [species] to Homo heidelbergensis (1–0.8Ma); (4) Homo heidelbergensis to larger-brained Homo (from 500 ka) [ka=thousand years ago], and (5) larger-brained Homo to H. sapiens (from 200 ka) . . . [Regarding social behavior,] "among archeologically based models, there is a total agreement that the emergence of basal hominin sociality, as part of our primate heritage, should be attributed to the very first evolutionary stages, possibly before the emergence of the Homo genus" (Anghelinu, 2013, p.13).

For Further Exploration

Explore Human Evolution in Print

- Boyd, Robert and Joan B. Silk. 2009. How Humans Evolved, 5th edition. New York: W. W. Norton.
- Campbell, Bernard G. and James D. Loy. 2000. Humankind Emerging, 8th edition. Boston: Allyn & Bacon.
- Johanson, Donald and Kate Wong. 2010. Lucy's Legacy: The Quest for Human Origins. New York: Harmony Books.
- Stringer, Chris and Peter Andrew. 2006. The Complete World of Human Evolution. New York: Thames & Hudson.
- Tattersall, Ian. 2008. The Fossil Trail: How We Know What We Think We Know About Human Evolution. New York: Oxford University Press.

Explore Human Evolution on the Web

- Becoming Human
- Talk: Origins Fossil Hominids
- Hall of Human Origins
- Science Daily: Human Evolution News
- Rediscovering Biology:Unit 9 Human Evolution
- BBC: The Evolution of Man
- Human Evolution: The Fossil Evidence in 3D

Proto-hominins

The oldest hominin discovered to date is from between 7.2 to 6.8 mya (million years ago).

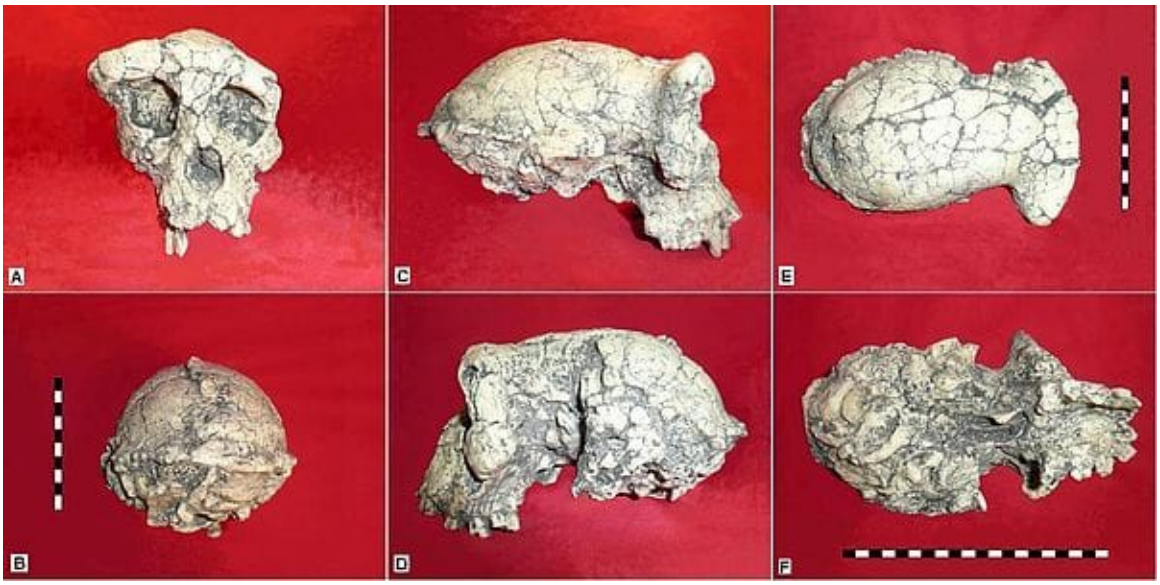


Figure 9.3.9: *Sahelanthropus tchadensis*. The oldest known hominin.

The skull is a combination of ape-like and human-like features. Ape-like features include brain size, heavy brow ridge. Its human-like features include forward position of the foramen magnum, smaller canine teeth, and intermediate thickness of the premolar and molar enamel. Due to the pronounced brow ridge, Brunet's team suggests that the specimen is male.

There is debate among researchers as to whether this fossil is a hominin or an ape. Some suggest that the specimen belongs to that of a female ape because it is likely to find canines worn at the tips in female apes.

Hominins

While the hominins will be presented more or less in chronological order, do not mistake chronological order for linear evolutionary relationships; some hominins that are presented are not in the direct line to modern humans. It is also important to keep in mind that new discoveries are made each year that refine what we know about human evolution.

It is highly recommended that you begin your exploration of human evolution by watching the PBS documentary, Becoming Human (https://www.pbs.org/wgbh/nova/video/...-human-part-1/).

Early hominins

Australopithecus afarensis

Discovered in 1974 at Hadar, Ethiopia, *Australopithecus afarensis* is arguably the most well know fossil hominin species. It is dated from 3.7-3.0 mya (Scarre 2014). Over 40% of the skeleton was recovered, which allowed the team to fully reconstruct the skeleton. This fossil specimen, named Lucy, coupled with footprints found at Laetoli, Tanzania, in 1978 by Mary Leakey, confirmed that *Au. afarensis* was fully bipedal, albeit not exactly like modern humans. The footprints at Laetoli indicate that *Au. afarensis* had a short stride and a strolling gait. Since the 1970s, hundreds of specimens of Au. afarensis have been found (60 individuals at least from Hadar alone!) in Ethiopia, Kenya, and Tanzania, allowing paleoanthropologists to make "definitive statements about the locomotor pattern and stature of" (Jurmain 2013: 211) this early hominin.



Figure 9.3.10: Reconstruction of the fossil skeleton of "Lucy" the *Australopithecus afarensis*

Au. afarensis has several primitive, or ape-like, features, including a relatively small brain in comparison to *Homo*, a u-shaped dental arcade, a flat nose, a flattened forehead (referred to as platycephaly) and prognathic face (characterized by a protruding lower jaw). Its canines, while larger than *Homo*, are smaller than earlier hominins. While its brain was larger than earlier hominins, it is still small in comparison to genus Homo. There is evidence for sexual dimorphism; *Au. afarensis* males were no taller than 5 feet and females about 3-4 feet, similar in proportion to modern African apes. *Au. afarensis* has a suite of derived traits associated with bipedalism; i.e., bowl-shaped pelvis, s-curve of the vertebral column, and knee anatomy. However, the curvature of the fingers and toes and the proportion of the arms to legs suggest to some researchers that *Au. afarensis* spent some time in the trees.

In 2006, a 3.3 million year old *Au. afarensis* child was discovered less than 4 km from where Lucy was found in 1974. It is not only the oldest juvenile fossil ever found, it is also the most complete hominin fossil found to date. Selam, as the fossil was nicknamed (or Lucy's baby or Dikika's baby), confirmed earlier suggestions that *Au. afarensis* was bipedal, yet spent time in the trees. The shoulder structure with its upward pointing shoulder joints and the bony ridge running along the shoulder blades are like that of apes, which would have facilitated arboreal movement even if they were not as fully capable as chimpanzees at moving in trees.

Paleoecological data indicates that *Au. afarensis* lived in both grassland (savanna) and woodland environments.

Australopithecus africanus



Figure 9.3.11: *Australopithecus africanus* (Mrs. Ples)

Australopithecus africanus (see Figure 3.7.2, above) has been dated to 3-2 mya (Scarre 2014). In comparison to *Au. afarensis*, *Au. africanus* has smaller incisors and larger molars; the canines no longer have the pointed, triangular appearance seen in apes and *Au. afarensis*; however, *Au. africanus* still exhibits some protrusion of the lower jaw and has a small brain like that of *Au. afarensis*. There is general consensus that *Au. africanus* is a direct descendent of *Au. afarensis*. Its relationship to *Homo* is less clear.

Australopithecus garhi

Found in Bouri, Ethiopia in 1997, *Au. garhi* (see Figure 3.7.2, above) dates to 2.5 mya. Few fossil specimens have been found and those that have are relatively fragmentary. One cranium and other skull fragments were found and serve as the basis of the species identification. The size and shape of its molar teeth suggest to some researchers that *Au. garhi* is related to *Paranthropus aethiopicus* (see below), but its other features, e.g., braincase, face, and other teeth, are more like genus *Homo*. In light of this, some researchers contend it is ancestral to *Homo*.



Figure 9.3.12: *Australopithecus garhi*.

Australopithecus sediba

Australopithecus sediba (Figure 3.3.13) was found in 2008 at Malapa Cave, South Africa, dating to 1.95-1.75 mya, has a mosaic of characteristics that suggest it may be transitional from the australopiths to genus *Homo*. However, this claim is controversial as

the earliest dates for *Homo* predate *Au. sediba* by about 500,000 years (Becoming Human 2008).



Figure 9.3.13: *Australopithecus sediba*.

The features that link *Au. sediba* to *Homo* include the pelvis shape, more vertical brain case, smaller cheek bones, and molar shape.

Robust Australopiths

Three robust species of hominins emerged in the Plio-Pleistocene period: *Paranthropus aethiopicus*, *Paranthropus boisei*, and *Paranthropus robustus* (see Figures 3.3.14-17). They have morphological features that suggest they were well adapted for eating hard foods that needed grinding, which led to their being identified as “robust.”

Note

There is debate over whether the differences mentioned above qualify the robust australopiths to be in a separate genus from the australopithecines. In some anthropological works the genus *Australopithecus* is used. In others, such as this work, *Paranthropus* is used.



Figure 9.3.14: *Paranthropus aethiopicus*.



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Figure 9.3.15. *Paranthropus boisei*.

There is no evidence to suggest that *P. boisei* is ancestral to any subsequent hominin.

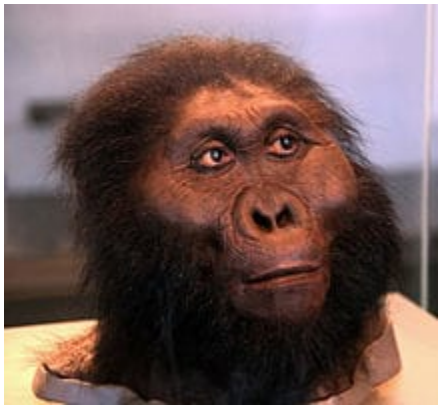


Figure 9.3.16. *Paranthropus boisei*; model of adult male (Smithsonian Museum of Natural History).



Figure 9.3.17. *Paranthropus robustus*.

Homo Genus

Above we described our oldest human ancestors, primarily members of the genus Australopithecus who lived between 2 million and 4 million years ago. Here we introduce the earliest members of the **genus Homo**, focusing on the species *Homo habilis* and *Homo erectus* (see Figure 3.3.19 and Figure 3.3.20, below).

Defining The Genus Homo

When grouping species into a common genus, biologists will consider criteria such as physical characteristics (morphology), evidence of recent common ancestry, and adaptive strategy (use of the environment). However, there is disagreement about which of those criteria should be prioritized, as well as how specific fossils should be interpreted in light of the criteria. There is general agreement that species classified as Homo should share characteristics broadly similar to our species. These include the following:

- a relatively large brain size, indicating a high degree of intelligence;
- a smaller and flatter face;
- smaller jaws and teeth; and
- increased reliance on culture, particularly the use of stone tools, to exploit a greater diversity of environments (adaptive zone).

Some researchers would include larger overall body size and limb proportions (longer legs/shorter arms) in this list. There is also an apparent decline in sexual dimorphism (body-size differences between males and females). While these criteria seem relatively clear-cut, evaluating them in the fossil record has proved more difficult, particularly for the earliest members of the genus. There are several reasons for this. First, many fossil specimens dating to this time period are incomplete and poorly preserved, making them difficult to evaluate. Second, early Homo fossils appear quite variable in brain size, facial features, and teeth and body size, and there is not yet consensus about how to best make sense of this diversity.

In this section, we will take several pathways toward examining the origin and evolution of the genus Homo. First, we will explore the environmental conditions of the Pleistocene epoch in which the genus Homo evolved. Next we will examine the fossil evidence for the two principal species traditionally identified as early Homo: Homo habilis and Homo erectus. Then we will use data from fossils and archeological sites to reconstruct the behavior of early members of Homo, including tool manufacture, subsistence practices, migratory patterns, and social structure. Finally, we will consider these together in an attempt to characterize the key adaptive strategies of early Homo and how they put our early ancestors on the trajectory that led to our own species, Homo

sapiens.

Climate

The early hominin species covered previously, such as Ardipithecus ramidus and Australopithecus afarensis, evolved during the late Pliocene epoch. The Pliocene (5.3 million to 2.6 million years ago) was marked by cooler and drier conditions, with ice caps forming permanently at the poles. Still, Earth's climate during the Pliocene was considerably warmer and wetter than at present.

The subsequent Pleistocene epoch (2.6 million years to 11,000 years ago) ushered in major environmental change. The Pleistocene is popularly referred to as the Ice Age. Since the term "Ice Age" tends to conjure up images of glaciers and woolly mammoths, one would naturally assume that this was a period of uniformly cold climate around the globe. But this is not actually the case. Instead, climate became much more variable, cycling abruptly between warm/wet (interglacial) and cold/dry (glacial) cycles.

In Africa, paleoclimate research has determined that grasslands expanded and shrank multiple times during this period, even as they expanded over the long term, becoming increasingly common during the Pleistocene. One solution adopted by some hominins was to specialize in feeding on the new types of plants growing in this landscape. The robust australopithecines probably developed their large molar teeth with thick enamel in order to exploit this particular dietary niche.

Members of the genus Homo took a different route. Faced with the unstable African climate and shifting landscape, they evolved bigger brains that enabled them to rely on cultural solutions such as crafting stone tools that opened up new foraging opportunities. This strategy of behavioral flexibility served them well during this unpredictable time and led to new innovations such as increased meat-eating, cooperative hunting, and the exploitation of new environments outside Africa, including Europe and Asia.

The Emergence of Homo (our Genus)

The emergence of the genus *Homo* marks the advent of larger brains, the emergence of material culture (at least material culture that survives in the archeological record), and the eventual colonization of the world outside of Africa. The earliest *Homo* species are contemporaneous with several australopiths: *Au. africanus*, *Au. garhi*, *Au. sediba*, and all of the *Paranthropus* species. Africa was flush with hominins (Figure 9.3.16). There are several trends we see in the evolution of the earliest *Homo* species to humans, *Homo sapiens*:

- Rounding of the cranium
- Enlargement and rewiring of the brain (judged from endocasts)
- Smaller faces and teeth
- Decreasing prognathism
- Tallness
- Diversity of cultural traits

As with the overview on early hominins, we will continue taking the "lumper" approach - a tendency to lump specimens into fewer species rather than tending to differentiate and hypothesizing a greater number of species. Several *Homo* species will not be discussed in detail, but may be mentioned in passing, e.g., *Homo rudolfensis*, *Homo ergaster*, *Homo gautengensis*, *Homo antecessor*, *Homo cepranensis*, *Homo rhodesiensis*, *Homo tsaichangensis*. We will first examine the morphological characteristics of various *Homo* species. Cultural traits will be addressed separately.

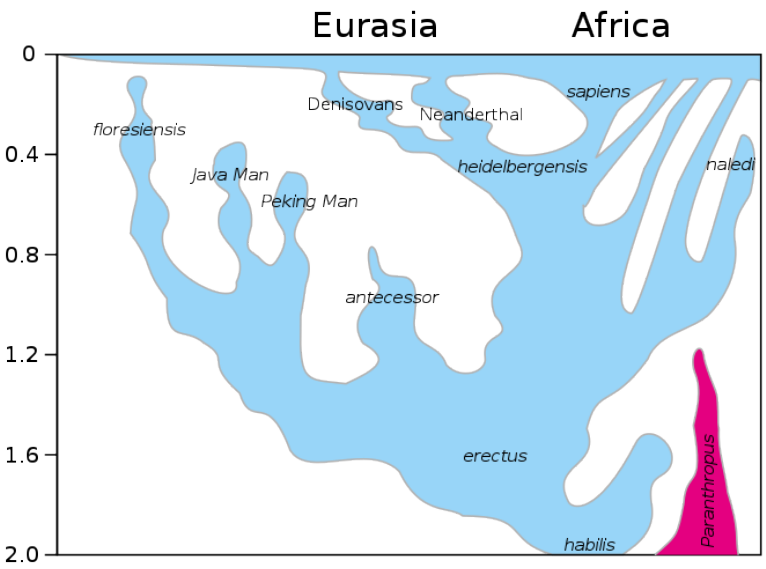


Figure 9.3.18: A model of the evolution of the genus Homo over the last 2 million years (millions of years, Mya, is on the vertical axis). The rapid "Out of Africa" expansion of H. sapiens is indicated at the top of the diagram by the lateral expansion of blue all the way across the top of the diagram, with admixture indicated with Neanderthals, Denisovans, and unspecified archaic African hominins. The late survival of robust australopithecines (Paranthropus) alongside Homo until 1.2 Mya is indicated in purple.

- H. heidelbergensis is shown as the link between Neanderthals, Denosiovans and H. sapiens
- Division of Asian H. erectus into Java Man and Peking Man
- H. antecessor shown as a branch of H. erectus reaching Europe
- After H. sapiens emerge from Africa some 60 kya they spread across the globe and interbred with other descendants of H. heidelbergensis, and Neanderthals, Denisovans

(Image from Wikimedia Commons; File:Homo lineage 2017update.svg; https://commons.wikimedia.org/wiki/F...2017update.svg; by User:Conquistador, User:Dbachmann; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Homo Habilis: The Earliest Members of our Genus

Homo habilis has traditionally been considered the earliest species placed in the genus Homo. However, as we will see, there is substantial disagreement among paleoanthropologists about the fossils classified as Homo habilis, including whether they come from a single or multiple species, or even whether they should be part of the genus Homo at all.

Compared to the australopithecines, **Homo habilis has a somewhat larger brain size–an average of 650 cubic centimeters (cc) compared to less than 500 cc for Australopithecus.** Additionally, the skull is more rounded and the face less prognathic. However, the postcranial remains show a body size and proportions similar to Australopithecus. Known dates for fossils identified as Homo habilis range from about 2.5 million years ago to 1.7 million years ago.

Summary features of Homo habilis (adapted by Kenneth A. Koenigshofer, PhD, Chaffey College, from *Explorations: An Open Invitation to Biological Anthropology;* https://explorations.americananthro.....php/chapters/; Chapter 10, "Early Members of the Genus Homo" by Bonnie Yoshida-Levine Ph.D.; Beth Shook, Katie Nelson, Kelsie Aguilera, and Lara Braff, Eds.; licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, except where otherwise noted).

Hominin: Homo habilis

Dates 2.5 million years ago to 1.7 million years ago
Region(s): East and South Africa
Famous Discoveries: Olduvai Gorge, Tanzania; Koobi Fora, Kenya; Sterkfontein, South Africa

Brain Size: 650 cc average (range from 510 cc to 775 cc)
Dentition: Smaller teeth with thinner enamel compared to Australopithecus; parabolic dental arcade shape
Cranial Features: Rounder cranium and less facial prognathism than Australopithecus
Postcranial Features: Small stature; similar body plan to Australopithecus
Culture: Oldowan tools; oldest of known stone tool type; scrapers, choppers; indication of changing cognitive abilities

Stone tools almost certainly predated Homo habilis (possibly by Australopithecus garhi or the species responsible for the tools from Kenya dating to 3.7 million years ago). However, stone tools become more frequent at sites dating to about 2 million years ago, the time of Homo habilis (Roche, Blumenschine, and Shea 2009). This suggests that these hominins were increasingly reliant on stone tools to make a living.

Stone tools are assigned a good deal of importance in the study of human origins. **Studying the form of the tools, the raw materials selected, and how they were made and used can provide insight into the thought processes of early humans** and how they modified their environment in order to survive. Paleoanthropologists have traditionally classified collections of stone tools into industries, based on their form and mode of manufacture. There is not an exact correspondence between a tool industry and a hominin species; however, some general associations can be made between tool industries and particular hominins, locations, and time periods. The names for the four primary tool industries in human evolution (from oldest to most recent) are the Oldowan, Acheulean, Mousterian, and Upper Paleolithic. The oldest stone tool industry is the Oldowan, named after the site of Olduvai Gorge where the tools were first discovered. The time period of the Oldowan is generally considered to last from about 2.5 mya to 1.6 mya. The tools of this industry are described as “flake and chopper” tools—the choppers consisting of stone cobbles with a few flakes struck off them. To a casual observer, these tools might not look much different from randomly broken rocks. However, they are harder to make than their crude appearance suggests. The rock selected as the core must be struck by the rock serving as a hammerstone at just the right angle so that one or more flat flakes are removed. This requires selecting rocks that will fracture predictably instead of chunking, as well as the ability to plan ahead and envision the steps needed to create the finished product. The process leaves both the core and the flakes with sharp cutting edges that can be used for a variety of purposes.

What were the hominins doing with the tools? One key activity seems to have been butchering animals. Animal bones with cutmarks start appearing at sites with Oldowan tools. Studies of animal bones at the site show leg bones are often cracked open, suggesting that they were extracting the marrow from the bone cavities. It is interesting to consider whether the hominins hunted these animals or acquired them through other means. The butchered bones come from a variety of African mammals, ranging from small antelope to animals as big as wildebeest and elephants! It is difficult to envision slow, small-bodied Homo habilis with their Oldowan tools bringing down such large animals. One possibility is that the hominins were scavenging carcasses from lions and other large cats. Regardless of how they were acquiring the meat, all these activities suggest an important dietary shift from the way that the australopithecines were eating. The Oldowan toolmakers were exploiting a new ecological niche that provided them with more protein and calories. Overall, increasing use of stone tools allowed hominins to expand their ecological niche and exert more control over their environment. As we’ll see shortly, this pattern continued and became more pronounced with Homo erectus.

Discovery of *Homo habilis*

Homo habilis was first discovered by Louis and Mary Leakey at Olduvai Gorge, Tanzania in 1960. Associated with stone tools (Oldowan), the Leakeys named their discovery “handy man.” *H. habilis* fossils have been found in Tanzania, Kenya, Ethiopia, and South Africa, although there is some debate as to whether the South Africa specimens should be included in the species. Some researchers contend that there was another early *Homo* species, *Homo rudolfensis*, which dates back to 2.4-2.5 mya. The *H. rudolfensis* fossils are slightly larger than those of *H. habilis*, leading some researchers to suggest the *H. habilis* exhibited sexual dimorphism and what we are seeing are male and female specimens of *H. habilis*. Others claim the size differences are significant enough to warrant the two species designations (O’Neil 1999-2012). In 2013 a *Homo* mandible was discovered in the Ledi-Geraru research area, Afar, Ethiopia. Dated to 2.8 to 2.75mya, the mandible exhibits an *Australopithecus*-like chin and *Homo*-like teeth (Villmoare et al. 2015). While still early in the research process, this discovery and further research may push back the date of the origin of *Homo* and help to resolve the debate between the *H. rudolfensis* and *H. habilis* fossils. For our purpose, we will consider them all *H. habilis*, making the approximate date range for this hominin 2.5 to 1.4mya or less conservatively to 1.7mya.



Figure 9.3.19: *Homo habilis*.

Morphologically, *H. habilis* has a larger brain than the australopiths, about 35% larger (O'Neil c1999-2012). You will recall from the section on trends in human evolution that it is speculated that the brain also began to rewire at this point. *H. erectus* exhibits less prognathism (protrusion of the lower jaw) and platycephaly (flattening of the back of the head) than early hominins. The brow ridge is also smaller. All of these traits together make the face smaller than the australopiths. Postcranially, *H. habilis* exhibit a mix of primitive and derived traits. Primitive traits connecting it to an australopith ancestor are the longer forearms and the size of the finger bones along with how the tendons attach to the wrist bones. The tips of the finger bones are broad like humans. Smaller teeth, a dental arcade in the shape of a parabolic arch, foot morphology, and a more rounded skull complete the human-like traits. Microanalysis of tooth wear indicates that *H. habilis* was omnivorous.

Table 3.3.2

Key Homo habilis fossil locations and the corresponding fossils and dates (adapted by Kenneth A. Koenigshofer, PhD, Chaffey College, from *Explorations: An Open Invitation to Biological Anthropology;* https://explorations.americananthro.....php/chapters/; Chapter 10, "Early Members of the Genus Homo" by Bonnie Yoshida-Levine Ph.D.; Beth Shook, Katie Nelson, Kelsie Aguilera, and Lara Braff, Eds.; licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, except where otherwise noted).

Location of Fossils Dates (mya = millions of years ago) Description
Ledi-Gararu, Ethiopia 2.8 mya Partial lower jaw with evidence of both Australopithecus and Homo traits; tentatively considered oldest Early Homo fossil evidence.
Olduvai Gorge, Tanzania 1.7 mya to 1.8 mya. Several different specimens classified as Homo habilis, including the type specimen found by Leakey, a relatively complete foot, and a skull with a cranial capacity of about 600 cc.
Koobi Fora, Lake Turkana Basin, Kenya 1.9 mya. Several fossils from Lake Turkana basin show considerable size differences, leading some experts to classify the larger specimen as a separate species, *Homo rudolfensis*.
Sterkfontein and other possible about 1.7 mya South African caves have yielded fragmentary remains identified as Homo habilis, but South African cave sites secure dates and specifics about the fossils are lacking.

Homo erectus

About 1.9 mya, a new species of Homo appeared. Known as *Homo erectus*, the prevailing scientific view was that this species was much more like us. These hominins were equipped with bigger brains and large bodies with limb proportions similar to our own. Perhaps most importantly, their way of life is now one that is recognizably human, with more advanced tools, hunting, use of fire, and colonizing new environments outside of Africa.

Compared to Homo habilis, Homo erectus had a larger brain size (average of about 900 cc compared to 650 cc to 750 cc for habilis). Instead of having a rounded shape like our skulls have, the erectus skull was long and low like a football, with a receding forehead, and a horizontal ridge called an occipital torus that gave the back of the skull a squared-off appearance. The cranial bones are thicker than those of modern humans, and some Homo erectus skulls have a slight thickening along the sagittal suture called a sagittal keel. Large, shelf-like brow ridges hang over the eyes. As noted above, the climate was increasingly arid and the forest canopy in parts of Africa was being replaced with a more open grassland environment, resulting in increased sun exposure for our ancestors. Compared to the earlier australopithecines, members of the genus Homo were also developing larger bodies and brains, starting to obtain meat by hunting or scavenging carcasses, and crafting sophisticated stone tools. For purposes of cooling, H. erectus may have had little body hair accompanied by darkened skin to protect against sun exposure. It is generally agreed that Homo erectus was the first hominin to migrate out of Africa and colonize Asia and later Europe (although recent discoveries in Asia may challenge this view).

Homo erectus Fossils

Based on current fossil data, *Homo erectus* existed between 1.9 million (mya) to 25 thousand years ago (Jurmain 2013). *H. erectus*, literally "upright human," fossils have been found in Java (Indonesia), Africa, China, Europe, and Israel. Based on morphological differences in the cranium, some scientists identify two species, *H. erectus* in Asia and *H. ergaster* in Africa with the African specimens being smaller than the Asian; however, we will use the *H. erectus* designation for both.



Figure 9.3.20: *Homo erectus,* Turkana Boy.

In 1984, a nearly complete *H. erectus* skeleton was found along a river in northern Kenya. Potassium-argon dating places "Turkana Boy" between 1.64 and 1.33 million years ago (mya). Aging and sexing of the fossil remains indicate that the individual was a male about age eight. He stood about 5'3" tall. Recent studies indicate that Turkana Boy followed the growth pattern of apes, so would have been near his adult height at the time of his death (Jurmain et al. 2013).

Homo erectus has a long history in Indonesia; fossils from Java were dated by argon dating to about 1.6 million to 1.8 million years. *H. erectus* fossils from the site of Ngandong in Java have yielded very recent dates of 43,000 years, although a more recent study with different dating methods concluded that they were much older—between 140,000 and 500,000 years old.

The pattern of increased brain size continued with *H. erectus*; its brain is up to 50% larger than its predecessor, *H. habilis* (O'Neil c1999-2012). This large brain was supported by a diet heavy in meat and other proteins. Its distinguishing characteristics include its sagittal keeling (a thickening of bone that runs from front to back on top of the skull; likely for muscle attachment) massive brow ridges (supraorbital tori) and bony prominences on the back of the skull. Postcranially, *H. erectus*' bones are thicker than *H. habilis*, as were its jaws and face bones, and the proportion of arms to legs is like that of modern humans, causing some to suggest that its bipedal gait was like ours. The length of its leg bones indicates that *H. erectus* would have been an efficient long-distance runner, allowing them to "run down small and even medium size game animals on the tropical savannas of East Africa" (O'Neil c1999-2012). If so, as mentioned above, it is likely that *H. erectus* had much less body hair than its predecessors,

as they would have needed to be able to sweat efficiently to cool the body. It is possible that *H. erectus* had little body hair (NOVA 2011). During the Pleistocene, the climate was increasingly arid and the forest canopy in parts of Africa was being replaced with a more open grassland environment, resulting in increased sun exposure for our ancestors.

Compared to the earlier australopithecines, members of the genus *Homo* were also developing larger bodies and brains, starting to obtain meat by hunting or scavenging carcasses, and crafting sophisticated stone tools. According to Nina Jablonski, an expert on the evolution of human skin, the loss of body hair and increased sweating capacity are part of the package of traits characterizing the genus *Homo*. While larger brains and long-legged bodies made it possible for humans to cover long distances while foraging, this new body form had to cool itself effectively to handle a more active lifestyle. Preventing the brain from overheating was especially critical. The ability to keep cool may have also enabled hominins to forage during the hottest part of the day, giving them an advantage over savanna predators, like lions, that typically rest during the heat of the day.

As noted above, scientists generally agree that *H. erectus* was the first hominin to leave Africa. As mentioned previously, fossils have been found in Africa, northern China, Indonesia, Europe, and Israel. In the Republic of Georgia, fossils were found in strata dated to 1.7mya suggesting that *H. erectus* left Africa soon after it evolved. A recent report (Dembo et al. 2015) posits that *H. habilis* was the first hominin to leave Africa, not *H. erectus*. Should this contention be supported with more data, it can still be argued that *H. erectus* was quite successful in colonizing the Old World (Africa, Europe, and Asia), helped, no doubt, by its advanced cultural behaviors.

Now we can address the question of why *Homo erectus* traveled such vast distances to these far-flung regions. To do this, we have to consider what we have learned about the biology, culture, and environmental circumstances of *Homo erectus*. The larger brain and body size of *Homo erectus* were fueled by a diet consisting of more meat, and longer more powerful legs made it possible to walk and run longer distances to acquire food. Since they were eating higher on the food chain, it was necessary for them to extend their home range to find sufficient game. Cultural developments including better stone tools and new technology such as fire gave them greater flexibility in adapting to different environments. Finally, the major Pleistocene climate shift discussed earlier in the chapter certainly played a role. Changes in air temperature, precipitation, access to water sources, and other habitat alteration had far-reaching effects on animal and plant communities; this included *Homo erectus*. If hominins were relying more on hunting, the migration patterns of their prey could have led them increasingly long distances.

There is evidence of *Homo erectus* in China from several regions and time periods. *Homo erectus* fossils from northern China, collectively known as “Peking Man,” are some of the most famous human fossils in the world, dated to about 400,000–700,000 years ago. The discovery of stone tools from China dating to 2.1 million years, older than any *Homo erectus* fossils anywhere, opens up the intriguing possibility that hominins earlier than *Homo erectus* could have migrated out of Africa.

At this time, researchers aren’t in agreement as to whether the first Europeans belonged to *Homo erectus* proper or to a later descendent species.

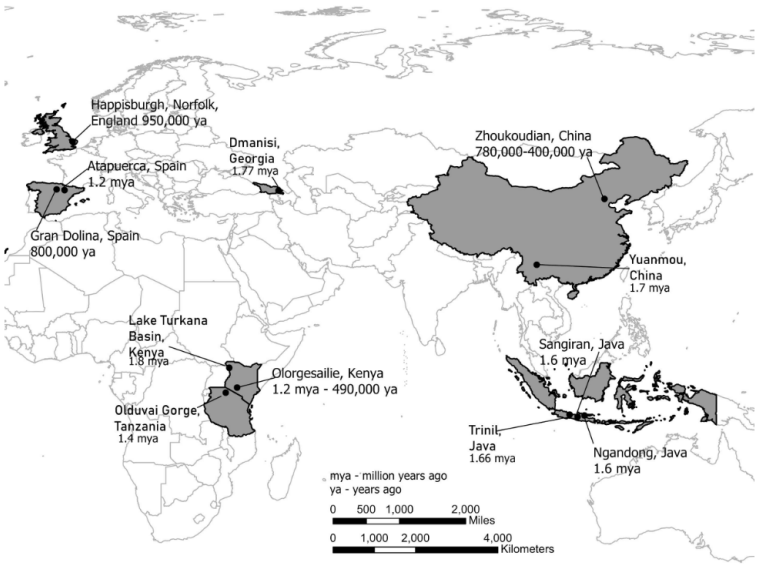


Figure 9.3.21: Map showing the locations of Homo erectus fossils around Africa and Eurasia (adapted by Kenneth A. Koenigshofer, PhD, Chaffey College, from *Explorations: An Open Invitation to Biological Anthropology;*

https://explorations.americananthro.....php/chapters/; Chapter 10, "Early Members of the Genus Homo" by Bonnie Yoshida-Levine Ph.D.; Beth Shook, Katie Nelson, Kelsie Aguilera, and Lara Braff, Eds.; licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, except where otherwise noted).

Homo erectus Culture

Homo erectus shows significant cultural innovations in diet, technology, life history, environments occupied, and perhaps even social organization, some that you will probably recognize as more “human-like” than any of the hominins previously covered. About 1.5 million years ago, some Homo erectus populations began making different forms of tools (known as "material culture"). These tools–classified together as constituting the Acheulean tool industry–are more complex in form and more consistent in their manufacture. Unlike the Oldowan tools, which were cobbles modified by striking off a few flakes, Acheulean toolmakers carefully shaped both sides of the tool. This type of technique, known as bifacial flaking, requires more planning and skill on the part of the toolmaker; he or she would need to be aware of principles of symmetry when crafting the tool. One of the most common tool forms of this period was the handaxe. Besides handaxes, forms such as scrapers, cleavers, and flake tools are present at Homo erectus sites. One striking aspect of Acheulean tools is their uniformity. They are more standardized in form and mode of manufacture than the earlier Oldowan tools. For example, the aforementioned handaxes vary in size, but they are remarkably consistent in regard to their shape and proportions. They were also an incredibly stable tool form over time—lasting well over a million years with little change.

Recently, newer methods—including microscopic analysis of burned rock and bone—have revealed clear evidence of fire use at Koobi Fora, Kenya, dating to 1.5 million years ago (Hlubik et al. 2017).

There is general consensus that *H. erectus* evolved from *H. habilis* and *Homo heidelbergensis* evolved from *H. erectus* in Africa, eventually supplanting *H. erectus* populations in the Old World--Africa, Asia, and Europe (Figure 9.3.18).

Tool Use and Cognitive Abilities of Homo erectus

What (if anything) do the Acheulean tools tell us about the mind of Homo erectus? Clearly, they took a fair amount of skill to manufacture. Apart from the actual shaping of the tool, other decisions made by toolmakers can reveal their use of foresight and planning. Did they just pick the most convenient rocks to make their tools, or did they search out a particular raw material that would be ideal for a particular tool? Analysis of Acheulean stone tools suggest that at some sites, the toolmakers selected their raw materials carefully—traveling to particular rock outcrops to quarry stones and perhaps even removing large slabs of rock at the quarries to get at the most desirable material. Such complex activities would require advanced planning. They also likely required cooperation and communication with other individuals, as such actions would be difficult to carry out solo. However, other Homo erectus sites lack evidence of such selectivity; instead of traveling even a short distance for better raw material, the hominins tended to use what was available in their immediate area (Shipton et al. 2018). In contrast to Homo erectus tools, the tools of early modern Homo sapiens during the Upper Paleolithic display tremendous diversity across regions and time periods. Additionally, Upper Paleolithic tools and artifacts communicate information such as status and group membership. Such innovation and social signaling seem to have been absent in Homo erectus, suggesting that they had a different relationship with their tools than did Homo sapiens (Coolidge and Wynn 2017). Some scientists assert that these contrasts in tool form and manufacture may signify key cognitive differences between the species, such as the ability to use a complex language.

Table 3.3.3. Characteristics of Homo erectus. (adapted by Kenneth A. Koenigshofer, PhD, Chaffey College, from *Explorations: An Open Invitation to Biological Anthropology;* https://explorations.americananthro.....php/chapters/; Chapter 10, "Early Members of the Genus Homo" by Bonnie Yoshida-Levine Ph.D.; Beth Shook, Katie Nelson, Kelsie Aguilera, and Lara Braff, Eds.; licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, except where otherwise noted).

Hominin	*Homo erectus*
Dates	1.8 million years ago to about 200,000 years ago
Region(s)	East and South Africa; West Eurasia; China and Southeast Asia

Famous Discoveries	Lake Turkana, Olorgesailie, Kenya; Zhoukoudian, China; Dmanisi, Republic of Georgia
Brain Size	Average 900 cc; range between 650 cc and 1,100 cc
Dentition	Smaller teeth than *Homo habilis*
Cranial Features	Long, low skull with robust features including thick cranial vault bones and large brow ridge, sagittal keel, and occipital torus
Postcranial Features	Larger body size compared to *Homo habilis*; body proportions (longer legs and shorter arms) similar to *Homo sapiens*
Culture	Acheulean tools (in Africa); evidence of increased hunting and meat-eating; use of fire; migration out of Africa

THE BIG PICTURE OF EARLY *HOMO*

We are discovering that the evolution of the genus *Homo* is more complex than what was previously thought. The earlier prevailing view of a simple progression from *Australopithecus* to *Homo habilis* to *Homo erectus* as clearly delineated stages in human evolution just doesn't hold up anymore.

Variability in the Fossil Record of Early Homo

As is apparent from the information presented here, there is tremendous variability during this time. While fossils classified as *Homo habilis* show many of the characteristics of the genus *Homo*, such as brain expansion and smaller tooth size, the small body size and long arms are more akin to australopithecines. There is also tremendous variability within the fossils assigned to *Homo habilis*, so there is no consensus on whether it is a single or multiple species of *Homo*, a member of the genus *Australopithecus*, or even a yet-to-be-defined new genus.

What does this diversity mean for how we should view early *Homo*? First, there isn't an abrupt break between *Australopithecus* and *Homo habilis* or even between *Homo habilis* and *Homo erectus*. Characteristics we define as *Homo* don't appear as a unified package; they appear in the fossil record at different times. This is known as mosaic evolution.

We can consider several explanations for the diversity we see within early *Homo* from about 2.5 million to 1.5 million years ago. One possibility is the existence of multiple contemporaneous species of early *Homo* during this period. In light of the pattern of environmental instability discussed earlier, it shouldn't be surprising to see fossils from different parts of Africa and Eurasia display tremendous variability. Multiple hominin forms could also evolve in the same region, as they diversified in order to occupy different ecological niches. However, even the presence of multiple species of hominin does not preclude their interacting and interbreeding with one another.

Diversity of brain and body sizes could also reflect developmental plasticity—short-term adaptations within a lifetime (Anton, Potts, and Aiello, 2014). These have the advantage of being more flexible than genetic natural selection, which could only occur over many generations. For example, among human populations today, different body sizes are thought to be adaptations to different climate or nutritional environments.

Trends in the Behavior of Early Homo

New discoveries are also questioning old assumptions about the behavior of *Homo habilis* and *Homo erectus*. Just as the fossil evidence doesn't neatly separate *Australopithecus* and *Homo*, evidence of the lifeways of early *Homo* show similar diversity. For example, one of the traditional dividing lines between *Homo* and *Australopithecus* was thought to be stone tools: *Homo* made them; *Australopithecus* didn't. However, the recent discovery of stone tools from Kenya dating to 3.3 million years ago challenges this point of view. Similarly, the belief that *Homo erectus* was the first species to settle outside Africa may now come into question with the report of 2.1 million-year-old stone tools from China. If this find is supported by additional evidence, it may cause a reevaluation of *Homo erectus* being first to leave. Instead, there could have been multiple earlier migrations of hominins such as *Homo habilis* or even *Australopithecus* species.

Rather than obvious demarcations between species and their corresponding behavioral advancements, it now looks like many behaviors were shared among species. Despite the haziness dominating the early *Homo* narrative, we can identify some overall trends for the million-year period associated with early *Homo*. These trends include brain expansion, a reduction in facial prognathism, smaller jaw and tooth size, larger body size, and evidence of full terrestrial bipedalism. These traits are associated with a key behavioral shift that emphasizes culture as a flexible strategy to adapt to unpredictable environmental circumstances. Included in this repertoire are the creation and use of stone tools to process meat obtained by scavenging and later hunting, a utilization of fire and cooking, and the roots of the human life history pattern of prolonged childhood, cooperation in child raising, and the practice of skilled foraging techniques. In fact, it's apparent that the cultural innovations are driving the biological changes, and vice versa, fueling a feedback loop that will continue during the later stages of human evolution.

Homo heidelbergensis : the common ancestor of *Homo neanderthalensis* in Europe and *Homo sapiens* in Africa.

Some publications, e.g. Larsen 2014, refer to *H. heidelbergensis* as archaic *Homo sapiens*, but for our purposes, we will use the *H. heidelbergensis* designation. Otto Schoetensack found the first *Homo heidelbergensis* fossils in 1907 in Mauer, Germany. Since then *H. heidelbergensis* fossils have been found in Africa, Europe, and Asia. The date range for the species is 800 kya (thousand years ago) to 350 kya. Primitive traits (traits like the ancestors) include its large supraorbital tori (brow ridge), sagittal keeling, and low frontal bone. Derived traits (traits different from the ancestor) include separate supraorbital tori over each eye orbit, a more vertical posterior cranial vault, wide parietal bones in relation to the cranial base, and a larger cranial capacity than *H. erectus* (Becoming Human c2008). Additionally, they exhibit sexual dimorphism similar to that of modern humans.



Figure 9.3.22: *Homo heidelbergensis* skull on mirrored steel stand showing reflection of palate and dentition in upper jaw.

There is regional variation in the morphology of *H. heidelbergensis*. European specimens found at Atapuerca, (Spain), Petralona (Greece), Seinheim (Germany), and Swancombe (England) show that they had compact bodies, which could have been a response to living in the cold climates of the north as it would help to conserve heat. Additionally, the cranium is a mosaic of *H. erectus* traits and derived traits. In Asia, data from sites such as Zhoukoudian, Jinniushan, and Dali (China) show a mix of *H. erectus* and *H. sapiens* traits; the latter includes large cranial capacity and thin braincase walls. African specimens from Kabwe (Zambia),

Florisbad (South Africa), Laetoli (Tanzania), and Bodo (Ethiopia) also show a combination of *H. erectus* and *H. sapiens* traits. It shares the massive supraorbital tori and prominent occipital torus with *H. erectus* and thin cranial vault bones, less angulated occipital, and cranial base with *H. sapiens*.

Significantly, *H. heidelbergensis* is the common ancestor of *Homo neanderthalensis* in Europe and *Homo sapiens* in Africa.

Homo neanderthalensis

Numerous Neanderthal fossils have been recovered since its discovery in 1856 in the Neander Valley, Germany. Neanderthals have been the speculation of scientists and the general public ever since. Some anthropologists classify Neanderthals as a subspecies of *Homo sapiens*, *Homo sapiens neanderthalensis*, while others interpret the morphological differences as significant enough to warrant classifying them as a different species, *Homo neanderthalensis*. Here, we will use the latter designation.



Figure 9.3.23: *Homo neanderthalensis*.

True Neanderthals first appear in the fossil record about 200,000 years ago (200 kya), with fossils exhibiting Neanderthal-like characteristics appearing as early as 400 kya. Recent research indicates that Neanderthals went extinct only about 40,000 years ago, between 41 kya and 39 kya (Higham et al., 2014). Molecular research denotes that some Neanderthal DNA lives on in modern humans, approximately 2% of the DNA of "people who descend from Europeans, Asians, and other non-Africans is Neanderthal" (Callaway, 2014). The Neanderthal genes are involved in fighting infections, dealing with ultraviolet radiation (Callaway, 2014), and living at high altitudes (Callaway, 2015). Neanderthal DNA has recently been linked with depression, obesity, and certain skin disorders, e.g., lesions caused by sun exposure (Callaway, 2015).

Neanderthals are the only hominin to originally evolve in a glacial environment, leading to some characteristics adapted for the cold climate. Many scientists contend that the midface prognathism (protruding midface) allowed for enlarged sinuses that functioned to warm and add moisture to the cold, dry air before entering the lungs. Small holes below the eye orbits, called the infraorbital foramina, are larger in the European Neanderthals that modern humans, suggesting that the blood vessels were larger, which allowed for more blood flow to the face. This would have helped keep the face warmer. They are relatively short and stocky, males averaging 5' 5" and females 5'1", with shorter appendages, both of which would help to conserve heat by providing less surface area from which to radiate heat. Their leg bones are thick and dense, suggesting that they frequently walked and ran, most likely in food procurement activities. Some postulate that some Neanderthals had pale skin that would have helped increase Vitamin D synthesis by increasing the amount of UV radiation to be absorbed by the body (O'Neil, c1999-2014). The width of their body trunks and short tibias fit the predictions for cold weather adaptation as proposed by Christopher Ruff (Larsen, 2013). The brain size of Neanderthals may also be related to cold weather. Averaging a cranial capacity between 1300 to 1400 cm3, they have the largest brains of all hominins, including our own species, Homo sapiens. The size may be associated with increased metabolic efficiency in cold weather, which is similar to modern Inuit peoples today who have a larger brain size than other human populations (Jurmain et al., 2013).

The presence of an occipital bun (a prominent bulge at the lower back of the skull) is one of the characteristics used to identify *H. neanderthalensis* specimens, although it should be noted that this characteristics persists in a small percentage of modern

human populations. The occipital bun may have evolved to counterbalance Neanderthal's heavy face when running; it prevents the head from making huge horizontal accelerations (NOVA 2002). The occipital bun also makes the skull elongated in comparison to most *Homo sapiens*. They had heavy brow ridges like those of *H. heidelbergensis*. Neanderthal skulls recovered from Amud and Tabun in Israel exhibit more *H. sapiens*-like cranial characteristics, including lack of an occipital bun, smaller eye orbits, tall and wide nasal openings, and smaller teeth (Larsen 2014).

Denisovans

The Denisovans were archaic humans closely related to Neanderthals, whose populations overlapped geographically with the ancestors of modern-day humans who existed at the same time. In 2010, scientists announced the discovery and DNA analysis of a finger bone and two teeth found in Denisova Cave, Siberia (Reich et al., 2010). The artifacts were recovered from a deposit dated to 50 kya to 30 kya. Data suggest that the remains were from an individual who shared a common origin with Neanderthals, but was not a Neanderthal, nor was it a modern human. The Denisovan individual(s) share 4-6% of its genetic material with modern peoples living in New Guinea, Bougainville Islands, and China. Further studies (Cooper and Stringer, 2013) indicate that the Denisovans crossed Eurasia and interbred with modern humans, but genetically the Denisovans were more closely related to Neanderthals than modern humans (Meyer et al., 2012). While further finds will shed more light on the Denisovans, it is clear that there was more genetic variability during the Pleistocene than previously thought (Larsen, 2014), but that gene flow between the various populations had implications for the emergence of modern humans (Pääbo, 2015).

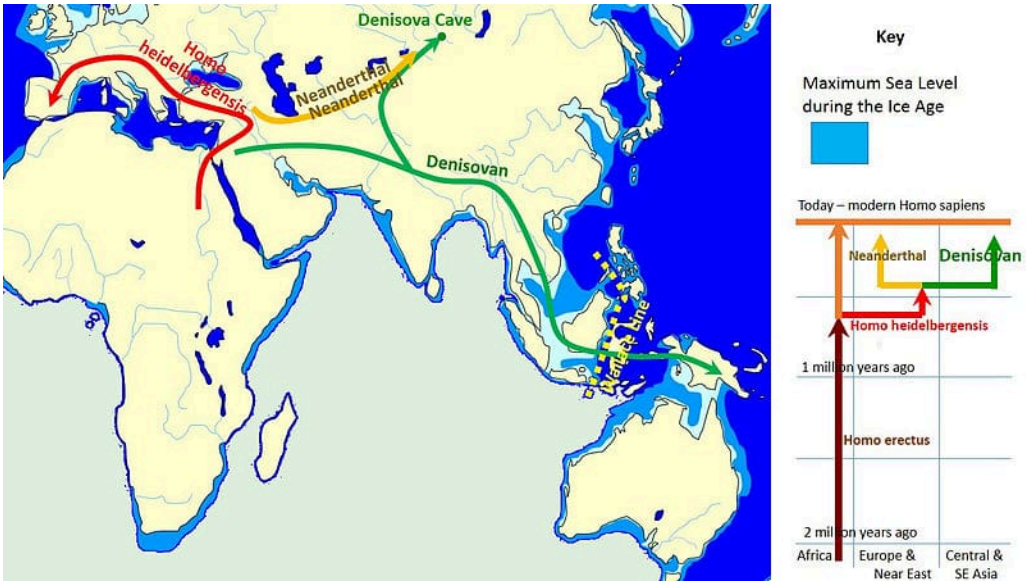


Figure 9.3.24: Spread and Evolution of Denisovans.

Homo floresiensis

In 2003, a team of scientists discovered unusual fossils in Liang Bua cave, Flores Island, Indonesia. The small stature of the individual led to the naming of a new species, *Homo floresiensis*. Since then twelve individuals have been found ranging in time from 74 kya to 17 kya. *H. floresiensis* had a small brain and stood only about 3.5' tall as an adult. They had receding foreheads, no chins, shrugged-forward shoulders, and large feet relative to their short legs. They share some characteristics with *H. sapiens*, including smaller dentition, separate brow ridges, and a non-prognathic face (flattened face).



Figure 9.3.25: *Homo floresiensis*.

Several hypotheses have been proposed to explain the appearance of *H. floresiensis*. One suggests that we are seeing island dwarfism, which is an evolutionary process resulting from long-term isolation on a small island. Limited resources and lack of predators selects for smaller bodied individuals who need fewer resources then large-bodied individuals. Another hypothesis claims that *H. floresiensis*is is not a separate species, but *H. sapiens* exhibiting microcephaly or some other developmental deficiency such as hyperthyroid cretinism (Oxnard et al. 2010) because the "...cranial features...are within the modern range of variation seen in living populations from the larger region [of Indonesia]" (Larsen 2014: 409), lending support to the second hypothesis. How *H. floresiensis* fits into the evolutionary picture is unclear based on the current data.

Homo sapiens

At present, only one hominin species inhabits planet Earth, *Homo sapiens*. All other *Homo* species became extinct by approximately 30,000 to 40,000 years ago. Many scientists believe that these extinctions were driven by competition from *Homo sapiens*. Morphologically, *H. sapiens* characteristics include the presence of a chin, a large brain, flat face, rounded or globular cranium, and a continuous, reduced brow ridge. Its bones are gracile (slender) in comparison to earlier hominins, although the earliest *H. sapiens* are more robust than modern populations and show none of the cold weather adaptations of Neanderthals. The more gracile nature lends credence to the hypothesis that modern humans evolved first in Africa. The leaner body proportions are more adaptive to the tropical African environments as there would be more body surface area to radiate heat. DNA evidence also supports an African origin. Modern African populations have more genetic diversity than any other modern human population, inferring that they have been evolving longer (Becoming Human c2008).



Figure 9.3.26: *Homo sapiens*.

The oldest *Homo sapiens* fossils were found in Africa at Omo Kibish, Ethiopia, dated to almost 200,000 years ago (195 kya; kya = 1,000 years ago). *Homo sapiens* fossils found at Herto, Ethiopia (160 kya–154 kya), Klasies River Mouth and Border Cave, South Africa (120 kya – 89 kya), Skhūl, Israel (130 kya–100 kya), and Qafzeh, Israel (120 kya–92 kya), add further support to the age of *Homo sapiens*. Sites in Asia, e.g., in China and Borneo, Indonesia date to 40 kya or younger and in Europe date no earlier then 31 kya (Mladeč, Czech Republic). Modern humans somehow made it to Australia over open ocean by 55 kya; however, no human remains have been found on the Australian continent dating earlier than 30 kya at Lake Mungo. This data lends little support for the Multiregional Hypothesis, a model that proposed that modern *H. sapiens* evolved in separate places in the Old World from local archaic *H. sapiens* populations. This model suggested that gene flow between the populations led to the genetic similarity of modern humans. Most anthropologists support the model of an African origin. There are two variants of this model. The Out of Africa model claims that modern humans arose in Africa and spread to Europe after 50 kya, replacing non-*H. sapiens* population with no gene flow. An alternative is the Assimilation model that also claimed modern human first arose in Africa and spread to Europe and Asia. The primary difference between the Out of Africa and Assimilation models is that the latter does claim gene flow between *H. sapiens* and *H. neanderthalensis*. Taking into account the recent DNA analyses of Neanderthals discussed above, multiple lines of evidence support the Assimilation model.

The case of the disappearing Neanderthals

We know that some Neanderthal genes are in the genome of modern humans, so in essence, some part of the Neanderthals survives today. However, there are no Neanderthals walking around in the modern world. So, what happened to the Neanderthals? Scientists suggest that *H. sapiens* out-competed Neanderthals with their more diverse diet and "sophisticated and cognitive abilities" (Becoming Human c2008), which may have included superior ability to form visual imagery in imagination to forecast outcomes of future actions, thereby enhancing planning and inventiveness (Koenigshofer, 2017). These traits allowed *H. sapiens* to readily adapt to rapidly changing climatic conditions during the Upper Paleolithic.

A recent hypothesis suggests that Neanderthals died out during a period of powerful volcanic activity in western Eurasia. Excavations at Mezmaiskaya Cave in the Caucasus Mountains in southern Russia have recovered a plethora of Neanderthal bones, stone tools, and remains of prey animals. The Neanderthal remains and artifacts appear in strata above a layer of volcanic ash and below a second layer of volcanic ash. No Neanderthal bones or artifacts have been found above the second level, suggesting that Neanderthals no longer occupied the area. Both of the ash layers contain levels of pollen associated with cooler, drier climates. "The ash layers correspond chronologically to what is known as the Campanian Ignimbrite super-eruption, which occurred around 40,000 years ago in modern day Italy, and a smaller eruption thought to have occurred around the same time in the Caucasus Mountains" (University of Chicago Press Journals 2010). The ensuing volcanic winter caused a dramatic climate shift that led to the demise of the Neanderthals. This data correlates with Higham et al.'s (2014) research that claims Neanderthals went extinct between 41,000 and 39,000 years ago.

Brain Evolution

Many scientists (Cajal, 1937; Crick & Koch, 1990; Edelman, 2004) believe that the human brain is the most complex machine in the known universe. Its complexity points to one undeniable fact—that it has evolved slowly over time from simpler forms. Evolution of the brain is intriguing not only because we can marvel at this complicated biological structure, but also because it reveals a long history of many less complex nervous systems (Figure 3.3.25), suggesting a record of adaptive behaviors in life forms other than humans. Thus, evolutionary study of the nervous system is important, and it is the first step in understanding its design, its workings, and its functional interface with the environment.

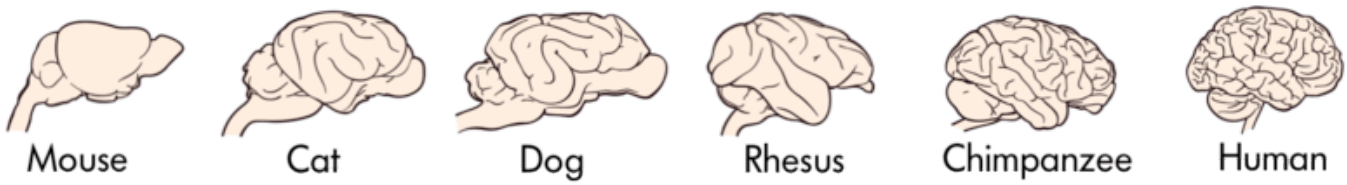


Figure 9.3.27: The brains of various mammals (not to scale). The brains shown are artificially depicted as approximately equal in size. Though the vast differences in the actual size of these brains is not shown, it is still possible to see the increasing degree of folding of the cerebral cortex as indicated by the greater number of fissures and gyri (valleys and hills on the surface of the cortex, indicated by the number of lines) on the surface of the chimpanzee and human brains compared to the others. Note that the mouse cortex is smooth, showing no folding at all indicating less corticalization--cortical development. The greatest folding of the cerebral cortex occurs in humans revealing a trend in mammalian and primate evolution toward increasing corticalization along with increasing brain size.

The brains of some animals, other mammals, like apes, monkeys, and rodents, are structurally similar to humans (Figure 3.3.27), while others are not (e.g., invertebrates such as the octopus). Does anatomical similarity of these brains suggest that behaviors that emerge in these species are also similar? Indeed, many animals display behaviors that are similar to humans, e.g., apes use nonverbal communication signals with their hands and arms that resemble nonverbal forms of communication in humans (Gardner & Gardner, 1969; Goodall, 1986; Knapp & Hall, 2009). If we study very simple physiological responses made by individual neurons (nerve cells), the neural responses of invertebrates such as the sea slug (Kandel & Schwartz, 1982) look very similar to the neural responses of single neurons in mammals, including humans, suggesting that from time immemorial such basic functions of individual nerve cells in the brains of many simple animal forms have been conserved over the course of evolution of more complex animals and that in fact these fundamental features of nerve cells are the foundation of more complex behaviors in animals that evolved later (Bullock, 1984).

Although basic physiological processes in nerve cells are very similar across species, nevertheless even at the micro-anatomical level, we note that individual neurons differ in complexity in some respects across animal species. Human neurons exhibit more intricate complexity than neurons in other animals; for example, neuronal processes (dendrites, which receive input from other neurons) in humans have many more branch points, branches, and dendritic spines associated with connections between neurons.

Complexity in the structure of the nervous system, both at the macro- and micro-levels, gives rise to complex behaviors. We can observe similar movements of the limbs, as in nonverbal communication, in apes and humans, but the variety and intricacy of nonverbal behaviors using hands in humans surpasses apes. This is related to the fact that humans have more neurons for the control of movement of the hands than apes do. Deaf individuals who use American Sign Language (ASL) express themselves in English nonverbally; they use this language with such fine gradation that many accents of ASL exist (Walker, 1987). Complexity of behavior with increasing complexity of the nervous system, especially the cerebral cortex, can be observed in the genus *Homo* (Figures 3.3.27 and 3.3.28). If we compare sophistication of material culture in **Homo habilis** (2 million years ago; brain volume ~650 cm3) and **Homo sapiens** (300,000 years to now; brain volume ~1400 cm3), the evidence shows that *Homo habilis* used crude stone tools in stark contrast with modern tools used by *Homo sapiens* to erect cities, develop written languages, create complex industries, and embark on space travel. All of this is due to increasing complexity of the brain.

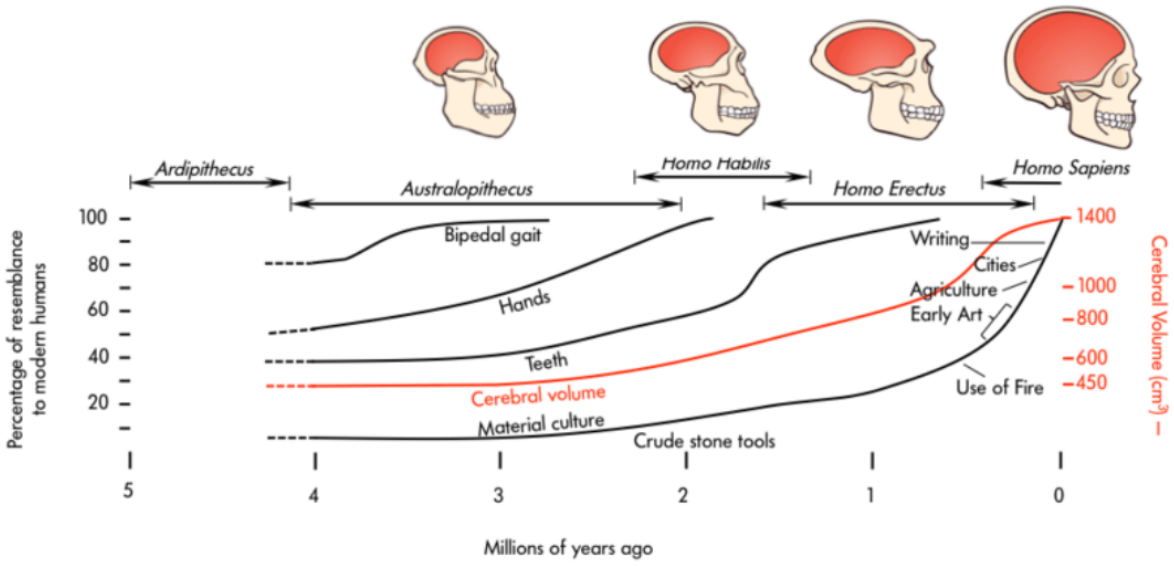


Figure 9.3.28: Increasing brain volume and other anatomical and behavioral features including development of material culture (including stone tools) over hominin evolution. Note that both brain volume and cultural advances accelerate after first use of fire. Missing from this diagram is the 1,400 cubic centimeter brain of Neanderthals, equal or slightly larger than the brain of modern humans.

What led to the complexity of the brain and nervous system during evolution, and the accompanying refinement of behavior and cognition? Darwin (1859, 1871) proposed two forces: natural selection and sexual selection as work engines driving these changes. As noted previously, Darwin prophesied, “psychology will be based on a new foundation, that of the necessary acquirement of each mental power and capacity by gradation.” In other words, Darwin predicted that psychology will be based on evolution (Rosenzweig, Breedlove, & Leiman, 2002).

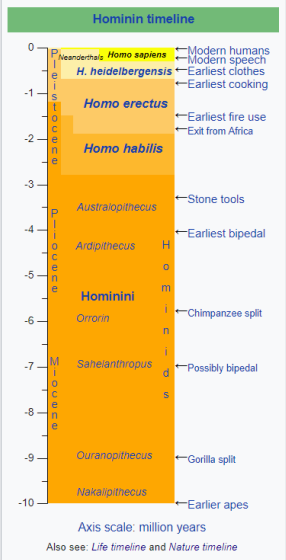


Figure 9.3.29: Hominin timeline highlighting evolutionary splits (divergences) from gorilla and chimpanzee genetic lines, major behavioral/cultural innovations, and migration out of Africa. Not shown is migration of Homo sapiens into Europe about 45,000 years ago where they co-existed with Neanderthals for thousands of years (Image from Wikimedia Commons; File:HumanTimeline-TemplateImage-20181222.png; https://commons.wikimedia.org/wiki/F...e-20181222.png; by Drbogdan; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Tool Use, Evolution of Intelligence, and the Brain

As the discussion above attests, tool construction and use is ancient in the genus *Homo* dating back millions of years at least to Australopithecus. Cachel (2012, p. 222) states, "Human tool behavior is species-specific. It remains a diagnostic feature of humans." According to Osiurak and Massen (2014, p.1107),"Tool use has also been often viewed as an important step during evolution (van Schaik et al., 1999) or even as a marker of the evolution of human intelligence." Vaesen (2012, p. 203) argues that human tool making and tool use provide evidence of "unique higher cognitive ability" in humans and mark "a major cognitive discontinuity" between humans and apes. According to Vaesen (p. 203), there are "nine cognitive capacities deemed crucial to tool use: enhanced hand-eye coordination, body schema plasticity, causal reasoning, function representation, executive control, social learning, teaching, social intelligence, and language. Since striking differences between humans and great apes stand firm in eight out of nine of these domains, [he] conclude[s] that human tool use still marks a major cognitive discontinuity between us and our closest relatives." He also "address[es] the evolution of human technologies. In particular, [he] show[s] how the cognitive traits reviewed help to explain why technological accumulation evolved so markedly in humans, and so modestly in apes." Technological accumulation refers to the accumulation of technological innovations over generations leading to ever increasing technological complexity. This is closely tied to the great capacity of humans for efficient cultural transmission of learned behaviors over successive generations, an ability that occurs in apes only to a relatively limited degree. Vaesen (p. 213) explains: "The complexity of human technologies is tightly linked to our remarkable ability for **cumulative culture** [bold added]: Humans have been able to build complex systems by accumulating modifications over successive generations, gradually improving on previous achievements." This requires "sophisticated mechanisms for social learning and active teaching," in which language certainly played a part, but it is "likely that other cognitive capacities need to be added; for example, . . . causal thought is part and parcel of human social learning, and hence," is also needed for "high-fidelity cultural transmission" (p. 214). Vaesen further emphasizes this point: "causal thought (whenever it emerged) is a plausible explanans for why cumulative culture evolved so markedly in humans and so modestly in apes" (p.214). Cachel (2012, p. 222) goes further and states that experiments demonstrate the "great gulf that exists between human causal reasoning and the reasoning abilities of chimpanzees. In fact, chimpanzees do not seem to have a “theory of how the world works.” If this is so, then it epitomizes the unique character of human tool behavior – that it is based on the unconscious, sophisticated knowledge of energy, movement, objects, and the interaction of objects that Povinelli et al. (2000) label 'folk physics'.” Causal reasoning lowers individual learning costs, making learning by individuals more efficient, "by making individual learning reasoned rather than random" (Vaesen, 2012, p.215). Vaesen also argues that executive control involving inhibition of current drives and focus of attention contributes in a similar way.

Vaesen (2012) describes the work of other researchers who have identified brain areas involved in tool use. Vaesen (p.204) writes "Orban and colleagues (2006) identified a set of functional regions in the **dorsal intraparietal sulcus** (IPS) of the human brain

that is involved in representations of the central visual field and in the extraction of three-dimensional form from motion. Crucially, these brain regions were not found in the brains of monkeys. The regions subserve, the authors conjectured, the enhanced visual analysis necessary for the precision with which humans manipulate tools. Second, Stout and Chaminade (2007) found that parts of these regions were indeed recruited when modern human subjects engaged in Oldowan-like tool making. Importantly, no increased activation was observed when the human subjects were asked just to strike cobbles together without intending to produce flakes. Human dorsal IPS, thus, may allow for better identification of suitable targets on the core, and as such, explain in part why humans outperform other primates in matters of tool use."

Additional insights regarding tool use and the brain come from study of brain-damaged individuals. Osiurak and Massen (2014, p. 1107) review results of studies of "patients with tool use disorders, also called apraxia of tool use. When asked to light a candle, for example, those patients can light the candle correctly but then put it to the mouth in an attempt to smoke it. Such observations have led traditional cognitive models of apraxia to assume that tool use is supported by sensorimotor knowledge about tool manipulation . . . This sensory-motor hypothesis assumes that manipulation knowledge stored within **inferior fronto-parietal** areas [of the cerebral cortex] is critical to tool use skills." This may be the case because "the **left inferior parietal lobe** might rather support technical reasoning, namely, the ability to reason about physical object properties. . . . the ability to understand mechanical actions might be the specificity of the **anterior** portions of the **inferior parietal lobe** (particularly the supramarginal gyrus) while the **posterior parietal cortex** might be involved in the planning of the grasping and reaching components of both tool-use and non-tool-use actions."

File:ParietCapts lateral.png

Figure 9.3.30: The human right cerebral cortex highlighting parts of the parietal lobe. Folds on the surface of the cortex form hills (gyri, singular, gyrus) and valleys (fissures or sulci; singular, sulcus). The central sulcus divides the frontal lobe from the parietal lobe behind it. The parietal lobe, especially on the right side of the brain, processes information about space and spatial relations. Regions of the parietal lobe are involved in tool construction and tool use, important in human evolution. See text for details. (Image from Wikimedia Commons; File:ParietCapts lateral.png; https://commons.wikimedia.org/wiki/F...ts_lateral.png; author, Sebastian023; licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. Caption by Kenneth A. Koenigshofer, PhD).

Tool construction and use, although critically important in human evolution as indicated by the discussion above, are just a single narrow aspect of the complex of abilities that make up human intelligence.

References

Alemseged Z, Spoor F, Kimbel WH, Bobe R, Geraads D, Reed D, Wynn JG. (2006). A juvenile early hominin skeleton from Dikika, Ethiopoa. Nature 443 (Sep 21): 296-301. Available from: http://www.nature.com.offcampus.lib....ture05047.html. doi:10.1038/nature05047.

Anghelinu, M. (2013). Fitting the ladder to the tree: A common sense view on the cognitive evolution of the Pleistocene human lineage. *Arheologia Moldovei*, *36* (1), 7-24.

Bailey SE. (2006). Sahelanthropus tchadensis. In: Encyclopedia of anthropology, Vol. 5. Thousand Oaks (CA): SAGE Reference. p. 2044-2045.

Barras C. (2014). Human 'missing link' fossils may be a jumble of species. New Sci [Internet] [cited 2015 Aug 13]; 222(2964). Available from:https://www.newscientist.com/article/mg22229643-200-human-missing-link-fossils-may-be-jumble-of-species/

Becoming Human. c2008. The human lineage through time. Institute of Human Origins [Internet] [cited 2015 Aug 3]. Available from: http://www.becominghuman.org/node/human-lineage-through-time

Cachel, S. (2012). Human tool behavior is species-specific and remains unique. *Behavioral and Brain Sciences*, *35*(4), 222.

Callaway E. (2014). Modern human genomes reveal our inner Neanderthal. Nature [Internet] [cited 2015 Aug 21]. Available from: http://www.nature.com/news/modern-hu...erthal-1.14615

Callaway E. (2015). Neanderthals had outsize effect on human biology. Nature [Internet] [cited 2015 Aug 21]; 523 (7562): 512-513. Available from: http://www.nature.com.offcampus.lib....iology-1.18086. doi: 10.1038/523512a

Campbell BG. (2000). *Humankind Emerging*, 8th edition. Needham Heights (MA): Allyn&Bacon.

Cooper A, Stringer CB. (2013). Did the Denisovans cross Wallace's Line? Science [Internet] [cited 2015 Aug 21]; 342 (6156): 321-323. Available from: http://www.sciencemag.org.offcampus....d-963a99b700ea. doi: 10.1126/science.1244869.

Cosmides, L., & Tooby, J. (2002). Unraveling the enigma of human intelligence: Evolutionary psychology and the multimodular mind. *The evolution of intelligence*, 145-198.

Dembo M, Matzke NJ, Mooers AØ, Collard M. (2015). Bayesian analysis of a morphological supermatrix sheds light on controversial hominin relationships. Proc R Soc B [Internet] [cited 2015 Aug 20]; 282(1812). Available from: http://rspb.royalsocietypublishing.o...0943.e-letters. doi: 10.1098/rspb.2015.0943.

Domínguez-Rodrigo M, Pickering TR, Baquedano E, Mabulla A, Mark DF, Musiba C, et al. (2013). First partial skeleton of a 1.34-million-year-old Paranthropus boisei from Bed II, Olduvai Gorge, Tanzania. PLoS ONE 8(12): e80347. Available from: http://journals.plos.org/plosone/art...l.pone.0080347. doi:10.1371/journal.pone.0080347

Dunbar, R. I. (1998). The social brain hypothesis. *Evolutionary Anthropology: Issues, News, and Reviews: Issues, News, and Reviews*, *6* (5), 178-190.

eFossils [Internet] [cited 2015 Aug 10]. Department of Anthropology, The University of Texas at Austin. Available from: http://efossils.org/

eLucy: Step-by-step: the evolution of bipedalism [Internet]. c2007. Austin (TX): Department of Anthropology, University of Texas-Austin. [cited 2015 Aug 3]. Available from: elucy.org/Main/LessonOverview.html

Geertz, A. W. (2013). The meaningful brain: Clifford Geertz and the cognitive science of culture. In: *Mental Culture: Classical Social Theory and the Cognitive Science of Religion*. Edited by Dimitris Xygalatas and William W. McCorkle Jr., 176-196.

Gibbons, A. (2012). Generation Gaps Suggest Ancient Human-Ape Split. *Science*, August 13, 2012. American Association for the Advancement of Science. https://www.science.org/content/arti...%20years%20ago. Retrieved July 4, 2022.

Hawks J. (2005). The Great Rift Valley. John Hawks weblog [Internet] [cited 2015 Aug 2]. Available from:http://johnhawks.net/weblog/topics/geology/rift/rift_valley_overview.html

Harmand S, Lewis JE, Feibel CS, Lepre CJ, Prat S, Lenoble A, Boës X, Quinn RL, Brenet M, Arroyo A, Taylor N, Clément S, Daver G, Brugal JP, Leakey L, Mortlock RA, Wright JD, Lokorodi S, Kirwa C, Kent DV, Roche H. 2015. 3.3-million-year-old tools from Lomekwi 3, West Turkana, Kenya. Nature 521 (May 21): 310-315. Available from: http://www.nature.com.offcampus.lib....ture14464.html. doi:10.1038/nature14464.

Hunt KD. Australopithecines. In: Encyclopedia of anthropology, Vol. 1. Thousand Oaks (CA): SAGE Reference, 2006. p.311-317.

Higham T, Douka K, Wood R et al. (2014). The timing and spatiotemporal patterning of Neanderthal disappearance. Nature [Internet] [cited 2015 Aug 21]; 512 (7514): 306-309. Available from: http://www.nature.com.offcampus.lib....ture13621.html. doi:10.1038/nature13621

Jurmain R, Kilgore L, Trevathan W. (2013). Essentials of physical anthropology, 9th edition. Belmont (CA): Wadsworth Cengage Learning.

Koenigshofer, K. A. (2017). General Intelligence: Adaptation to Evolutionarily Familiar Abstract Relational Invariants, Not to Environmental or Evolutionary Novelty. *The Journal of Mind and Behavior*, *38* (2), 119-153.

Larsen, CS. (2014). Our origins: discovering physical anthropology. New York (NY): W. W. Norton & Company, Inc.

Lebatard AE, Bouriès DL, Duriner P, Jolivet M, Braucjer R, Carcaillet J, Schuster M, Arnaud N, Monié P, Lihoreau F, Likius A, Macaye HT, Vignaud P, Brunet M. 2008. Cosmogenic nuclide dating of Sahelanthropus tchadensis and Australopithecus bahrelghazali: Mio-Pliecene hominids from Chad. Proc Natl Acad Sci U S A [Internet] [cited 2015 Aug 3]; 105(9): 3226-3231. Available from: http://www.pnas.org/content/105/9/3226.full. doi: 10.1073/pnas.0708015105

Lice and human evolution [Internet]. 2011 Feb 6. NOVAscienceNow. [cited 2015 Aug 20]. Available from: www.pbs.org/wgbh/nova/evolution/lice.html

Meyer M, Kircher M, Gansauge MT, et al. (2012). A high-coverage genome sequence from an archaic Denisovan individual.

Science [Internet] [cited 2015 Aug 21]; 338 (6104): 222-226. Available from: http://www.sciencemag.org.offcampus..../6104/222.full. doi: 10.1126/science.1224344.

NOVA [Internet]. 2002 Jan 22. Neanderthals on trial. PBS [cited 2015 Aug 21]. Available from: http://www.pbs.org/wgbh/nova/transcr...nderthals.html

O'Neil D. c1999-2012. Early human evolution: a survey of the biological and cultural evolution of Homo habilis and Homo erectus. Behavioral Sciences Department, Palomar College [Internet] [cited 2015 Aug 16]. Available from: anthro.palomar.edu/homo/Default.htm

O'Neil D. c1999-2014. Evolution of modern humans: a survey of the biological and cultural evolution of archaic and modern Homo sapiens. Behavioral Sciences Department, Palomar College [Internet] [cited 2015 Aug 16]. Available from: anthro.palomar.edu/homo2/default.htm

Osiurak, F., & Massen, C. (2014). The cognitive and neural bases of human tool use. *Frontiers in psychology*, *5*, 1107.

Oxnard, C., Obendorf, P.J., Kefford, B.J. (2010). Post-cranial skeletons of hyperthyroid cretins show a similar anatomical mosaic as Homo floesiensis. PLoS One [Internet] [cited 2015 Aug 21]; 5 (9). Available from: http://www.sciencedaily.com/releases...0928025514.htm. doi: 10.1371/journal.pone.0013018.

Pääbo S. 2015. The diverse origins of the human gene pool. Nat Rev Genet [Internet] [cited 2015 Aug 21]; 16: 313-314. Available from: http://www.nature.com.offcampus.lib....l/nrg3954.html. doi:10.1038/nrg3954

Reich D, Green RE, Kircher M, et al. (2010). Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature [Internet] [cited 2015 Aug 21]; 468 (7327). Available from: http://www.nature.com/nature/journal...ture09710.html

Richmond BG, Jungers WL. (2008). Orrorin tugenensis femoral morphology and the evolution of hominin bipedalism. Science [Internet] [cited 2015 Aug 3]; 319(5870): 1662-1665. Available from: www.jstor.org/stable/20053635

Scarre C. (2005).*The Human Past: World Prehistory&the Development of Human Societies*. London (UK): Thames & Hudson Ltd.

Scarre C. (2013). The human past. London (UK): Thames & Hudson.

Sci-News.com [Internet]. 2013 Dec 6. Paranthropus boisei: 1.34-million-year-old hominin found in Tanzania. [cited 2015 Aug 12]. Available from: http://www.sci-news.com/othersciences/anthropology/science-paranthropus-boisei-hominin-tanzania-01603.html

Smithsonian Institution [Internet]. 2015 Aug 4. What does it mean to be human? [cited 2015 Aug 11]. Available from: http://humanorigins.si.edu/evidence/human-fossils/species

Su DF. (2013). The earliest hominins: Sahelanthropus, Orrorin, and Ardipithecus. The Nature Education Knowledge Project [Internet] [cited 2015 Aug 3]. Available from: http://www.nature.com/scitable/knowl...hecus-67648286

Vaesen, K. (2012). The cognitive bases of human tool use. *Behavioral and brain sciences*, *35* (4), 203-218.

Ward CV, Manthi FK, Plavcan JM. (2013). New fossils of Australopithecus anamensis from Kanapoi, West Turkana, Kenya (2003-2008). J Hum Evol 65(5): 501-524. Available from doi:10.1016/j.jhevol.2013.05.006

Wong K. 2006. Special report: Lucy's baby: an extraordinary new human fossil comes to light. Sci Am [Internet] [cited 2015 Aug 10]; Sep 20. Available from: http://www.scientificamerican.com/ar...rt-lucys-baby/

Wood, B. (2010). Reconstructing human evolution: Achievements, challenges, and opportunities. *Proceedings of the National Academy of Sciences*, *107* (supplement_2), 8902-8909.

University of Chicago Press Journals [Internet]. Volcanoes wiped out Neanderthals, new study suggests. ScienceDaily 2010 Oct 7 [cited 2015 Aug 21]. Available from: http://www.sciencedaily.com/releases...1006094057.htm

References from Brain Evolution:

American Association for the Advancement of Science (AAAS). (1880). Dr. Paul Broca. *Science*, 1(8), 93. http://www.jstor.org/stable/2900242

Bullock, T. H. (1984). Comparative neuroscience holds promise for quiet revolutions. *Science*, 225(4661), 473–478.

Cachel, S. (2012). Human tool behavior is species-specific and remains unique. *Behavioral and Brain Sciences*, *35* (4), 222.

Crick, F., & Koch, C. (1990). Towards a neurobiological theory of consciousness. *Seminars in the Neurosciences*, 2, 263–275.

Darwin, C. (1871). *The descent of man, and the selection in relation to sex*. London: J. Murray.

Darwin, C. (1859). On the origins of species by means of natural selection, or, *The preservation of favoured races in the struggle for life*. London, UK: J. Murray.

Demonet, J. F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J. L., Wise, R., . . . Frackowiak, R. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain*, 115(6), 1753–1768.

Edelman, G. (2004). *Wider than the sky: The phenomenal gift of consciousness*. New Haven, CT: Yale University Press.

Gardner, R. A., & Gardner, B. T. (1969). Teaching sign language to a chimpanzee. *Science*, 165(3894), 664–672.

Goodall, J. (1986). *The chimpanzees of Gombe: Patterns of behavior*. Cambridge, MA: Harvard University Press.

Hubel, D. H. (1995). *Eye, brain, and vision*. Freeman & Co., NY: Scientific American Library/Scientific American Books.

Knapp, M. L., & Hall, J. A. (2009). *Nonverbal communication in human interaction*. Boston, MA: Wadsworth Cengage Learning.

Osiurak, F., & Massen, C. (2014). The cognitive and neural bases of human tool use. *Frontiers in psychology*, *5*, 1107.

Ramón y Cahal, S. (1937). Recollections of my life. *Memoirs of the American Philosophical Society*, 8, 1901–1917.

Rolls, E. T., & Cowey, A. (1970). Topography of the retina and striate cortex and its relationship to visual acuity in rhesus monkeys and squirrel monkeys. *Experimental Brain Research*, 10(3), 298–310.

Rosenzweig, M. R., Breedlove, S. M., & Leiman, A. L. (2002). *Biological psychology* (3rd ed.). Sunderland, MA: Sinauer Associates.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science*, 283(5408), 1657–1661.

Smith, E. E., & Jonides, J. (1997). Working memory: A view from neuroimaging. *Cognitive psychology*, 33, 5–42.

Van Essen, D. C., Anderson, C. H., & Felleman, D. J. (1992). Information processing in the primate visual system: An integrated systems perspective. *Science, 255*(5043), 419–423.

Walker, L. A. (1987). *A loss for words: The story of deafness in a family*. New York, NY: Harper Perennial.

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9.4: Fundamental Genetics and Genetic Variation

Genetic variation, the genetic difference between individuals, contributes to a species' adaptation to its environment (Spielman et al., 2020). In humans, genetic variation begins with an egg, about 100 million sperm, and fertilization. Roughly once per month, active ovaries release an egg from follicles. During the egg's journey from the ovary through the fallopian tubes to the uterus, a sperm may fertilize the egg.

The egg and the sperm each contain 23 chromosomes. **Chromosomes** are long strings of **deoxyribonucleic acid (DNA)**. DNA is a helix-shaped molecule made up of nucleotide base pairs. In each chromosome, sequences of DNA make up **genes** that control or partially control a number of visible characteristics, known as traits, such as eye color, hair color, and so on. A single gene may have multiple possible variations or **alleles**. So, a given gene may code for the trait of hair color, and the different alleles of that gene affect which hair color an individual has.

When a sperm and egg fuse, each of their 23 chromosomes combine to create a zygote with 46 chromosomes (23 pairs). Therefore, each parent contributes half the genetic information carried by the offspring; the resulting physical characteristics of the offspring (called the phenotype) are determined by the interaction of genetic material supplied by the sperm and egg (called the genotype). A person's **genotype** is the genetic makeup of that individual. **Phenotype**, on the other hand, refers to the individual's inherited physical characteristics, which are a combination of genetic and environmental influences (Figure 3).

Photos show Genotype vs Phenotype

Figure 3. (a) Genotype refers to the genetic makeup of an individual based on the inherited genetic material (DNA). (b) Phenotype describes an individual's observable characteristics, such as hair color, skin color, height, and build. (credit a: modification of work by Caroline Davis; credit b: modification of work by Cory Zanker)

Most traits are controlled by multiple genes, but some, like cleft chin, are influenced by a single gene from each parent. Let's call the gene for cleft chin "B" and for smooth chin "b." Cleft chin is dominant, meaning having the **dominant allele** from one (Bb) or both (BB) parents results in a cleft chin. Individuals with two copies of the same allele are **homozygous**, while those with different alleles are **heterozygous**. Smooth chin is a recessive trait, requiring two **recessive alleles** (bb) to appear.

When a person with a cleft chin mates with someone with a smooth chin, the offspring's chin type depends on the parents' alleles. If the cleft-chinned parent is homozygous (BB), offspring will always have a cleft chin. If the cleft-chinned parent is heterozygous (Bb), the offspring will have a 50% chance of cleft chin (Bb) and 50% chance of smooth chin (bb) because the smooth-chinned parent (bb) will always contribute the recessive allele (bb) (Figure 4).

Images of a Punnett square versus cleft chin

Figure 4. (a) A Punnett square is a tool used to predict how genes will interact in the production of offspring. The capital B represents the dominant allele, and the lowercase b represents the recessive allele. In the example of the cleft chin, where B is the cleft chin (dominant allele), wherever a pair contains the dominant allele, B, you can expect a cleft chin phenotype. You can expect a smooth chin phenotype only when there are two copies of the recessive allele, bb. (b) A cleft chin, shown here, is an inherited trait.

In sickle cell anemia, heterozygous carriers (like Luwi from the example) can develop blood resistance to malaria infection while those who are homozygous (like Sena) have a potentially lethal blood disorder. Sickle-cell anemia is just one of many genetic disorders caused by the pairing of two recessive genes. For example, phenylketonuria (PKU) is a condition in which individuals lack an enzyme that normally converts harmful amino acids into harmless byproducts. If someone with this condition goes untreated, they will experience significant deficits in cognitive function, seizures, and an increased risk of various psychiatric disorders. Because PKU is a recessive trait, each parent must have at least one copy of the recessive allele in order to produce a child with the condition.

So far, we have discussed traits that involve just one gene, but few human characteristics are controlled by a single gene. Most traits are **polygenic**: influenced by more than one gene. Examples of polygenic traits include height, skin color, weight, intelligence, schizophrenia, cancer, heart disease, and diabetes.

Harmful genes, like those causing PKU, often arise from **mutations**—sudden, permanent changes in genes. While many mutations are harmful or lethal, some can be beneficial, giving individuals advantages over others. This genetic variability is crucial for evolution, as it provides variability in traits that allow for adaptability to environmental changes. If a population consisted of identical individuals, then any dramatic environmental changes would affect everyone the same, and there would be no variation in selection. Instead, diversity in genes and associated traits allows some individuals to better survive and reproduce, passing

their genes to future generations. This process underlies the theory of evolution, where those best adapted to their environments are more likely to reproduce and transmit their genes.

DIG DEEPER

Human Diversity

This chapter focuses on biology. Other areas of psychology, such as social psychology, study issues of race, prejudice, and discrimination. When we focus strictly on biology, race becomes a weak construct. After the human genome was completely sequenced at the turn of the 21st century, many scientists began to argue that race was not a useful variable in genetic research and that its continued use represents a potential source of confusion and harm. The racial categories that some believed to be helpful in studying genetic diversity in humans are largely irrelevant. A person's skin tone, eye color, and hair texture are functions of their genetic makeup, but there is actually more genetic variation within a given racial category than there is between racial categories. In some cases, focus on race has led to difficulties with misdiagnoses and/or underdiagnoses of diseases ranging from sickle cell anemia to cystic fibrosis. Some argue that we need to distinguish between ancestry and race and then focus on ancestry. This approach would facilitate a greater understanding of human genetic diversity (Yudell et al., 2016).

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definition

a long strand of genetic information

×Close definition

Helix-shaped molecule made of nucleotide base pairs

×Close definition

A sequence of DNA that controls or partially controls physical characteristics

×Close definition

Specific version of a gene

×Close definition

Genetic makeup of an individual

×Close definition

The observable characteristics of an individual

×Close definition

Allele whose phenotype will be expressed in an individual that possesses that allele

×Close definition

Consisting of two identical alleles

×Close definition

Consisting of two different alleles

×Close definition

Allele whose phenotype will be expressed only if an individual is homozygous for that allele

×Close definition

Multiple genes affecting a given trait

×Close definition

Sudden, permanent change in a gene

×Close definition

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9.5: DNA, Chromosomes, and Gene-Environment Correlations

Learning Objectives

1. Explain the role chromosomes play in carrying genetic information.
2. Explain the relationship between genes and environment including types of gene-environment correlations.
3. Discuss the role of twin and adoption studies in investigating genetic influences on mind and behavior.

Overview

Chromosomes are structures in the nucleus of a cell containing DNA, histone protein, and other structural proteins. Chromosomes also contain genes, most of which are made up of DNA and RNA. But our genes and chromosomes interact with environmental factors to determine our actual physical and behavioral traits (our phenotype). Teasing out the relative effects of genetic and environmental influences on the phenotype is often difficult because of the complex interactions between them. All traits, including psychological and behavioral traits, are determined by complex interactions between genetic and environmental factors.

DNA and the Genetic Code

DNA, or deoxyribonucleic acid, determines whether our eyes are blue or brown, how tall we will be, and even our dispositions for certain types of behavior. DNA holds our "genetic code;" it is shaped like a double helix, made of sequences of nucleic acids attached to a sugar phosphate backbone. Genes are subsections of DNA molecules linked together that encode a particular characteristic.

Each chromosome is made up of a single DNA molecule coiled around histone proteins. Research dating back to the 1800s shows that every living creature has a specific set of chromosomes in the nucleus of each of its cells.

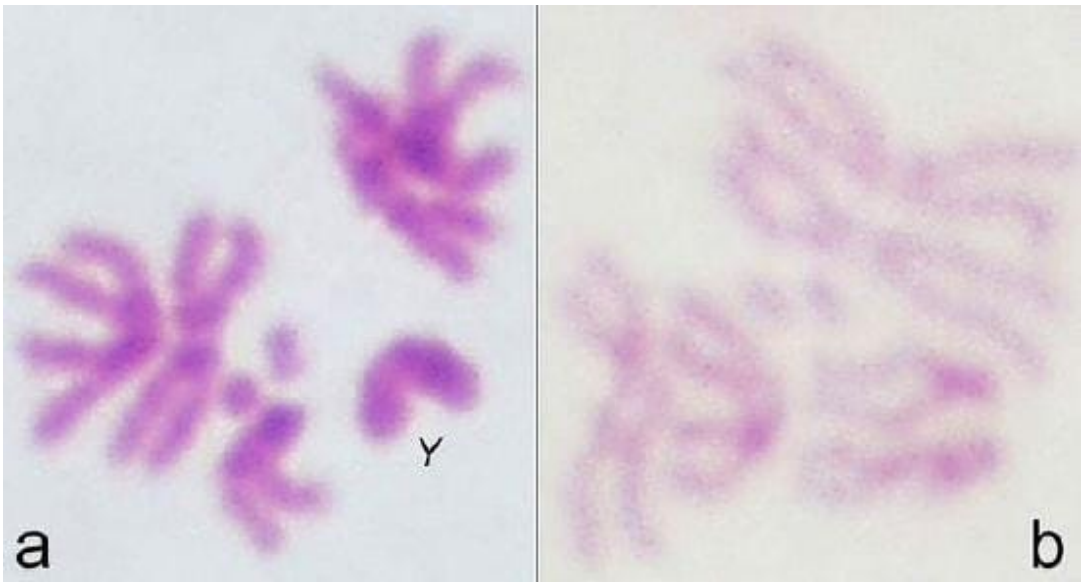


Figure 9.5.1: Human chromosome structure: Chromosomes are made up of a variety of gene sequences. By studying chromosomes and genes, scientists are able to determine the genetic basis for many diseases.

Human chromosomes are divided into two types—autosomes and sex chromosomes. Some genetic traits are linked to a person's sex and therefore passed on by the sex chromosomes. The autosomes contain the remainder of a person's genetic information. All human beings have 23 pairs of chromosomes by which genetic material is developed and characteristically demonstrated; 22 of these are autosomes, while the remaining pair (either XX, female, or XY, male) represents a person's sex chromosomes. These 23 pairs of chromosomes work together to create the person we ultimately become.

Chromosomal abnormalities can occur during fetal development if something goes wrong during the replication of the cells. Common abnormalities include Down syndrome (caused by an extra chromosome #21), Klinefelter syndrome (caused by an extra X chromosome), and Turner syndrome (caused by a missing X chromosome). Genetic counseling is available for families in order to determine if any abnormalities exist that may be passed along to offspring. Many chromosomal abnormalities are of psychological importance, with substantial impacts on mental processes; for example, Down syndrome can cause mild to moderate intellectual disabilities.

As science advances, the ability to manipulate genes and chromosomes is becoming increasingly sophisticated. Cloning is an example of taking chromosomal and genetic material and creating a new animal, and was first successfully achieved in the famous example of Dolly the sheep. There is much controversy surrounding the manipulation of chromosomes in human beings, with many people believing it to be unethical.



Figure 9.5.2: Dolly the sheep: The first successfully cloned animal.

Gene-Environment Correlations: Nature or Nurture

Our genetic destiny is not necessarily written in stone. Genetic expression can be influenced by the environment, including various social factors, as well as physical environmental factors, ranging from light and temperature to exposure to chemicals.

The environment in which a person is raised can trigger the expression of behavior for which a person is genetically predisposed, while the same person raised in a different environment may exhibit different behavior.

Long-standing debates have taken place over which factor is more important, genes or environment. Is a person destined to have a particular outcome in life because of his or her genetic makeup, or can the environment (and the people in it) work to change what might be considered “bad” genes? Today, it is generally agreed that neither genes nor environment work alone; rather, the two work in tandem to create the people we ultimately become. However, because of gene-environment correlations, discriminating the effects of environment from the effects of genes can be very difficult.

We now know that genes can be turned on and off. Environmental elements like light and temperature have been shown to induce certain changes in genetic expression; additionally, exposure to drugs and chemicals can significantly affect how genes are expressed. People often inherit sensitivity to the effects of various environmental risk factors, and therefore different individuals may be differently affected by exposure to the same environment in medically significant ways. For example, some people become very ill from exposure to peanuts, while others are entirely unaffected. Another example is exposure to sunlight. Sunlight exposure has a much stronger influence on skin cancer risk in fair-skinned humans than in individuals with an inherited tendency for darker skin. The color of a person’s skin is largely genetic, but the environment also affects these genes in different ways.

Gene-environment Correlations by Type

Gene-environment correlations, represented as rGE, occur when genetic factors influence environmental exposure. Genes can affect environmental exposure indirectly via behavior. For example, high IQ parents may have more books in their homes than lower IQ parents leading to greater exposure to books and ideas in homes with high IQ parents compared to homes with lower IQ parents. In such a case, children of high IQ parents may read earlier and have greater facility with a wider range of ideas partly indirectly through the influence of genes for higher IQ on the selection of environments which facilitate exposure to books and ideas during childhood. However, the relation between early exposure to books and intellectual ability later in life may be misinterpreted as evidence of a purely environmental relationship and therefore support the view that nurture is the predominant influence. Such an interpretation would be mistaken because it missed the significant influence of the genes of the parents on selection of the home environment, along with direct genetic effects on intelligence, that led to later intellectual abilities of their children.

Gene-environment correlations, rGEs, can be causally related or non-causally related and can be categorized as passive, evocative, or active.

Passive Gene-Environment Correlations

In passive gene-environment correlation, an association exists between a person's genetic makeup and the environment in which he or she is raised. In other words, the person's environment, particularly in the case of children, is significantly determined by the parent's genetic characteristics. Parents create a home environment that is influenced by their own heritable characteristics. When the children's own genotype influences their behavior or cognitive outcomes, the result can be misinterpreted as a relationship between environment and psychological outcome. For example, an intelligent parent is likely to create a home environment rich in educational materials and experience. Since intelligence is moderately heritable, it can be argued that intelligence in the child is inherited rather than a factor of the home environment created by the parents. It is relatively unclear whether the genetic or environmental factors had more to do with the child's development because both genes and environment affected the child's development and many aspects of the child's environment were affected by the parents' genes when the home environment was created by the parents. Thus, correlations between environment and a child's cognitive characteristics may be misinterpreted as evidence for environmental influence that is really due more to genetic factors involved in selection of the environment, factors which have been missed and therefore left out of the analysis of causation.

Evocative Gene-Environment Correlations

Evocative gene-environment correlation happens when an individual's (heritable) behavior evokes an environmental response. For example, the association or correlation between marital conflict (arguing) and depression may reflect or be due to the tensions that arise from interacting with a depressed spouse rather than a causal effect of marital conflict on risk for depression. In other words, marital conflict may not cause increased risk for depression, but instead a genetic disposition for depression in one marriage partner may cause tensions between partners that lead to marital conflict. Therefore, what first appears as an environmental factor in depression may actually have genetic roots. Genes cause a disposition for depression, and depression in one partner leads to increased marital conflict. Therefore a correlation between marital conflict and depression may not be evidence for the influence of environment on depression, but the influence of genetics for depression on the environment (marital conflict).

Active Gene-Environment Correlations

In active gene-environment correlation, the person's genetic makeup may lead them to select particular environments. For example, a shy person is likely to choose quiet activities and less boisterous environments than an extroverted individual. He or she may be more likely to spend time at the library than at a dance club. Thus, a correlation between spending time at libraries and shyness may not indicate the influence of libraries, an environmental factor, on shyness, but instead reflects the effect of genes for shyness on selection of libraries as a place to spend time.

Adoption and Twin Studies in the Nature vs. Nurture Debate

Adoption and twin studies can help make sense of the influence of genes and the environment. Studies of adult twins are used to investigate which traits are heritable. Identical twins share the same genotype, meaning their genetic makeup is the same.

Identical twins raised apart tend to be similar in intelligence and, in some cases, life events and circumstance, when studied years later, even when raised separately. However, researchers have discovered that the phenotype (or the observable expression of a gene) of identical twins grows apart as they age.

In adoption studies, identical twins raised by different families can give insight into the nature-versus-nurture debate. Since the child is being raised by parents who are genetically different from his or her biological parents, the influence of the environment shows in how similar the child is to his or her adoptive parents or adoptive siblings vs. how similar the child is to his or her biological parents and siblings. Adoption studies and twin studies make a strong case for genetic influence. However, it is now generally accepted among scientists, that all traits are influenced by both genetic and environmental differences among individuals.

KEY TAKEAWAYS

Key Points

- Chromosomes are structures in the nucleus of a cell containing DNA coiled around histone proteins.
- All animals have some number of chromosomes, which transmit genetic material. Human beings have 46 chromosomes (23 pairs).
- Humans have two types of chromosomes: autosomes and sex chromosomes.
- Chromosomal abnormalities can result in genetic conditions such as Down syndrome.
- Today it is generally accepted that nature and nurture work in tandem to create the people we ultimately become.
- Adoption and twin studies show that both nature and nurture are factors in human development.
- The environment in which a person is raised can trigger expressions of behavior for which that person is genetically predisposed; genetically identical people raised in different environments may exhibit different behavior.
- Three types of gene -environment correlations (rGE) exist: passive (ambiguous correlation), evocative (one factor invokes a response in the other), and active (one factor influences a preference for another).

Key Terms

- **chromosome**: A structure in the cell nucleus that contains DNA, histone protein, and other structural proteins.
- **gene**: A unit of heredity; a segment of DNA or RNA transmitted from one generation to the next, carrying genetic information such as the sequence of amino acids for a protein.
- **autosome**: Any chromosome that is not a sex chromosome.
- **gene-environment correlation**: A relationship in which exposure to environmental conditions correlates with an individual's genotype.
- **phenotype**: The observable expression of a gene.

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9.6: The Nature-Nurture Question and Behavior Genetics

Nature-Nurture and Twin Studies

People have a deep intuition about what has been called the "nature–nurture question" (Turkheimer, 2023). Some aspects of our behavior feel as though they originate in our genetic makeup, while others feel like the result of our upbringing or our hard work. The scientific field of behavioral genetics attempts to study these differences empirically, either by examining similarities among family members with different degrees of genetic relatedness or, more recently, by studying differences in the DNA of people with different behavioral traits. The scientific methods that have been developed are ingenious but often inconclusive. Many of the difficulties encountered in the empirical science of behavioral genetics turn out to be conceptual, and our intuitions about nature and nurture get more complicated the harder we think about them. In the end, it is an oversimplification to ask how "genetic" some particular behavior is. Genes and environments always combine to produce behavior, and the real science is in the discovery of how they combine for a given behavior.

It may seem obvious that we are born with certain characteristics while others are acquired, yet in the history of psychology, the "nature–nurture debate" has caused much controversy and offense: We are so concerned with nature–nurture because our very sense of moral character seems to depend on it. While we may admire the athletic skills of a great basketball player, we think of his height as simply a gift, a payoff in the "genetic lottery." For the same reason, no one blames a short person for his height or someone's congenital disability on poor decisions. To state the obvious, it's "not their fault." But we do praise the concert violinist (and perhaps her parents and teachers as well) for her dedication, just as we condemn cheaters, slackers, and bullies for their bad behavior.

The problem is that most human characteristics aren't usually as clear-cut as height or instrument mastery, affirming our nature–nurture expectations strongly one way or the other. In fact, even the great violinist might have some inborn qualities—pitch perception talent or long, nimble fingers—that support and reward her hard work. And the basketball player might have eaten a diet while growing up that promoted his genetic tendency to be tall. When we think about our own qualities, they seem under our control in some respects yet beyond our control in others. Often, the traits that don't seem to have an obvious cause are the ones that concern us the most and are far more personally significant. What about how much we drink or worry? What about our honesty, or religiosity, or sexual orientation? They all come from that uncertain zone, neither fixed by nature nor totally under our control.

Photo of two puppies

Figure 5. Researchers have learned a lot about the nature-nurture dynamic by working with animals. But of course, many techniques used to study animals cannot be applied to people. Separating these two influences in human subjects is a greater research challenge.

One major problem with answering nature-nurture questions about people is how to set up an experiment. In nonhuman animals, relatively straightforward experiments can tackle nature–nurture questions. Say, for example, you are interested in aggressiveness in dogs. You want to test for the more important determinant of aggression: being born to aggressive dogs or being raised by them. You could mate two aggressive dogs—angry Chihuahuas—together, and mate two nonaggressive dogs—happy beagles—together, then switch half the puppies from each litter between the different sets of parents to raise. You would then have puppies born to aggressive parents (the Chihuahuas) but raised by nonaggressive parents (the Beagles), and vice versa. The big questions are: Would the Chihuahua parents raise aggressive beagle puppies? Would the beagle parents raise nonaggressive Chihuahua puppies? Would the puppies' nature win out, regardless of who raised them? Or... would the result be a combination of nature and nurture? Much of the most significant nature–nurture research has been done in this way (Scott & Fuller, 1998), and animal breeders have been doing it successfully for thousands of years. In fact, it is fairly easy to breed animals for behavioral traits.

With people, however, we can't assign babies to parents at random, or select parents with certain behavioral characteristics to mate, merely in the interest of science (though history does include horrific examples of such practices in misguided attempts at "eugenics," the shaping of human characteristics through intentional breeding). In typical human families, children's biological parents raise them, so it is difficult to know whether children act like their parents due to genetic (nature) or environmental (nurture) reasons. Nevertheless, despite our restrictions on setting up human-based experiments, we see real-world examples of nature-nurture at work in the human sphere—though they only provide partial answers to our many questions.

The science of how genes and environments work together to influence behavior is called **behavioral genetics**. The easiest

opportunity we have to observe this is the **adoption study**. When children are put up for adoption, the parents who give birth to them are no longer the parents who raise them. This setup isn't quite the same as the experiments with dogs (children aren't assigned to random adoptive parents to suit the particular interests of a scientist), but adoption still tells us some interesting things. For instance, if the biological child of tall parents were adopted into a family of short people, do you suppose the child's growth would be affected? What about the biological child of a Spanish-speaking family adopted at birth into an English-speaking family? What language would you expect the child to speak? And what might these outcomes tell you about the difference between height and language in terms of nature-nurture?

Photo of identical twins dressed with bunny ears holding stuff animals

Figure 6. Studies focused on twins have led to important insights about the biological origins of many personality characteristics.

Another option for observing nature-nurture in humans involves **twin studies**. There are two types of twins: monozygotic (MZ) and dizygotic (DZ). Monozygotic twins, also called "identical" twins, result from a single zygote (fertilized egg) and have the same DNA. They are essentially clones. Dizygotic twins, also known as "fraternal" twins, develop from two zygotes and share 50% of their DNA. Fraternal twins are ordinary siblings who happen to have been born at the same time. To analyze nature–nurture using twins, we compare the similarity of MZ and DZ pairs. Sticking with the features of height and spoken language, let's look at how nature and nurture apply: Identical twins, unsurprisingly, are almost perfectly similar in height. The heights of fraternal twins, however, are like any other sibling pairs: more similar to each other than to people from other families, but hardly identical. This contrast between twin types gives us a clue about the role genetics plays in determining height. Now consider spoken language. If one identical twin speaks Spanish at home, the co-twin with whom she is raised almost certainly does too. But the same would be true for a pair of fraternal twins raised together. In terms of spoken language, fraternal twins are just as similar as identical twins, so it appears that the genetic match of identical twins doesn't make much difference.

Twin and adoption studies are two instances of a much broader class of methods for observing nature-nurture called **quantitative genetics**, the scientific discipline in which similarities among individuals are analyzed based on how biologically related they are. We can do these studies with siblings and half-siblings, cousins, and twins who have been separated at birth and raised separately (Bouchard et al., 1990; such twins are very rare and play a small role in the science of nature–nurture), or with entire extended families (see Plomin et al., 2012, for a complete introduction to research methods relevant to nature–nurture).

For better or for worse, contentions about nature–nurture have intensified because quantitative genetics produces a number called a **heritability coefficient**, varying from 0 to 1, that is meant to provide a single measure of genetics' influence on a trait. In a general way, a heritability coefficient measures how strongly differences among individuals are related to differences in their genes. But beware. Heritability coefficients, although simple to compute, are deceptively difficult to interpret. Nevertheless, numbers that provide simple answers to complicated questions tend to have a strong influence on the human imagination, and a great deal of time has been spent discussing whether the heritability of intelligence or personality or depression is equal to one number or another.

Photo of viral DNA

Figure 7. Quantitative genetics uses statistical methods to study the effects that both heredity and environment have on test subjects. These methods have provided us with the heritability coefficient which measures how strongly differences among individuals for a trait are related to differences among their genes.

One reason nature–nurture continues to fascinate us is that we live in an era of great scientific discovery in genetics. DNA was discovered by Watson and Crick in the 1950s; the human genome—about 3 billion base pairs long—was completely sequenced at the turn of the 21st century, and we are now on the verge of being able to obtain the specific DNA sequence of anyone at a relatively low cost (the cost of sequencing a human genome has fallen from around $10 million in 2007 to below $500 today; Collins, 2024; National Human Genome Research Institute, 2021). Every day, it seems, new discoveries are made, and new possibilities are proposed. No one knows what this new genetic knowledge will mean for the study of nature–nurture, but as we will see in the next section, answers to nature–nurture questions have turned out to be far more difficult and mysterious than anyone imagined.

What Have We Learned About Nature–Nurture?

It would be satisfying to be able to say that nature–nurture studies have given us conclusive and complete evidence about where traits come from, with some traits clearly resulting from genetics and others almost entirely from environmental factors such as childrearing practices and personal will, but that is not the case. Instead, everything has turned out to have some footing in genetics. The more genetically related people are, the more similar they are—for everything: height, weight, intelligence, personality, mental illness, etc. Sure, it seems like common sense that some traits have a genetic bias. For example, adopted

children resemble their biological parents even if they have never met them, and identical twins are more similar to each other than are fraternal twins. However, while certain psychological traits, such as personality or mental illness (e.g., schizophrenia), seem reasonably influenced by genetics, it turns out that the same is true for political attitudes, how much television people watch (Plomin et al., 1990), and whether or not they get divorced (McGue & Lykken, 1992). The message is clear: You can't leave genes out of the equation. But keep in mind, no behavioral traits are completely inherited, so you can't leave the environment out altogether, either.

Photo of son mimic father with a smoking pipe.

Figure 8. Research over the last half-century has revealed how central genetics are to behavior. The more genetically related people are, the more similar they are, not just physically but also in terms of personality and behavior.

Trying to untangle nature-nurture influences on human behavior can be messy, and common-sense notions can get in the way of good science. Behavioral genetics has taught us a crucial lesson: with biologically related subjects, we can't assume behavior stems solely from nurture, even when environmental influence seems clear. For example, data showing better reading scores in children whose mothers read to them frequently might suggest that parental reading is key to academic success. But the study as described is inconclusive because both genetic and environmental factors could affect the parenting practices and the abilities of their children.

An issue with the heritability coefficient is that it divides traits' determinants into two portions—genes and environment—which are then calculated together for the total variability. This is a little like asking how much of the experience of a symphony comes from the horns and how much from the strings; the ways instruments or genes integrate is more complex than that.

The heritability coefficient does not capture the complexity of the nature-nurture relationship. Genetics affect traits under some environmental circumstances but not others—a phenomenon called gene-environment interaction, or G x E. In one well-known example, Caspi et al. (2002) found that among maltreated children, those who carried a particular allele of the MAOA gene showed a predisposition to violence and antisocial behavior, while those with other alleles did not. However, in children who had not been maltreated, the gene had no effect. In another example of gene-environment interaction, adoptees whose biological mothers had schizophrenia and who had been raised in a disturbed family environment were much more likely to develop schizophrenia than were any of the other groups in the study (Tienari et al., 2004):

- Of adoptees whose biological mothers had schizophrenia (high genetic risk) and who were raised in disturbed family environments, 36.8% were likely to develop schizophrenia.
- Of adoptees whose biological mothers had schizophrenia (high genetic risk) and who were raised in healthy family environments, 5.8% were likely to develop schizophrenia.
- Of adoptees with a low genetic risk (whose mothers did not have schizophrenia) and who were raised in disturbed family environments, 5.3% were likely to develop schizophrenia.
- Of adoptees with a low genetic risk (whose mothers did not have schizophrenia) and who were raised in healthy family environments, 4.8% were likely to develop schizophrenia.

The study shows that adoptees with high genetic risk were most likely to develop schizophrenia if they were raised in disturbed home environments. This research suggests genetic vulnerability and environmental stress both contribute to developing schizophrenia and that genes (or environment) alone do not tell the full tale (Spielman et al., 2020). Making matters even more complicated are recent studies of what is known as epigenetics (covered in the next section), a process in which genes can be turned "on" or "off" in response to environmental events, and those epigenetic changes transmitted to children.

Photo of mother and son holding hands and embracing.

Figure 9. The answer to the nature–nurture question has not turned out to be as straightforward as we would like. The many questions we can ask about the relationships among genes, environments, and human traits may have many different answers, and the answer to one tells us little about the answers to the others.

Nature-nurture questions often focus on trait malleability and whether we "have a choice" about it. These are complex issues, as illustrated by phenylketonuria—a genetic disorder caused by a single gene that could result in intellectual disability and death, but is manageable through diet, and height—firmly rooted genetics, but affected by environmental factors as shown by the height increases in some Asian and European populations over the last 100 years due to changes in diet and reduced poverty.

With the Human Genome Project and DNA sequencing, it was believed that we would easily be able to link specific genes with specific behaviors. That has not happened. A few rare genes have been found to have significant effects, such as the single genes that cause Huntington's disease or early-onset dementia in some Alzheimer's cases. Most genetic influences on behavior are distributed across many genes, each with tiny effects, making them difficult to catalog. Similarly, environmental effects are

typically hard to pinpoint. Extreme environmental hardship is catastrophic for behavioral outcomes, but fortunately, such extreme cases are very rare. Within the normal range of environments, events responsible for differences (e.g., why some children in a suburban third-grade classroom perform better than others) are much more difficult to pinpoint.

Nature-nurture problems resist simple solutions. With nature-nurture, what seems straightforward and possible to index with a single number becomes more complicated the closer we look. Questions about gene-environment interactions in human traits (e.g., sensitivity to environmental change, parental versus cultural influence, genetic variability in a population, whether traits involve single or multiple genes, etc.) may have different answers, with limited implications for the others. We should continue studying nature-nurture relationships without oversimplifying their complexity.

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definition

The empirical science of how genes and environments combine to generate behavior.

×Close definition

A behavioral genetic research method that involves the comparison of adopted children to their adoptive and biological parents.

×Close definition

A behavior genetic research method that involves a comparison of the similarity of identical (monozygotic; MZ) and fraternal (dizygotic; DZ) twins.

×Close definition

Scientific and mathematical methods for inferring genetic and environmental processes based on the degree of genetic and environmental similarity among organisms.

×Close definition

An easily misinterpreted statistical construct that purports to measure the role of genetics in the explanation of differences among individuals.

×Close definition

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9.7: Epigenetics

What Is the Epigenome, and What Does It Do?

Your genes play an important role in your health, but so do your environment and behaviors, such as exercise and diet (NHGRI, 2020). Epigenetics is the study of how your behaviors and environment can cause changes that affect the way your genes work. Epigenetic changes do not change your DNA sequence, but they can change how your body reads a DNA sequence. Since your environment and behaviors can result in epigenetic changes, it is easy to see the connection between your behaviors and environment, your genes, and your physical and mental health.

The **epigenome** is a multitude of chemical compounds that can tell the genome what to do. As discussed above, the genome is the DNA that holds instructions for building the proteins that carry out a variety of functions in a cell. The epigenome consists of chemical compounds and proteins that can attach to DNA and direct such actions as turning genes "on" or "off". The epigenome can control **gene expression** or the production of proteins in particular cells. When epigenomic compounds attach to DNA and modify its function, they are said to have "marked" the genome. These marks do not change the sequence of the DNA; rather, they change the way cells use the DNA's instructions.

A human being has trillions of cells, specialized for different functions in muscles, bones, and the brain, and each of these cells carries essentially the same genome in its nucleus. The differences among cells are determined by how and when different sets of genes are turned on or off in various kinds of cells. Specialized cells in the eye turn on genes that make proteins that can detect light, while specialized cells in red blood cells make proteins that carry oxygen from the air to the rest of the body. The epigenome controls many of these changes to the genome. The modifications occur as a natural process of development and tissue differentiation, can be heritable, and can be altered in response to environmental exposures or disease[1].

How Does Epigenetics Work?

Epigenetic changes affect gene expression in different ways. Two of the most well-studied types of epigenetic changes are **DNA methylation** and **histone modification** (Figure 10).

DNA Methylation. DNA methylation works by adding a chemical group to DNA. Typically, this group is added to specific places on the DNA, where it blocks the proteins that attach to DNA to "read" the gene. This turns genes "off." The chemical group can be removed through a process called demethylation, which turns genes "on."

Histone modification. DNA wraps around proteins called histones, which form spool-like structures that enable DNA's very long molecules to be wound up neatly into chromosomes inside the cell nucleus. When histones are tightly packed together, the DNA is tightly coiled and bunched together, so proteins that 'read' the gene cannot access the DNA, and the gene is turned "off." When histones are loosely packed, more DNA is exposed or not wrapped around a histone and can be accessed by proteins that 'read' the gene, so the gene is turned "on." Chemical groups can be added to or removed from histones to make the histones more tightly or loosely packed, turning genes "off" or "on."[2]

Illustration of the epigenetic mechanisms can affect health endpoints

Figure 10. A Scientific Illustration of How Epigenetic Mechanisms Can Affect Health. Epigenetic mechanisms are affected by several factors and processes, including development in utero and in childhood, environmental chemicals, drugs and pharmaceuticals, aging, and diet. DNA methylation occurs when methyl groups, an epigenetic factor found in some dietary sources, tag DNA to activate or repress genes. Histones are proteins around which DNA can wind for compaction and gene regulation. Histone modification occurs when epigenetic factors bind to histone "tails" altering how DNA wraps around histones and the availability of genes in the DNA to be activated. These processes can influence people's health, possibly resulting in cancer, autoimmune disease, mental disorders, diabetes, or other illnesses.

Can the Epigenome Change?

Although all cells in the body contain essentially the same genome, the DNA marked by chemical tags on the DNA and histones gets rearranged when cells become specialized. The epigenome can also change throughout a person's lifetime. Lifestyle and

environmental factors (such as smoking, diet, and infectious disease) can expose a person to pressures that prompt chemical responses. These responses, in turn, often lead to changes in the epigenome, some of which can be damaging. However, the ability of the epigenome to adjust to the pressures of life appears to be required for normal human health. Your epigenetics change as you age, both as part of normal development and aging and in response to your behaviors and environment (CDC, 2022).

Photo of Ashley and Mary Kate Olsen

Figure 11. "Identical" twins are the perfect example of epigenetics. Although they share exactly the same DNA, their unique experiences in life will cause some genes (and not others) to express themselves. This is why, over time, identical twins come to look and behave differently.

Epigenetics and Development. Epigenetic changes begin before you are born. All your cells have the same genes but look and act differently. As you grow and develop, epigenetics helps determine which function a cell will have, for example, whether it will become a heart cell, skin cell, or nerve cell. Epigenetics allows nerve cells to turn "on" genes that produce proteins important for its job, while turning "off" genes important for other cell types, such as a heart cells.

Epigenetics and Reversibility. Not all epigenetic changes are permanent. Some epigenetic changes can be added or removed in response to changes in behavior or environment.

EXAMPLE: SMOKERS VS. NON-SMOKERS VS. FORMER SMOKERS. Smoking can result in epigenetic changes. For example, at certain parts of the AHRR gene (related to tumors, Zudaire et al. 2008), smokers tend to have less DNA methylation than non-smokers. The difference is greater for heavy smokers and long-term smokers. After quitting smoking, former smokers can begin to have increased DNA methylation at this gene. Eventually, they can reach levels similar to those of non-smokers. In some cases, this can happen in under a year, but the length of time depends on how long and how much someone smoked before quitting (McCartney et al. 2018)[3].

Epigenetics and Physical Health

Epigenetic changes can affect your health in different ways (CDC, 2022).

Infections. Germs can change your epigenetics to weaken your immune system. This helps the germ survive.

EXAMPLE: MYCOBACTERIUM TUBERCULOSIS. Mycobacterium tuberculosis causes tuberculosis. Infections with these germs can cause changes to histones in some of your immune cells that result in turning "off" the IL-12B gene. Turning "off" the IL-12B gene weakens your immune system and improves the survival of Mycobacterium tuberculosis (Chandran et al., 2015).

Cancer. Certain genetic mutations make you more likely to develop cancer. Likewise, some epigenetic changes increase your cancer risk. For example, having a mutation in the BRCA1 gene that prevents it from working properly makes you more likely to get breast and other cancers. Similarly, increased DNA methylation that results in decreased BRCA1 gene expression raises your risk for breast and other cancers (Tang et al. 2016).

Nutrition During Pregnancy and Beyond. A pregnant woman's environment and behavior during pregnancy, such as whether she eats healthy food, can change the baby's epigenetics. Some of these changes can remain for decades and might make the child more likely to get certain diseases.

EXAMPLE: DUTCH HUNGER WINTER FAMINE (1944-1945). People whose mothers were pregnant with them during the famine were more likely to develop certain diseases such as heart disease, type 2 diabetes, and schizophrenia (Rosenboom, 2019). Around 60 years after the famine, researchers looked at methylation levels in people whose mothers were pregnant with them during the famine. These people had increased methylation at some genes and decreased methylation at other genes compared with their siblings who were not exposed to famine before their birth (Heijmans et al. 2008). These differences in methylation could help explain why prenatal exposure to famine can be associated with an increased likelihood of certain diseases and structural brain abnormalities later in life (Hulsfhoff et al., 2000; Pidsley et al., 2012; Rosenboom, 2019).

Photo of mother produce shopping with daughter.

Figure 12. Whether or not your parents knew the science behind it, telling you to eat your veggies as a kid really does make you healthier and stronger—at least your DNA, that is.

The old adage "you are what you eat" might be true on more than just a physical level. The food you choose (and even

what your parents and grandparents chose) is reflected in your personal development and risk for disease in adulthood (Wells, 2003). Nutrients can reverse or change DNA methylation and histone modifications, thereby modifying the expression of critical genes associated with physiological and pathological processes, including embryonic development, aging, and cancer formation. Nutrients can influence the epigenome via DNA methylation or histone modifications. Data suggest that early-life nutrition has the potential to influence epigenetic programming in the brain not only during early development but also in adult life. In this regard, nutritional epigenetics has been viewed as an attractive tool to prevent pediatric developmental diseases and cancer, as well as to delay aging-associated processes[4].

Epigenetics in Psychology

Mental health and cognition can be affected by environmental factors during childhood and adolescence via changes in gene expression. Thus, examining genetic–epigenetic–environment interactions may help determine the nature of gene misregulation in psychological disorders (Weaver, 2023).

Early childhood experience, parental investment, and programming of stress responses in the offspring

Early childhood experiences and parenting impact an individual's development. For example, the degree of positive attachment in the parent–infant bond and parental investment (including the nutrients provided by the parent) also program the development of the stress responses in the brain via epigenetic markers, which then affect the organization and function of neural circuits and molecular pathways involved in memory, attention, and emotion.

The most comprehensive study of parental investment and epigenetic inheritance is on the maternally transmitted responses to stress in rats. In rat pups, maternal nurturing (licking and grooming) during the first week of life is associated with long-term programming of stress responsiveness, emotionality, cognitive performance, and reproductive behavior (Caldji et al., 1998; Liu et al., 1997). In adulthood, the offspring that received more maternal licking and grooming during the first week of life showed increased expression of the glucocorticoid receptor in the hippocampus (a brain structure associated with stress responsivity, learning, and memory) and a lower hormonal response to stress (Francis et al., 1999; Liu et al., 1997). Moreover, rat pups that received little maternal licking and grooming showed decreased histone acetylation and increased DNA methylation of the glucocorticoid receptor gene (Weaver et al., 2004). This led to reduced expression of this gene, fewer glucocorticoid receptors in the brain, and higher hormonal response to stress throughout their life. The effects of maternal care on an offspring's stress-hormone responses and behavior can be eliminated with pharmacological treatments targeting histone modification and DNA methylation (Weaver et al., 2004; Weaver et al., 2005). This research shows that histone modification and DNA methylation of the glucocorticoid-receptor gene leads to the long-term physiological and behavioral outcomes of poor maternal care, and suggests a possible molecular target for treating the effects of childhood maltreatment in humans.

Photo of father holding baby next to mother.

Figure 13. Parental care during one's childhood has important and consequential effects on the development of an individual, effects that persist even into adulthood.

Several studies have attempted to determine to what extent the findings from model animals are transferable to humans. A study examining newborn humans showed that methylation of the glucocorticoid receptor gene promoter may be an early epigenetic marker of maternal mood and risk of increased hormonal responses to stress in infants (Oberlander et al., 2008). These findings are consistent with epigenetics, glucocorticoid gene expression, and hormonal responses in rat offspring of low-grooming mothers discussed above. Examination of brain tissue from suicide victims found that the human glucocorticoid receptor gene promoter is also more methylated in the brains of individuals who had experienced maltreatment during childhood (McGowan et al., 2009). These findings suggest that DNA methylation mediates the effects of early environment in both rodents and humans and points to the possibility of new therapeutic approaches stemming from translational epigenetic research.

Epigenetic regulation of learning and memory

Epigenetic mechanisms influence genomic activities in the brain to produce long-term changes in synaptic signaling, organization, and structure, which in turn support learning and memory (Day & Sweatt, 2011).

Neuronal activity in the hippocampus of mice is associated with changes in DNA methylation (Guo et al., 2011), and disruption

to DNA methylation machinery causes learning and memory impairments (Feng et al., 2010). Pharmacological inhibition of DNA methylation can impair memory (Day & Sweatt, 2011). These findings highlight the role of DNA methylation in mediating synaptic plasticity and cognitive functions, both of which are often impaired in psychological disorders.

Changes in histone modifications can also influence long-term memory formation by altering the expression of genes relevant to learning and memory (Guan et al., 2002; Schaefer et al., 2009).

In humans, genetic defects in genes encoding the DNA methylation and histone modification machinery exhibit profound effects on cognitive function and mental health (Jiang et al., 2004). The two best-characterized examples are Rett syndrome (Amir et al., 1999) and Rubinstein-Taybi syndrome (Alarcon et al., 2004), which are profound intellectual disability disorders.

Together, these studies demonstrate that misregulation of epigenetic modifications and their regulatory enzymes can cause prominent deficits in neuronal plasticity and cognitive function. Knowledge from these studies may provide greater insight into other mental disorders such as depression and suicidal behaviors.

Image of cortical neuron stained with antibody to neurofilament subunit in green.

Figure 14. Neural plasticity is the change of neural pathways and synapses which allows for our ability to learn new things and remember them.

Epigenetic mechanisms in psychological disorders

Epigenome-wide studies have identified several dozen sites with DNA-methylation alterations in genes involved in brain development and neurotransmitter pathways that were associated with mental illness (Mill et al., 2008). These disorders are complex and typically start at a young age and cause lifelong disability. Often, limited benefits from treatment make these diseases some of the most burdensome disorders for individuals, families, and society. Efforts to identify the primary causes of complex psychiatric disorders may benefit from studying links between the environment and changes within the individual cells.

Epigenetic events that regulate gene expression have been associated with depression-related behavior and action of antidepressant medications; increasing evidence is emerging for similar mechanisms in post-mortem brains of depressed individuals. In mice, social avoidance resulted in decreased expression of hippocampal genes important in mediating depressive responses (Tsankova et al., 2006). Consistent with these findings, levels of histone markers were downregulated in human post-mortem brain samples from individuals with a history of clinical depression (Covington et al., 2009).

Administration of antidepressants increased histone markers of increased gene expression and reversed the gene repression induced by defeat stress (Lee et al., 2006). These results provide support for the use of histone deacetylase inhibitors against depression, and they have been found to exert antidepressant effects by modifying distinct cellular targets (Cassel et al., 2006).

Aberrant gene expression resulting from altered epigenetic regulation is also associated with the pathophysiology of suicide (McGowan et al., 2008; Poulter et al., 2008). Thus, it is tempting to speculate that there is an epigenetically determined reduced capacity for gene expression, which is required for learning and memory, in the brains of suicide victims.

Finally, environmental factors such as air and water pollution interact with the genome. For example, living close to a freeway while in utero is associated with higher rates of autism in childhood, and the negative effects of pollution are likely mediated by epigenetic effects (Tordjman et al., 2014). With such clear links between environment, genes, and epigenetics, effective public policy that regulates environmental factors and mitigates pollution is crucial for protecting public health and reducing the prevalence of mental and physical disorders[5].

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definition

The genome-wide distribution of epigenetic marks. These marks tell the genome what to do and where and when to do it.

×Close definition

Gene expression is the process by which the information encoded in a gene is used to direct the assembly of a protein molecule and ultimately affect the phenotype.

×Close definition

An epigenetic mechanism wherein a methyl group can tag DNA and activate or repress genes

×Close definition

An epigenetic mechanism in which a chemical group can be attached to a histone to alter the extent to which DNA is wrapped around histones and thereby alters the availability of genes in the DNA and gene expression

×Close definition

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9.8: Genes and Behavior

Learning Objectives

1. Describe the field of behavioral genetics.
2. Define epigenetics.
3. Describe the major ideas that comprise an evolutionary and computational view of the mind.
4. Explain the steps involved in how genes make proteins including how gene expression is regulated.
5. Describe the types of variation in the genetic code.
6. Discuss the ways in which behavior can influence genes.
7. Describe gene-environment interactions.

Overview

Genes, in interaction with the environment, have an enormous influence on the organization of minds and behavior. Each species, with its own unique genetic makeup, has an evolved brain structure and functional organization that determines its innate psychological nature. Human nature is one example, but other species possess their own psychological natures as well, determined by their own brain evolution. Wolves have an innate wolf nature, lions have an innate lion nature, hawks have an innate hawk nature, and so on (Koenigshofer, 2010, 2016). The innate psychological nature of each species is the result of the genes affecting brain organization and function that each species carries in its cells, and the complement of genes that each species possesses is a consequence of the evolutionary history of that species. Behavior genetics studies the effects of genes on behavior and on the information processing operations of the brain, as expressed in behavior. It also investigates the influence of environment and behavior on the expression of genes in the organism--a field called epigenetics.

The Influence of Genes on Mind and Behavior

Genetic makeup has a large role in determining human behavior. The influence of genes on behavior has been well established in the scientific community. To a large extent, who we are and how we behave is a result of our genetic makeup. While genes do not strictly determine behavior or our mental processes, they play a huge role in what we do and why we do it.

An Evolutionary and Computational View of the Mind

Since we will be talking not only about behavior, but also about the mind, it is best to talk a little bit about what the mind is. Everyone knows something about what the mind is because we each have a mind and we experience our own mental activities such as conscious awareness of our surroundings, feelings, thoughts, and memories each and every moment of our waking lives. You are using some parts of your mind right now as you read this. So, we know the mind as the collection of our own mental processes and experiences.

But there is another way to think about the mind--as a form of biological adaptation, as a collection of information processing solutions to problems of survival and reproduction that have persisted over much of our evolutionary history as a species. On this evolutionary view, the mind is a collection or bundle of information processing "organs" or "modules" each of which has evolved, over our evolutionary history as a species, to process particular kinds of information from the environment in quite specific ways to help us to survive and reproduce our genes. This is a Darwinian or evolutionary model of what the mind is.

This evolutionary model of the mind makes several assumptions (Cosmides & Tooby, 1997): 1) the mind is brain activity (i.e. the mind is what the brain does), 2) the mind/brain of each species, including the human species, has been constructed to take its present day form as a result of evolution by natural selection in that species (therefore, minds just like bodies differ in some ways from species to species, but also like bodies are also similar across species in some ways), 3) this means that the human mind is "hard wired" in many ways by genetic evolution and thus each individual brain comes "hard wired" by genetic information (genes, DNA) which direct brain development from conception onward, 4) this means that each species has its own genetically evolved psychological nature--applied to humans this means that humans are born with an innate human nature, 5) the mind has many different parts that do many different information processing tasks important to survival and reproduction, especially in

the evolutionary past of each species, 6) different parts of our minds are localized in different parts of our brains or in different circuits in our brains (localization of function), 7) the human brain is not a general purpose learning machine but a collection of specialized information processing organs or modules that collectively create in our heads a workable model of reality that guides our behavior successfully toward effective adaptation to the environment, 8) although learning is important in shaping our minds and behavior, its role is secondary and supplementary compared to the much larger role played by our genes in shaping our innate human nature.

The following quote from Steven Pinker (1997) expresses these ideas eloquently:

"The mind is a system of organs of computation, designed by natural selection to solve the kinds of problems our ancestors faced in their foraging way of life, in particular, understanding and outmaneuvering objects, animals, plants, and other people. [This view] can be unpacked into several claims. The mind is what the brain does; specifically, the brain processes information, and thinking is a kind of computation. The mind is organized into modules or mental organs, each with a specialized design that makes it an expert in one arena of interaction with the world. The modules' basic logic is specified by our genetic program. Their operation was shaped by natural selection to solve the problems of the hunting and gathering life led by our ancestors in most of our evolutionary history. The various problems for our ancestors were sub-tasks of one big problem for their genes, maximizing the number of copies that made it into the next generation."

How Genes Affect Body and Brain

Genes are responsible for producing the proteins that run everything in our bodies. Some proteins are visible, such as the ones that compose our hair and skin. Others work out of sight, coordinating our basic biological functions.

For the most part, every cell in our body contains exactly the same genes, but inside individual cells some genes are active while others are not. When genes are active, they are capable of producing proteins. This process is called gene expression. When genes are inactive, they are silent or inaccessible for protein production.

At least a third of the approximately 20,000 different genes that make up the human genome are active (expressed) primarily in the brain. This is the highest proportion of genes expressed in any part of the body. These genes influence the development and function of the brain, and ultimately control how we move, think, feel, and behave.

From DNA

In order to understand how genes work in the brain, we have to understand how genes make proteins. This begins with DNA (deoxyribonucleic acid).

DNA is a long molecule packaged into structures called chromosomes. Humans have 23 pairs of chromosomes, including a single pair of sex chromosomes (XX in females and XY in males). Within each pair, one chromosome comes from an individual's mother and the other comes from the father. In other words, we inherit half of our DNA from each of our parents.

DNA consists of two strands wound together to form a double helix. Within each strand, chemicals called nucleotides are used as a code for making proteins. DNA contains only four nucleotides – adenine (A), thymine (T), cytosine (C), and guanine (G) – but this simple genetic alphabet is the starting point for making all of the proteins in the human body, estimated to be as many as one million. Coding this many proteins with just 4 "letters" is possible because these "letters" can be combined into long chains in an enormous number of different combinations and sequences.

To Gene

A gene is a stretch of DNA that contains the instructions for making or regulating a specific protein.

Genes that make proteins are called protein-coding genes. In order to make a protein, a molecule closely related to DNA called ribonucleic acid (RNA) first copies the code within DNA. Then, protein-manufacturing machinery within the cell scans the RNA, reading the nucleotides in groups of three. These triplets encode 20 distinct amino acids, which are the building blocks for proteins. The largest known human protein is a muscle protein called titin, which consists of about 27,000 amino acids.

Some genes encode small bits of RNA that are not used to make proteins, but are instead used to tell proteins what to do and where to go. These are called non-coding or RNA genes. There are many more RNA genes than protein-coding genes.

To Protein

Proteins form the internal machinery within brain cells and the connective tissue between brain cells. They also control the chemical reactions that allow brain cells to communicate with each other.

Some genes make proteins that are important for the early development and growth of the infant brain. For example, the ASPM gene makes a protein that is needed for producing new nerve cells (or neurons) in the developing brain. Alterations in this gene can cause microcephaly, a condition in which the brain fails to grow to its normal size.

Certain genes make proteins that in turn make neurotransmitters, which are chemicals that transmit information from one neuron to the next. Other proteins are important for establishing physical connections that link various neurons together in networks.

Still other genes make proteins that act as housekeepers in the brain, keeping neurons and their networks in good working order. Harmful mutations in these genes can cause some neurological diseases such as amytrophic lateral sclerosis (ALS, Lou Gehrig's Disease).

How Gene Expression Is Regulated

We know which protein a gene will make by looking at its code, also called its DNA sequence. What we cannot predict is the amount of protein that will be made, when it will be made, or what cell will make it.

Each cell turns on only a fraction of its genes, while it silences the rest. For example, genes that are expressed in brain cells may be silenced in liver cells or heart cells. Some genes are only turned on during the early months of human development and then are silenced later.

What determines these unique patterns of gene expression? Like people, cells have a unique lineage, and they tend to inherit traits from their parents. So, a cell's origins influence the genes it turns on to make proteins. The cell's environment – its exposure to surrounding cells and to hormones and other signals – also helps determine which proteins the cell makes. These cues from a cell's past and from its environment act through many regulatory factors inside the cell, some of which are described in the following sections.

DNA Binding Proteins
About 10 percent of the genes in the human genome encode DNA binding proteins. Some of these proteins recognize and attach to specific bits of DNA to activate gene expression. Another type of DNA binding protein, called a histone, acts as a spool that can keep DNA in tight coils and thus suppress gene expression.

sRNA
Scattered throughout the genome are many types of small RNA (sRNA) that actively regulate gene expression. Because of their short length, they are able to target, match, and deactivate small bits of genetic code.

Epigenetic Factors
The word epigenetics comes from the Greek word epi, meaning above or beside. In a broad sense, epigenetics refers to long-lasting changes in gene expression without any changes to the genetic code. Epigenetic factors include chemical marks or tags on DNA or on histones that can affect gene expression. We shall discuss more about epigenetics later in this chapter.

Variations In Genetic Code

A genetic variation is a permanent change in the DNA sequence that makes up a gene. Most variations are harmless or have no effect at all. However, other variations can have harmful effects leading to disease. Still others can be beneficial in the long run, helping a species adapt to change.

Single Nucleotide Polymorphism (SNP)
SNPs are variations that involve a change in just one nucleotide. It is estimated that the human genome contains more than 10 million different SNPs. Because SNPs are such small changes within DNA, most of them have no effect upon gene expression. Some SNPs, however, are responsible for giving us unique traits, such as our hair and eye color. Other SNPs may have subtle effects on our risk of developing common diseases, such as heart disease, diabetes, or stroke.

Copy Number Variation (CNV)
At least 10 percent of the human genome is made up of CNVs, which are large chunks of DNA that are deleted, copied, flipped or otherwise rearranged in combinations that can be unique for each individual. These chunks of DNA often involve protein-coding genes. This means that CNVs are likely to change how a gene makes its protein.

Since genes usually occur in two copies, one inherited from each parent, a CNV that involves a single missing gene could lower the production of a protein below the amount needed.

Having too many copies of a gene can be harmful, too. Although most cases of Parkinson's disease are sporadic (without a known cause), some cases have been linked to having two or more copies of the SNCA gene, which encodes a protein called alpha-synuclein. The excess alpha-synuclein accumulates in clumps inside brain cells, and appears to jam the cells' machinery. For reasons that are not clear, similar clumps are associated with sporadic Parkinson's disease.

Single Gene Mutation
Some genetic variations are small and affect only a single gene. These single gene mutations can have large consequences, however, because they affect a gene's instructions for making a protein. Single gene mutations are responsible for many rare inherited neurological diseases, such as Huntington's disease.

Behavioral Genetics

Behavioral genetics studies heritability of behavioral traits, and it overlaps with genetics, psychology, and ethology (the scientific study of human and animal behavior). Genetics plays a large role in when and how learning, growing, and development occurs. For example, although environment has an effect on the walking behavior of infants and toddlers, children are unable to walk at all before an age that is predetermined by their genome. However, while the genetic makeup of a child determines the age range for when he or she will begin walking, environmental influences determine how early or late within that range the event will actually occur.



Figure 9.8.1: Gregor Mendel, the father of genetics: Mendel's work with pea plants demonstrated that certain traits follow particular patterns.

Classical Genetics

Classical, or Mendelian, genetics examines how genes are passed from one generation to the next, as well as how the presence or absence of a gene can be determined via sexual reproduction. Gregor Mendel is known as the father of the field of genetics, and his work with plant hybridization (specifically pea plants) demonstrated that certain traits follow particular patterns. This is referred to as the law of Mendelian inheritance.

Genes can be manipulated by selective breeding, which can have an enormous impact on behavior. For example, some dogs are bred specifically to be obedient, like golden retrievers; others are bred to be protective, like German shepards. In another

example, Seymour Benzer discovered he could breed certain fruit flies with others to create distinct behavioral characteristics and change their circadian rhythms.

The Influence of Behavior on Genes

Behavior can influence genetic expression in humans and animals by activating or deactivating genes. Behavior can have an impact on genetic makeup, even as early as the prenatal period. It is important to understand the implications of behavior on genetic makeup in order to reduce negative environmental and behavioral influences on genes.

EEG and PET scans have the ability to show psychologists how certain behaviors trigger reactions in the brain. This has led to the discovery of specific genes, such as those that influence addictive behaviors. A variety of behaviors have been shown to influence gene expression, including—but not limited to—drug use, exposure to the elements, and dietary habits.

Drugs and Alcohol

Prenatal exposure to certain substances, particularly drugs and alcohol, has detrimental effects on a growing fetus. The most serious consequences of prenatal drug or alcohol exposure involve newborn addiction and fetal alcohol syndrome (FAS). Fetal alcohol syndrome affects both physical and mental development, damaging neurons within the brain and often leading to cognitive impairment and below-average weight. Exposure to drugs and alcohol can also influence the genes of children and adults. Addiction is thought to have a genetic component, which may or may not be caused by a genetic mutation resulting from drug or alcohol use.

Temperature

Temperature exposure can affect gene expression. For example, in Himalayan rabbits, the genetic expressions of fur, skin, and eyes are regulated by temperature. In the warm areas of the rabbits' bodies, the fur lacks pigment due to gene inactivity and turns white. On the extremities of the rabbits' bodies (nose, ears and feet) the gene is activated and therefore pigmented (usually black).



Figure 9.8.2: Himalayan rabbit: Exposure to cold temperatures activates pigment-producing genes in the rabbit's extremities.

Light

Light exposure also influences genetic expression. Thomas Hunt Morgan performed an experiment in which he exposed some caterpillars to light and kept others in darkness. Those exposed to certain light frequencies had corresponding wing colors when they became butterflies (for example, red produced vibrant wing color, whereas blue led to pale wings). Darkness resulted in the

palest wing color, leading him to conclude that light exposure influenced the genes of the butterflies. In this manner a caterpillar's behavior can directly affect gene expression; a caterpillar that actively seeks out light will appear different as a butterfly than one that avoids it.

Nutrition

Lack of proper nutrition in early childhood is yet another factor that can lead to the alteration of genetic makeup. Human children who lack proper nutrition in the first three years of life tend to have more genetic problems later in life, such as health issues and problems with school performance.

Gene-Environment Interactions

Genes do not exist in a vacuum. Although we are all biological organisms, we also exist in an environment that is incredibly important in determining not only when and how our genes express themselves, but also in what combination. Each of us represents a unique interaction between our genetic makeup and our environment; range of reaction is one way to describe this interaction. **Range of reaction** asserts that our genes set the boundaries within which we can operate, and our environment interacts with the genes to determine where in that range we will fall. For example, if an individual's genetic makeup predisposes her to high levels of intellectual potential and she is reared in a rich, stimulating environment, then she will be more likely to achieve her full potential than if she were raised under conditions of significant deprivation. According to the concept of range of reaction, genes set definite limits on potential, and environment determines how much of that potential is achieved. Some disagree with this theory and argue that genes do not set a limit on a person's potential.

Another perspective on the interaction between genes and the environment is the concept of genetic environmental correlation. Stated simply, our genes influence our environment, and our environment influences the expression of our genes. Not only do our genes and environment interact, as in range of reaction, but they also influence one another bidirectionally. For example, the child of an NBA player would probably be exposed to basketball from an early age. Such exposure might allow the child to realize his or her full genetic, athletic potential. Thus, the parents' genes, which the child shares, influence the child's environment, and that environment, in turn, is well suited to support the child's genetic potential.



Figure 9.8.3: Nature and nurture work together like complex pieces of a human puzzle. The interaction of our environment and genes makes us the individuals we are. (credit "puzzle": modification of work by Cory Zanker; credit "houses": modification of work by Ben Salter; credit "DNA": modification of work by NHGRI)

In another approach to gene-environment interactions, the field of epigenetics looks beyond the genotype itself and studies how the same genotype can be expressed in different ways. In other words, researchers study how the same genotype can lead to very different phenotypes. As mentioned earlier, gene expression is often influenced by environmental context in ways that are not entirely obvious. For instance, identical twins share the same genetic information (identical twins develop from a single fertilized egg that split, so the genetic material is exactly the same in each; in contrast, fraternal twins develop from two different eggs

fertilized by different sperm, so the genetic material varies as with non-twin siblings). But even with identical genes, there remains an incredible amount of variability in how gene expression can unfold over the course of each twin's life. Sometimes, one twin will develop a disease and the other will not. In one example, Tiffany, an identical twin, died from cancer at age 7, but her twin, now 19 years old, has never had cancer. Although these individuals share an identical genotype, their phenotypes differ as a result of how that genetic information is expressed over time. The epigenetic perspective is very different from range of reaction, because here the genotype is not fixed and limited.

Genes affect more than our physical characteristics. Indeed, scientists have found genetic linkages to a number of behavioral characteristics, ranging from basic personality traits to sexual orientation to spirituality (for examples, see Mustanski et al., 2005; Comings, Gonzales, Saucier, Johnson, & MacMurray, 2000). Genes are also associated with temperament and a number of psychological disorders, such as depression and schizophrenia. So while it is true that genes provide the biological blueprints for our cells, tissues, organs, and body, they also have significant impact on our experiences and our behaviors.

Let's look at the following findings regarding schizophrenia in light of our three views of gene-environment interactions. Which view do you think best explains this evidence?

In a study of people who were given up for adoption, adoptees whose biological mothers had schizophrenia *and* who had been raised in a disturbed family environment were much more likely to develop **schizophrenia** or another psychotic disorder than were any of the other groups in the study:

- Of adoptees whose biological mothers had schizophrenia (high genetic risk) and who were raised in disturbed family environments, 36.8% were likely to develop schizophrenia.
- Of adoptees whose biological mothers had schizophrenia (high genetic risk) and who were raised in healthy family environments, 5.8% were likely to develop schizophrenia.
- Of adoptees with a low genetic risk (whose mothers did not have schizophrenia) and who were raised in disturbed family environments, 5.3% were likely to develop schizophrenia.
- Of adoptees with a low genetic risk (whose mothers did not have schizophrenia) and who were raised in healthy family environments, 4.8% were likely to develop schizophrenia (Tienari et al., 2004).

The study shows that adoptees with high genetic risk were especially likely to develop schizophrenia only if they were raised in disturbed home environments. This research lends credibility to the notion that both genetic vulnerability and environmental stress are necessary for schizophrenia to develop, and that genes alone do not tell the full tale.

Summary

Genes are sequences of DNA that code for a particular trait. Different versions of a gene are called alleles—sometimes alleles can be classified as dominant or recessive. A dominant allele always results in the dominant phenotype. In order to exhibit a recessive phenotype, an individual must be homozygous for the recessive allele. Genes affect both physical and psychological characteristics. The mind has evolved as a bundle of information processing modules "designed" by natural selection to increase survival and reproduction. Like other biological traits, the computational modules of the brain/mind are organized by genetic information during brain development. Ultimately, how and when a gene is expressed, and what the outcome will be—in terms of both physical and psychological characteristics—is a function of the interaction between our genes and our environments.

KEY TAKEAWAYS

Key Points

- Classical, or Mendelian, genetics examines how genes are passed from one generation to the next.
- Behavioral genetics examines the role of genetic and environmental influences on animal (including human) behavior.
- There are many ways to manipulate genetic makeup, such as cross-breeding to achieve certain characteristics.
- It is difficult to ascertain whether genetics ("nature") or the environment ("nurture") has a stronger influence on behavior. It is generally believed that human behavior is determined by complex interactions of both nature and nurture.
- Drug use, environmental exposure, and eating habits have all been linked to changes in gene expression. While some such influences are harmless or even beneficial, others can be extremely detrimental. Researchers hope to identify these behaviors and their effects.
- EEG and PET scans show psychologists how certain behaviors trigger reactions in the brain, which can lead to the discovery of certain determinant genes, such as those that influence addictive behaviors.

- Exposure of a fetus to alcohol and drugs can lead to a host of developmental problems after birth, the most serious of which is fetal alcohol syndrome.

Key Terms

- **behavioral genetics**: The field of study that examines the role of genetics in animal (including human) behavior; often involves the nature-versus-nurture debate.
- **ethology**: The scientific study of human and animal behavior.
- **genetics**: The branch of biology that deals with the transmission and variation of inherited characteristics, particularly chromosomes and DNA.
- **gene**: A unit of heredity; a segment of DNA or RNA that is transmitted from one generation to the next and that carries genetic information such as the sequence of amino acids for a protein.
- **fetal alcohol syndrome**: Any of a spectrum of birth defects resulting from excessive alcohol consumption by the mother during pregnancy.

Review Questions

A(n) _____ is a sudden, permanent change in a sequence of DNA.

1. allele
2. chromosome
3. epigenetic
4. mutation

_____ refers to a person's genetic makeup, while _____ refers to a person's physical characteristics.

1. Phenotype; genotype
2. Genotype; phenotype
3. DNA; gene
4. Gene; DNA

_____ is the field of study that focuses on genes and their expression.

1. Social psychology
2. Evolutionary psychology
3. Epigenetics
4. Behavioral neuroscience

Humans have _____ pairs of chromosomes.

1. 15
2. 23
3. 46
4. 78

Critical Thinking Questions

The theory of evolution by natural selection requires variability of a given trait. Why is variability necessary and where does it come from?

Personal Application Questions

You share half of your genetic makeup with each of your parents, but you are no doubt very different from both of them. Spend a few minutes jotting down the similarities and differences between you and your parents. How do you think your unique environment and experiences have contributed to some of the differences you see?

References

Cosmides, L., & Tooby, J. (1997). *Evolutionary psychology: A primer*. Center for Evolutionary Psychology. University of California, Santa Barbara.

Pinker, S. (1997). *How the Mind Works*. Norton. New York.

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10: BRAIN DAMAGE AND NEUROLOGICAL DISORDERS

10.1: Causes of Brain Damage
10.2: Stroke
10.3: Brain Tumors
10.4: Traumatic Brain Injury
10.5: Neurological and Neurodegenerative Disorders
10.6: Epilepsy and Its Effects on Cognition
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10.9: Huntington's Disease
10.10: Multiple Sclerosis
10.11: Neuroplasticity and Recovery After Brain Damage

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10.1: Causes of Brain Damage

The complexity and capabilities of a well-functioning human brain are astonishing. The three-pound mass of molecules is organized in an intricate web of billions of neurons and support cells. These interconnected neural networks coordinate our most mundane functions and our most profound thoughts. The distributed patterns of brain activity enable us to perceive, learn, experience, create, communicate, empathize, and dream, propelling our species toward unending innovation and discovery. Yet, for all its capabilities and general resilience, the brain remains vulnerable.

The delicate balance in a well-functioning brain can be disrupted in many ways. Brain cells need oxygen and nutrients to survive—interrupted supply can be devastating. Neurons use neurotransmitters to communicate—too little or too much can stop communication or kill cells. Brain cells are fragile and easily damaged by force or invading agents. Proteins can build up and disrupt function. Brain cells can die and cause atrophy.

This chapter delves into the darker side of brain biology: brain damage and neurodegeneration. We will explore how things can go awry in this intricate organ and lead to serious alterations in behavior, cognition, and quality of life. Understanding these aspects is not only crucial for appreciating the brain's fragility but also for developing effective therapies for brain damage and neurodegeneration.

Brain damage can occur in many ways, including traumatic brain injury, tumor, stroke, encephalitis (inflammation of the brain often caused by infections), hydrocephalus (fluid buildup inside the skull that increases pressure), lack of oxygen, and meningitis (inflammation of the meninges, the protective membrane around the brain, usually caused by infection). In this section, we'll go into detail about three of the most common types of brain damage: brain tumor, stroke, and traumatic brain injury (TBI). With TBI, we focus on an under-recognized epidemic—TBI that stems from intimate partner violence.

There are also many forms of neurological diseases and neurodegeneration. We conclude this chapter with sections on three common ones—Parkinson's disease, Alzheimer's disease, and Multiple Sclerosis.

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10.2: Stroke

Overview. A stroke is a medical emergency involving an interruption of blood flow to the brain. The interrupted blood flow prevents brain tissue from getting oxygen and nutrients. In turn, neuronal function is impaired within seconds, and brain cells start to die within minutes. Stroke is the leading cause of long-term adult disability and was the fifth leading cause of death in the United States in 2021 (CDC, 2023a). Long-term effects of stroke depend on the extent and location of the brain damage and include paralysis, problems with cognition or memory, issues speaking or understanding speech, emotional disturbances, pain, and unusual bodily sensations (NINDS, 2023a).

Types of Strokes. Strokes can be classified into two major categories: ischemic (pronounced 'ih-**skee**-muhk') and hemorrhagic (pronounced "heh-mr-**a**-juhk"). Most strokes are ischemic. **Ischemic strokes** are caused by interruption of the blood supply to one or more regions of the brain. The interruption is most commonly caused by a blood clot or cellular debris that blocks a blood vessel in the brain (NINDS, 2023a). A clot might develop at the site of the blockage ("thrombosis") or it might create a blockage after moving from another part of the body ("embolism.") The third cause of ischemic stroke is "stenosis" in which an artery narrows, often due to plaques or fatty deposits on artery walls. The other major category of stroke, **hemorrhagic stroke**, happens when an artery in the brain leaks blood or ruptures (breaks open). The leaked blood puts too much pressure on brain cells and damages them.

Figure 1. A stroke, sometimes called a brain attack, happens in one of two ways: 1) ischemic strokes occur when an artery is blocked, and 2) hemorrhagic stroke occurs when a blood vessel ruptures.

Cell death. After a stroke, some brain cells die because they stop getting the oxygen and nutrients needed to function. Other brain cells die because they are damaged by sudden bleeding in or around the brain. Some brain cells die quickly, but many linger in a compromised or weakened state for several hours. Stroke causes permanent brain damage over minutes to hours (NINDS, 2023a).

One specific cellular mechanism underlying ischemic-induced cell death is glutamate excitotoxicity. Glutamate is a major excitatory neurotransmitter important for memory and long-term potentiation. Glutamate is key for healthy brain function, but too much glutamate can kill neurons—this is known as glutamate excitotoxicity. When a stroke blocks oxygen-rich blood supply to the brain, negatively charged ATP levels drop, making the interior of the neuron more positively charged. This leads to excess glutamate released into the synapse, which causes the postsynaptic neuron to fire excessively; calcium ions flood the postsynaptic cell, cytotoxic enzymes are activated, and it eventually dies. Critically, as a neuron dies, it releases its glutamate reserves, which restarts the process in nearby cells. This glutamate excitotoxicity repeats itself in a vicious cycle that spreads quickly and kills many neurons in minutes (Kuang, 2019; Mark, 2001).

Identifying stroke. With stroke, the sooner treatment begins, the better. Knowing the signs of stroke and calling 911 immediately can help save a relative, neighbor, or friend. A mnemonic for remembering the signs of strokes is FAST (standing for Facial droop, Arm weakness, Speech difficulty, Time to call emergency services, see Figure 2). With timely treatment, it is possible to save brain cells and greatly reduce the damage (NINDS, 2023a).

Figure 2. Acting F.A.S.T. is key to stroke survival. Face: Does one side of the face droop when smiling? Arms: Does one arm drift downward when both arms are raised? Speech: Is speech slurred or strange when repeating a simple phrase? Time: If you see any of these signs, call emergency services such as 9-1-1 immediately.

Treatments. At the emergency room, patients can receive drugs that dissolve a clot. These drugs will not work if the stroke occurred more than three hours before arriving at the hospital or was caused by a burst blood vessel (Clark et al., 2018). For those hemorrhagic strokes, surgeons may clip blood vessels to stop bleeding, drain excess fluid, or even temporarily remove part of the skull to relieve pressure from swelling.

Recovery from a stroke can take weeks, months, or even years. Some people fully recover, whereas others have lifelong disabilities. Treatment following a stroke can include blood pressure medication, healthy lifestyle changes to prevent future strokes, and physical and speech therapy.

Risk factors of stroke. Despite the possibility of death or long-term disability, there is some "good news": About 4 in 5 strokes

are preventable (CDC, 2023b). Risk factors can be categorized as modifiable and nonmodifiable. Nonmodifiable risk factors include age (older adults have a higher risk), sex (men have a higher risk), and race/ethnicity (stroke incidence among Black and Hispanic Americans is almost double that of White Americans, and Black and Hispanic Americans tend to have strokes at a younger age) (Boehme et al. 2017; NINDS, 2023a). The “good news” is that some risk factors are modifiable and can be controlled by lifestyle and behavior changes. High blood pressure is the most important risk factor and can be managed by eating a healthy diet (low fat, low cholesterol, low salt, whole grains, and veggies), exercising (2.5+ hours per week), not drinking too much alcohol, and not smoking (smokers are twice as likely to have a stroke) (CDC, 2023b).

Finally, air pollution, noise pollution, and even light pollution are linked to a higher risk of stroke, hypertension, and other cardiovascular diseases (Boehme, 2017; Van Kempen & Babisch, 2012). While these factors are modifiable, they are not controllable at the individual level, especially for poor people (who have fewer housing options and often can’t afford to move away from such environmental hazards) (Crea, 2021). Thus, some prevention measures are best viewed at the population level, and this underscores the connection between health and sensible public policy that mitigates risk factors.

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definition

Strokes caused by interruption of blood supply

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Strokes caused by a ruptured or leaking blood vessel

×Close definition

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10.3: Brain Tumors

A brain tumor is a mass of abnormal cells that form into a growth in the brain. Tumors occur when something goes wrong with genes that regulate cell growth, allowing cells to grow and divide out of control (NINDS, 2023c). Tumors can be noncancerous (benign) or cancerous (malignant). **Benign tumors** don't spread to other body parts and often can be removed surgically. **Malignant tumors** can invade surrounding tissue; some malignant brain tumors can be removed entirely through surgery, whereas others have hard-to-define edges so are difficult to remove completely.

Tumors can also be categorized as primary tumors, which start within the brain, and secondary or metastatic tumors, which are caused by cancer cells that break away from a primary tumor somewhere else in the body and spread to the brain. Metastatic tumors are more common than primary tumors in the brain and occur more often in adults than in children.

Symptoms. Brain tumors cause many different symptoms, and they depend on tumor type, location, size, and rate of growth. In infants, the most obvious sign of a brain tumor is a rapidly widening head or bulging crown (see Figure 3 for an image of a bulging skull in an adult). In older children and adults, a tumor can cause headaches, seizures, balance problems, and personality changes. As with all brain damage and neurological disorders, the effects are location-specific. For example, a tumor in the frontal lobe might contribute to poor cognition or inappropriate social behavior; a tumor in the cerebellum might cause poor balance and movement control; a tumor in emotional regions might cause new bouts of inappropriate laughter or rage. A good friend of author MH reported no symptoms until his face and head swelled up after a flight; an emergency MRI revealed a tennis-ball sized meningioma (a tumor in the meninges surrounding the brain; see Figure 3 for a meningioma in another person). In retrospect, he noted possible coordination deficits, that for example may have caused him to lose to his brother in golf. The tumor was surgically removed and he has resumed "trouncing" his brother in golf.

Black and white cross section of the human head demonstrating the meningioma of the sagittal sinus isolated.

Figure 3. A meningioma, a benign tumor that developed in the meninges (thin membrane covering the brain), has caused a large hyperostosis (excessive bone growth of the skull).

Diagnosis and Treatment. Diagnosing a brain tumor usually involves a neurological exam with a doctor, lab tests of blood and urine, and diagnostic imaging with magnetic resonance imaging (MRI). MRI scans can provide high-resolution information about tumor cell density and a precise map of the tumor and neighboring structures (see **Figure 4** for an MRI scan of a tumor). Surgery is used to obtain tissue for diagnosis and to remove as much tumor as safely possible. Radiation therapy and chemotherapy are often used to kill cancer cells or stop them from spreading. Biological or immunotherapies are being developed to enhance the body's immune response and to recognize and fight cancer cells. Outcomes for treatments differ greatly based on the tumor type, location, degree of spreading, etc. Malignant glioblastomas, an especially aggressive spreading cancer, usually have poor outcomes (median survival of 14 months; Delgado-Lopez, 2016); while benign meningiomas (non-spreading tumors that develop in the meninges membrane covering the brain) have good outcomes because they haven't invaded the brain and can be removed surgically.

black and white image of a metastatic tumor in the cerebral hemisphere from lung cancer, shown on magnetic resonance imaging

Figure 4. A metastatic tumor in the cerebral hemisphere from lung cancer, shown on magnetic resonance imaging.

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definition

Tumors that don't spread to other body parts

×Close definition

Tumors that can spread and invade surrounding tissue

×Close definition

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10.4: Traumatic Brain Injury

A traumatic brain injury (TBI) is an injury to the brain caused by an external force. TBIs can be caused by a forceful bump, blow, or jolt to the head or body (a “non-penetrating TBI”), or from an object that pierces the skull and enters the brain (a “penetrating TBI”). TBI is a major cause of death and disability: the United States had over 69,000 TBI-related deaths in 2021, and about 15% of all U.S. high-school students self-reported one or more sports or recreation-related concussions (a type of TBI) within the preceding 12 months (CDC, 2023c).

Some types of TBI can cause temporary or short-term problems with brain function, including problems with how the person thinks, understands, moves, communicates, sleeps, and acts. More serious TBI can lead to severe and permanent disability or death. TBI severity is categorized as mild, moderate, or severe. One common way to categorize severity uses a combination of three factors: 1) the Glasgow Coma scale (a test of eye, verbal, and motor responses); 2) duration of post-traumatic amnesia or memory loss (less than 1 day for mild TBI, more than 7 days for severe TBI); and 3) duration of Loss of Consciousness (0-30 minutes for mild TBI and more than 24 hours for severe TBI) (Departments of Defense and Veterans Affairs, 2008). Most TBIs are mild TBIs or concussions.

How TBI Affects the Brain

Primary effects on the brain include bleeding and tearing forces that injure nerve fibers and cause inflammation, metabolic changes, and brain swelling (NINDS, 2023d). Some examples include:

- Diffuse Axonal Injury, one of the most common types of brain injuries, refers to widespread damage to the myelinated white matter tracts. It usually results from rotational forces (twisting) or sudden forceful stopping that stretches or tears these axon bundles (see Figure 5). Diffuse Axonal Injury can disrupt and break down communication among neurons. It also leads to the release of brain chemicals that can cause further damage.

diagram of diffuse axonal injury

Figure 5. Diagram of diffuse axonal injury following TBI/concussion. Many types of damage can occur along the length of the axon, including stretching/pulling of axons which may affect myelination and localization of axonal channel proteins, and tearing and shearing, which will cause loss of axonal integrity.

- Concussion is a type of mild TBI that may be considered a temporary injury to the brain but could take several months to heal. A small minority of individuals report symptoms that persist for years or indefinitely. The individual can suddenly lose consciousness or have a sudden altered state of consciousness. A second concussion closely following the first one causes further damage to the brain, and may result in a slower recovery or the so-called “second impact syndrome” that could lead to permanent damage or even death (which is why concussion-monitoring protocols and sitting out while injured is critical in sports).

- Hematomas are bleeding around the brain caused by a rupture of a blood vessel. In a hematoma, blood can collect in or around the meninges (the protective membranes surrounding the brain) or into the brain itself, damaging the surrounding tissue.

- Contusions are bruising or swelling of the brain that occurs when small blood vessels bleed into brain tissue. Contusions can occur directly under the impact site (a **coup** injury) or, more often, on the complete opposite side of the brain from the impact (a **contrecoup** injury). Coup and contrecoup injuries generally occur when the head abruptly decelerates, which causes the brain to hit one side of the skull and then bounce back and hit the other side (such as in a high-speed car crash or in shaken baby syndrome) (**Figure 6**).

diagram of the forces on the brain in a coup-contrecoup injury.

Figure 6. A diagram of the forces on the brain in a coup-contrecoup injury.

- The blood-brain barrier that protects the central nervous system from toxins and pathogens can break down from a TBI. Once the blood-brain barrier is disrupted, blood and other foreign substances can leak into the space around neurons and trigger a chain reaction that causes brain swelling. It can also trigger harmful inflammation or the release of neurotransmitters that can kill nerve cells when depleted or overexpressed.[1]

Diagnosing and Treating TBIs

All TBIs require immediate assessment by a professional who has experience evaluating head injuries. A neurological exam will test motor, sensory, and speech skills, coordination and balance, cognitive and memory performance, and changes in mood or behavior. An exam might check for a normal pupil response to changes in light and assign a Glasgow Coma Score. In addition, diagnostic brain imaging with a CT or MRI scan can help evaluate the extent of the brain injuries and determine if surgery is needed.

Many factors—including the size, severity, and location of the brain injury—influence how a TBI is treated and how quickly a person might recover. Although brain injury often occurs at the moment of head impact, much damage in a severe TBI develops from secondary injuries that happen days or weeks after the initial trauma. For this reason, people who receive immediate medical attention at a certified trauma center tend to have the best health outcomes.

Some people with a mild TBI, such as concussion, may not require treatment other than rest and over-the-counter pain relievers. For more severe TBIs, immediate treatment focuses on preventing death, stabilizing vital organ function, ensuring proper breathing, and preventing further brain damage. Once the patient is stabilized, a rehabilitation program is employed to help recovery. This may include physical therapy, occupational therapy, speech-language therapy, cognitive or vestibular rehabilitation therapy, and psychological support for emotional well-being. Novel therapies, such as neuroprotective agents and stem cell therapy, are under active research and hold promise for future treatment possibilities.[2]

Chronic Traumatic Encephalopathy (CTE)

A history of experiencing repeated head traumas has been associated with Chronic Traumatic Encephalopathy (CTE). CTE is a progressive neurological disorder associated with symptoms that may include problems thinking, understanding, and communicating; motor disorders (affecting movement); problems with impulse control and depression; and irritability. CTE occurs in those with extraordinary exposure to multiple blows to the head, and symptoms generally start to appear 8-10 years after repeated head injuries (NINDS, 2023d; McKee, 2009). CTE can only be diagnosed after death. After death, a person's brain is removed, and doctors check whether the person had CTE or another disease, such as Alzheimer's disease, or no disease at all (CDC, 2019). A brain with CTE is characterized by atrophy (shrinkage) of several brain areas, including the cerebral hemispheres, the medial temporal lobe, the thalamus, and the brain stem, as well as dilation of the ventricles (**Figure 7**) (McKee 2009). Microscopic examination of brain tissue reveals the pathological signature of CTE–phosphorylated tau protein (p-tau) that builds up in neurons, astrocytes, and cell processes around small blood vessels of the cortex, typically at the depth of cortical sulci (Asken, 2017; McKee, 2009) (**Figure 8**). The distribution of tau protein in CTE differs from other tau-related disorders, such as Alzheimer's Disease. But in both tau pathologies, tau buildup and the neurofibrillary tangles formed from tau eventually disrupt brain cells' ability to communicate with other cells.

Researchers do not know how many people in the United States have CTE. Some evidence suggests rates around 30% for those with histories of repeated head injuries (Asken, 2017). Most studies on CTE have focused on a small group of people who experienced head or brain injuries over many years. People in this group had their brains donated for research, and according to reports from family members, they often had problems with thinking, emotions, or behavior while they were alive (CDC, 2019).[3]

Cross section of a normal brain and advanced CTE brain.

Figure 7. A normal brain (left) and one with advanced CTE (right).

Figure 8. Electron micrograph of tau protein clusters that occur in Alzheimer's Disease and CTE.

Causes of TBI

Traumatic brain injury has many causes, including falls, vehicle accidents, gunshots, explosions, and blows to the head. Recently attention has surged on brain injury in sports, especially soccer (from repeatedly heading the ball; Lipton et al., 2013), combat sports (e.g., boxing, kickboxing, and mixed martial arts), and contact sports (e.g., ice hockey, professional wrestling, and American football). In National Football League (NFL) players, repeated blows to the head over a career are linked to Traumatic Brain Injury and CTE. These links have been clearly established since a landmark 2006 study by pathologist Bennet Omalu (famously depicted

by Will Smith in the film “Concussion”). In a convenience sample of deceased NFL football players who donated their brains for research, 110 of 111 had neuropathological evidence of CTE, suggesting that CTE may be related to playing football [note that participation in the brain-donation program was likely motivated by players’ and their families’ awareness of links between head trauma and CTE; this could bias the sample, and accordingly the authors caution that “estimates of prevalence cannot be concluded or implied from this sample” (Mez et al., 2017)]. In addition, the high-profile suicides of former NFL players Junior Seau, Dave Duerson, and Aaron Hernandez, who had signs of CTE in their brains, thrust the topic of brain injury into the national consciousness.

In spite of extensive attention on professional football, the overall case count of brain injuries in NFL players (~hundreds per year) is dwarfed by the number of brain injuries in other domains, such as the military (~thousands per year) or from intimate partner violence (~millions per year) (Hillstrom, 2022). In the next section, we turn to Dr. Eve Valera, a professor at Harvard Medical School and expert on brain injury in intimate partner violence, to discuss this less-recognized and under-studied epidemic.

Traumatic Brain Injury from Intimate Partner Violence – By Prof. Eve Valera

Harvard Medical School and Massachusetts General Hospital

Content Notice – This section describes some possible effects on the brain from Intimate Partner Violence or Domestic Violence. The content may be distressing, especially for those who have been directly or indirectly affected by violence.

If you or someone you know has been affected, support resources are available, for example, through your university’s counseling center or various health agencies. In the U.S., the National Domestic Violence Hotline is available 24/7; Text LOVEIS to 22522, call 1-800-799-7233, or visit https://www.thehotline.org/get-help/ . In Canada, services can be found at: https://www.canada.ca/en/public-health/services/health-promotion/stop-family-violence/services.html

Intimate Partner Violence (IPV) is any violence perpetrated by a current or former partner, spouse, significant other, girlfriend, or boyfriend with whom one has had an intimate relationship. Though the term domestic violence is often used interchangeably with IPV, domestic violence is broader in scope and also includes child abuse, elder abuse, and abuse from a child to a parent. IPV does not need to occur within the home and can occur in the context of a relationship of any length.

Globally, approximately one in three women experience physical or sexual violence in their lifetime (García-Moreno et al., 2013). Women in peak reproductive age groups—18 to 24-year-olds, followed by 25 to 34-year-olds—experience the highest rates of IPV (Catalano, 2012). Furthermore, people from groups that are and have been marginalized, such as people from racial and ethnic minority groups or LGBTQ+ individuals, are at higher risk for more abuse and/or worse consequences (CDC, 2022).

IPV can take many forms, including physical, psychological, and sexual abuse. When considering physical abuse, 80-90% of injuries are to the head, face, and neck, with women having their heads punched, slapped, kicked, and slammed against other objects. These behaviors can result in traumatic brain injuries (TBIs) in which external forces result in alterations in brain function. Although women sustain TBIs of all severities, the majority of TBIs are concussions, which are on the milder end of the TBI spectrum.

Though limited, data show that IPV-related brain injuries are associated with negative emotional, cognitive, and neural outcomes. For example, women with higher brain injury scores (based on number, recency, and severity of brain injuries) performed worse on tests of memory, learning, and cognitive flexibility than women with lower brain injury scores. Similarly, women with higher brain injury scores also tended to have higher levels of depression, worry, anxiety, general distress, and PTSD symptomatology (Valera & Berenbaum, 2003). Higher brain injury scores and more IPV-related brain injuries were also associated with measures of functional and structural connectivity within the brain analogous to those occurring in people who sustained brain injuries from accidents or sports (Valera & Kucyi, 2017; Valera et al., 2019).

Strangulation is another form of IPV and can be defined as “sustained impairment of air or blood flow through the neck as a result of external pressure” (Armstrong & Strack, 2016). This can lead to alterations (including losses) in consciousness. Strangulation-related alterations in consciousness (AIC) can result in a strangulation-related acquired brain injury. As such, when considering injuries to the brain from IPV, it is important to consider both TBIs and strangulation-related brain injuries or what can be considered “concussion+”. In a study on the effects of strangulation-related AICs, we found that women who sustained strangulation-related AICs performed more poorly on tests of working and long-term memory and had higher levels of depression

and PTSD symptomatology (Valera et al., 2022). Furthermore, there's also been an alarming rise in consensual "rough sex" among young adults, particularly sexual strangulation or choking, which can damage the brain (Herbenick et al., 2023; Orenstein, 2024).[4]

Preventing intimate partner violence. Several factors may affect the prevalence and risk of intimate partner violence. To prevent intimate partner violence, we must understand and address the factors that put people at risk and protect them from violence. Promoting healthy, respectful, and nonviolent relationships and communities can help reduce the occurrence of IPV. For example, school curricula with courses on healthy relationships and communication are crucial. Such efforts are critical to prevent the harmful and long-lasting effects of IPV on individuals, families, and communities (CDC, 2022). See Figure 9 for ways to address and prevent intimate partner violence.[5]

infographic of icons and ways to address and prevent intimate partner violence.

Figure 9. Ways to address and prevent intimate partner violence.

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4. Additional Reading: Orenstein, P. (2024, April 12). The Troubling Trend in Teenage Sex. New York Times. https://www.nytimes.com/2024/04/12/opinion/choking-teen-sex-brain-damage.html. Hillstrom, C. (2022, March 1). The Hidden Epidemic of Brain Injuries From Domestic Violence. New York Times. https://www.nytimes.com/2022/03/01/magazine/brain-trauma-domestic-violence.html 11.04: Traumatic Brain Injury#return-footnote-291-4
5. This section contains material adapted from: Center for Disease Control and Prevention (CDC) (2022). Fast Facts: Preventing Intimate Partner Violence https://www.cdc.gov/violenceprevention/intimatepartnerviolence/fastfact.html Public Domain 11.04: Traumatic Brain Injury#return-footnote-291-5

definition

A brain injury that occurs under the site of impact (coup) and on the side opposite the impact due to the brain moving inside the skull (contrecoup)

×Close definition

A brain injury that occurs under the site of impact (coup) and on the side opposite the impact due to the brain moving inside the skull (contrecoup)

×Close definition

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10.5: Neurological and Neurodegenerative Disorders

Neurodegenerative disorders are illnesses characterized by a loss of nervous system functioning that are usually caused by neuronal death (Clark et al., 2018). Although some of these diseases occur in children and young adults, most occur in older adults. These diseases generally worsen over time as more and more neurons die. The resulting impairments may be predominantly cognitive, as in Alzheimer's-type dementia, or predominantly motor, as in Parkinson's disease, or a combination of the two, as in Huntington's disease. The symptoms of a particular neurodegenerative disease are related to where in the nervous system the death of neurons occurs. For example, spinocerebellar ataxia is associated with neuronal death in the cerebellum, which causes problems with balance and walking. Neurodegenerative disorders include Huntington's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease and other types of dementia disorders, multiple sclerosis (MS), and Parkinson's disease. Here, we discuss Alzheimer's, Parkinson's disease, and multiple sclerosis in more depth.

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10.6: Epilepsy and Its Effects on Cognition

Seizures and memory impairments

Epilepsy is a general term used to describe a condition in which an individual repeatedly has epileptic seizures, periods in which neuronal populations become hyperexcitable and abnormally fire in synchrony (Scharfman, 2007). One of the most common forms of epilepsy in humans is temporal lobe epilepsy (TLE), meaning structures in their temporal lobes are the source of the aberrant neuronal firing. It was this form of epilepsy that led H.M. to have his bilateral temporal lobes removed. For individuals who suffer from temporal lobe epilepsy, cognitive impairments, including memory problems, are a common complication that can interfere with daily life to the same degree as the seizures themselves. These impairments can be attributed to a number of factors, including the pathology underlying the seizures, the seizures themselves, the drug therapy, or interictal epileptiform discharges (IEDs), which are brief spikes of activity thought to reflect a transient disruption of local neural circuitry (Lenck-Santini & Scott 2015). Unlike most seizures, IEDs are not accompanied by overt symptoms. Only with EEG recordings have researchers been able to study the impact of IEDs on cognition (see Methods: EEG/ERP and Methods: Sleep Studies and EEG Technology). An example of what IEDs look like in an EEG recording is shown in Figure 18.8.

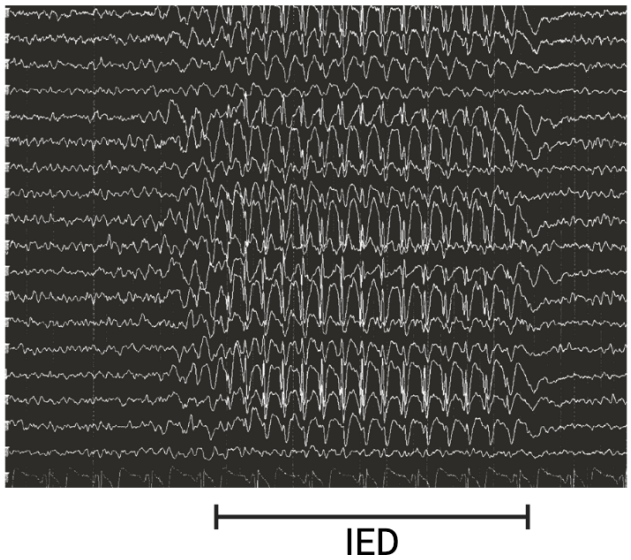


Figure 18.8 Seizures Interictal epileptiform discharges (IED) show up via EEG as a generalized 3 Hz signal. Image credits: EEG traces by Bromfield EB, Cavazos JE, Sirven JI, editors. - www.ncbi.nlm.nih.gov/books/N...ort=objectonly An Introduction to Epilepsy [Internet]. American Epilepsy Society; 2006. CC BY-SA 4.0, https://commons.wikimedia.org/w/inde...curid=57797002

Just because these seizures do not turn into obvious motor convulsions does not mean that they have no effect on behavior. One study (Kleen et al., 2013) investigated the impact of IEDs on short-term memory in a group of patients implanted with depth electrodes in their hippocampus in order to preoperatively localize the seizures. They found that IEDs that occurred at the time of memory maintenance or retrieval significantly decreased task choice accuracy, suggesting that IEDs can contribute to cognitive impairment in epilepsy. It therefore seems likely that undetected IEDs are contributing to memory impairments in patients' daily lives.

Another possible explanation for cognitive impairment in epilepsy is that an abnormality that causes the seizures also directly disrupts cognition. Evidence for this notion comes from studies done on a severe form of epilepsy called Dravet syndrome that is associated with cognitive impairments. In the majority of cases, there is a mutation in the SCN1a gene that codes for a voltage-gated sodium channel (Nav1.1). However, there is no relationship between the severity of the seizures and the severity of the cognitive impairment, as would be expected if the cognitive impairment resulted from the seizures themselves (Scheffer & Nabbout 2019). This finding suggests that the cognitive impairment is a direct consequence of the mutation rather than being a secondary effect of the seizures.

Drug therapy can also be the culprit of cognitive impairments for people who are living with epilepsy. Although cognition can improve with antiepileptic drug treatment by controlling seizures, some antiepileptic drugs, such as lacosamide, can have

cognitive side effects (Li et al., 2020).

Neuroscience across species: Normal age-related memory changes

Not long ago, it was a commonly held belief that dementia was an inevitable consequence of old age. Thankfully, we now know that this is not the case. Although cognition changes across the lifespan, it is possible to retain a high level of cognitive function into old age. Still, memory decline with aging is common and can be linked to age-related changes in brain structures that support memory processes.

A common means of studying changes in cognition with aging is to use animal models. The lifespan of a rat is about two years, so an 18 month old rat would be considered to be aged. Mice have a similar lifespan and are also common animal models used to study aging. One way that memory can be assessed in experimental animals like rats and mice is through spatial navigation tasks. Two common tasks are the Morris water maze and the Barnes maze.

The Morris water maze task is shown in Figure 18.9. In this task, an animal (usually a rat or mouse) is placed into a pool of murky water where they swim around until they find a hidden escape platform. Over many trials, the animal learns where the platform is, and as a result, swims more directly to it. A more direct path to the platform indicates learning and spatial memory. In many versions of this task, experimenters perform a probe trial, where they remove the platform and not only look at the path to the platform location but also at how much time the animal spends swimming right around the platform location. More time spent near the former platform location is often interpreted as a better spatial memory, like a person walking back and forth the same area where they feel sure they parked their car.

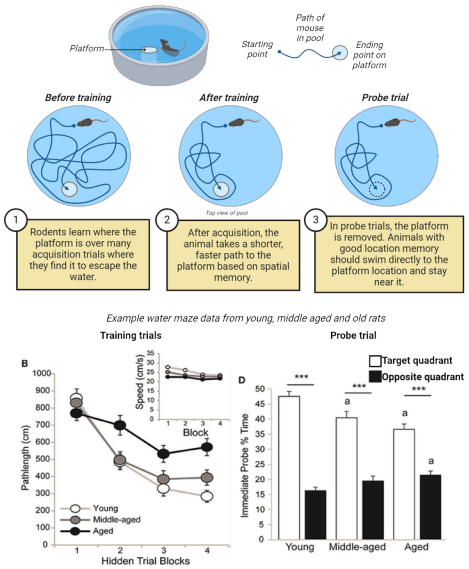


Figure 18.9 Morris water maze Data graphs from: McGuiness JA, Scheinert RB, Asokan A, Stadler V-C, Lee CS, Rani A, Kumar A, Foster TC and Ormerod BK (2017) Indomethacin Increases Neurogenesis across Age Groups and Improves Delayed Probe Trial Difference Scores in Middle-Aged Rats. Front. Aging Neurosci. 9:280. doi: 10.3389/fnagi.2017.00280. CC BY 4.0.

The bottom of Figure 18.9 shows some example data from old, middle-aged and young rats tested in the water maze. Notice how during acquisition, all the rats show shorter pathlengths to find the platform, but young and middle-aged mice show the greatest decrease in pathlengths, indicating that they are swimming more directly to the platform with repeated trials. We interpret this difference to mean that the younger rats are learning the platform location more quickly (with fewer trials). In the probe trial, experimenters quantified what percent of the time rats spent in the area around where the platform was during acquisition (i.e. the target quadrant of the pool). All the rats spend more time in the target quadrant than in the quadrant opposite it. The young rats, however, show the highest percent time swimming in the target quadrant, while middle-aged and old rats spend less time in the target quadrant. We interpret this decrease in time near the platform to indicate a poorer memory for where the platform was.

A similar task is the Barnes maze. Figure 18.10 shows this task, which is like a dry-land version of the water maze. In this task, the animal (again, usually a rat or mouse) is placed on an elevated platform that has holes around the periphery, but with only one hole leading to an escape hatch (rats do not like being out in the open). Over many trials, the animal learns where the escape hole is and, if they can remember it, takes a more direct path there, performing fewer errors (looking down in holes that do not have the escape) as they go. As with the water maze, experimenters often perform a probe trial, where the escape is removed and just

a hole open to the floor remains. In addition to a shorter path to the former escape and fewer errors looking in non-escape holes, the time spent hovering around and looking in the former escape hole can also be used as an indicator of good memory.

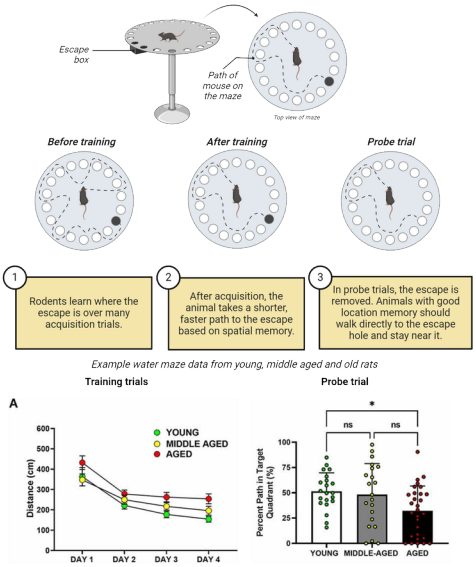


Figure 18.10 Barnes maze Data from: Souza KA, Powell A, Allen GC and Earnest DJ (2022) Development of an age-dependent cognitive index: relationship between impaired learning and disturbances in circadian timekeeping. Front. Aging Neurosci. 14:991833. doi: 10.3389/fnagi.2022.991833. CC BY 4.0

The bottom of Figure 18.10 shows some example data from old, middle-aged and young mice tested in the Barnes maze. Similar to the water maze, all the mice showed decreases in pathlength to the escape over multiple trials, with aged mice showing the least gains in pathlength efficiency and young mice showing the most. We interpret this difference to mean that the younger mice are learning the escape location more quickly (with fewer trials) than the aged mice. In the probe trial, experimenters quantified what percent of the time mice spent in the area around where the escape was during acquisition (i.e. the target quadrant of the maze). The young and middle-aged mice showed higher percent time swimming in the target quadrant than the old mice. We interpret this decrease in time near the platform to indicate a poorer memory for where the platform was in aged mice.

Work by Dr. Carol Barnes and many others in the field of aging neuroscience have helped us understand features of brain aging (see feature box on People Behind the Science: Student discovery becomes a key technique in aging neuroscience (Carol Barnes)). We looked at two studies in Figure 18.9 and Figure 18.10. These were just examples. Numerous studies confirm that aged rats and mice show impairments on both the Morris water maze and Barnes maze tasks, meaning that on probe trials they take longer paths to the escapes (or make more errors) and/or spend less time around the escapes than younger animals (Barnes, 1979; Frick, 1995; Gage et al., 1984; Gallagher & Burwell, 1989; Nyffeler et al., 2010). While these behavioral studies help show that age-related decline in memory is conserved across species, work using rats and mice has been particularly essential to advancing our understanding of what underlying changes occur in the brain that cause spatial navigation problems in older animals. It was thought in the 1970's that neurons shrivel up and die as we age. However, thanks to investigations in rats, mice, dogs, monkeys and humans, we now know that hippocampal cells do not decline in number as an animal ages. Moreover, biophysical properties of hippocampal cells are preserved in aged rats. So why do animals and humans do worse on spatial memory tasks as they age? The answer is that there are changes in the number of functional synapses and a decrease in synaptic plasticity, the ability for synapses to change their strength based on activity.

People Behind the Science: Student discovery becomes a key technique in aging neuroscience (Carol Barnes)

The Barnes maze got its name because it was developed by Dr. Carol Barnes, a Professor in the Department of Psychology at Arizona State University and Evelyn F. McKnight Chair for Learning and Memory in Aging. In addition to the maze that bears her name, Dr. Barnes is best known for her work on normal cognitive decline that occurs with aging and the associated changes that occur in the brain. She studies how the brain changes during the aging process by comparing behavioral and neurophysiological measures between aging and young animals. But when Dr. Barnes designed Barnes maze, she was a graduate student. At the time, she called the task the "circular platform task". This task has several advantages over the Morris water maze task. For example, it is thought to be less stressful for the rats. Another advantage is that the Barnes maze task

can be performed more easily by animals that have balance, motor, and coordination challenges. Other researchers started calling it the Barnes maze, and that is the name that has stuck. The Barnes maze has now been adapted and used in over 900 peer-reviewed studies to study brain systems that support memory, and it was developed by a graduate student!

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10.7: Alzheimer's Disease

Dementia describes a group of symptoms associated with a decline in memory, reasoning, or other cognitive skills. **Alzheimer's disease** is the most common cause of dementia in the elderly (Clark et al., 2018). In 2023, an estimated 6.7 million Americans are living with Alzheimer's disease, and costs for their care are estimated at $345 billion. Roughly one in every eight people age 65 or older has the disease. Due to the aging of the baby-boomer generation, there are projected to be as many as 13 million Alzheimer's patients in the United States in the year 2050.

Symptoms of Alzheimer's disease include disruptive memory loss, confusion about time or place, difficulty planning or executing tasks, poor judgment, and personality changes. Problems smelling certain scents can also be indicative of Alzheimer's disease and may serve as an early warning sign. Many of these symptoms are also common in people who are aging normally, so it is the severity and longevity of symptoms that determine whether a person is suffering from Alzheimer's.

Alzheimer's disease was named for Alois Alzheimer, a German psychiatrist who published a report in 1911 about a woman with severe dementia symptoms. He examined the woman's brain following her death and reported the presence of abnormal clumps, which are now called amyloid plaques, along with tangled brain fibers called neurofibrillary tangles. Amyloid plaques, neurofibrillary tangles, and an overall shrinking of brain volume are hallmarks of degeneration in the brains of Alzheimer's patients. Loss of neurons in the hippocampus is especially severe in advanced Alzheimer's patients. **Figure 10** compares a normal brain to the brain of an Alzheimer's patient.

diagram of a normal brain (left), the brain from a patient with Alzheimer's disease (right) shows a dramatic neurodegeneration, particularly at the shrunken hippocampus and enlarged ventricles.

Figure 10. Compared to a normal brain (left), the brain of a patient with Alzheimer's disease (right) shows a dramatic neurodegeneration, particularly at the shrunken hippocampus and enlarged ventricles.

Amyloid plaques and neurofibrillary tangles are the two main biological markers associated with Alzheimer's (The Brain from Top to Bottom, n.d.). Both are buildups of protein that occur as part of the normal aging process, but in people with Alzheimer 's-type dementias, the amounts of these proteins that build up are far greater.

Amyloid plaques. The beta-amyloid protein involved in Alzheimer's comes in several different molecular forms that collect between neurons (NIA, 2017). It is formed from the breakdown of a larger protein called amyloid-precursor protein. One form, beta-amyloid 42, is thought to be especially toxic. In the Alzheimer's brain, abnormal levels of this naturally occurring protein clump together to form plaques that collect between neurons and disrupt cell function. Research is ongoing to understand how and at what stage of the disease the various forms of beta-amyloid influence Alzheimer's disease symptoms.

Figure 11. Two amyloid plaques from the brain of a patient with Alzheimer's disease. In this photomicrograph, neurites are darkly stained, and the elements stained pink include the plaque cores. The black bar is 20 microns (0.02mm) in length.

Neurofibrillary tangles. Neurofibrillary tangles are abnormal accumulations of a protein called tau that collect inside neurons. Healthy neurons, in part, are supported internally by structures called microtubules, which help guide nutrients and molecules from the cell body to the axon and dendrites. In healthy neurons, tau normally binds to and stabilizes microtubules. In Alzheimer's disease, however, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons (Figure 12). These tangles block the neuron's transport system, harming synaptic communication between neurons.

Diagram of how microtubules disintegrate with Alzheimer's disease.

Figure 12. Diagram of how microtubules disintegrate with Alzheimer's disease. Source: National Institute on Aging.

Emerging evidence suggests that Alzheimer's-related brain changes may result from a complex interplay among abnormal tau and beta-amyloid proteins and several other factors. It appears that abnormal tau accumulates in specific brain regions involved in memory. Beta-amyloid clumps into plaques between neurons. As the level of beta-amyloid reaches a tipping point, there is a rapid spread of tau throughout the brain (NIA, 2017).

A rare form of early-onset Alzheimer's disease causes dementia beginning between the ages of 30 and 60; it is usually caused by mutations in one of three known genes (Clark et al., 2018). The more prevalent, late-onset form of the disease also has a genetic component; however research has not identified its genetic contributors as clearly as with the early-onset form of the disease.

That said, one particular gene, apolipoprotein E (APOE), has a variant that increases a carrier's likelihood of getting the disease. One APOE-E4 allele doubles or triples the chance of getting a diagnosis of Alzheimer's disease. Having two copies increases the risk about eight to twelvefold. Many other genes have been identified that might be involved in the pathology of late-onset Alzheimer's disease.

Unfortunately, there is no cure for Alzheimer's disease. Approved treatments focus on managing the symptoms of the disease. Because a decrease in the activity of cholinergic neurons (neurons that use the neurotransmitter acetylcholine) is common in Alzheimer's disease, several drugs used to treat the disease work by increasing acetylcholine neurotransmission, often by inhibiting the enzyme that breaks down acetylcholine in the synaptic cleft. Many treatments currently in development use humanized monoclonal antibodies from mouse models and aim to clear the bad proteins in human patients. While some clinical trials of compounds have shown clearing of the bad proteins on brain PET scans, serious side effects such as Amyloid-related imaging abnormalities (ARIA) have been detected in brain MRI, and the effects on cognition and daily functioning have been disappointing.

Other clinical interventions focus on behavioral therapies like psychotherapy, sensory therapy, and cognitive exercises. Since Alzheimer's disease appears to hijack the normal aging process, prevention research is prevalent. Smoking, obesity, and cardiovascular problems may be risk factors for the disease, so treatments for those may also help to prevent Alzheimer's disease. Studies show that engaging in mentally stimulating activities like puzzles, reading, playing music, and socializing in later life may reduce the risk of developing Alzheimer's disease.

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National Institute on Aging (NIA) (2017). What Happens to the Brain in Alzheimer's Disease? https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease Public Domain

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definition

A build-up of misfolded proteins in the brain that play a central role in Alzheimer's disease

×Close definition

abnormal accumulations of a protein called tau that collect inside neurons and is a key biological marker in Alzheimer's disease

×Close definition

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10.8: Parkinson's Disease

Like Alzheimer's disease, **Parkinson's disease** is a neurodegenerative disease. It was first characterized by James Parkinson in 1817. Each year, 50,000-60,000 people in the United States are diagnosed with the disease. Parkinson's disease causes the loss of dopamine neurons in the substantia nigra, a midbrain structure that regulates movement. Loss of these neurons causes many symptoms, including tremor (shaking of fingers or a limb), slowed movement, speech changes, balance, posture and gait problems, and rigid muscles. The combination of these symptoms often causes a characteristic slow, hunched, shuffling walk (**Figure 13**). Patients with Parkinson's disease can also exhibit cognitive and psychological symptoms, such as dementia or emotional problems (Clark et al., 2018).

Although some patients have a form of the disease known to be caused by a single mutation, for most patients the exact causes of Parkinson's disease remain unknown: the disease likely results from a combination of genetic and environmental factors (similar to Alzheimer's disease). Post-mortem analysis of brains from Parkinson's patients shows the presence of Lewy bodies—abnormal protein clumps—in dopaminergic neurons. The prevalence of these Lewy bodies often correlates with the severity of the disease.

There is no cure for Parkinson's disease, and treatment is focused on easing symptoms. One of the most commonly prescribed drugs for Parkinson's is L-DOPA, which is a chemical that is converted into dopamine by neurons in the brain. This conversion increases the overall level of dopamine neurotransmission and can help compensate for the loss of dopaminergic neurons in the substantia nigra. Other drugs work by inhibiting the enzyme that breaks down dopamine. L-DOPA can have side effects such as headache, dizziness, psychosis, delusions, and even an increased risk of pathological gambling. Additionally, the effectiveness of L-DOPA typically declines after a few years and many symptoms become "dopa-resistant."

Figure 13. Parkinson's patients often have a characteristic hunched posture and walk with slow, shuffling steps. People with Parkinson's also have an elevated fall risk.

Parkinson's disease can also be treated with non-pharmacological methods. For example, walking difficulties in Parkinson's have been effectively treated with music or metronome cues (Hove et al., 2012). Dancing is also an effective technique for treating motor, cognitive, and emotional symptoms of Parkinson's (Earhart, 2009).

An exciting and invasive tool for treating and relieving symptoms of Parkinson's disease is Deep Brain Stimulation (DBS). DBS requires neurosurgery and a medical device called a neurostimulator that sends electrical impulses through wire electrodes implanted in the brain (Figure 14). For movement disorders, electrodes target brain structures involved in motor control. Rigidity, tremor, and dopamine-induced dyskinesia (uncontrolled involuntary movement) in people with PD are treated with stimulation in basal-ganglia-system structures, including the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi). DBS to part of the thalamus is used to treat symptoms in PD (NINDS, n.d.). PD is treated by applying high-frequency (> 100 Hz) stimulation to the target site. The patient can typically control the stimulation; turning on the current often results in an almost immediate decrease in symptoms such as tremor, and turning stimulation off leads to a quick return of symptoms. Many videos on the internet demonstrate the sudden and dramatic effects of DBS.

Figure 14. Deep Brain Stimulation probes shown in an X-ray of the skull.

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Clark, M.A., Douglas, M. & Choi, J. (2023). 35.5 Nervous System Disorders. In Biology 2e. OpenStax. Access for free at https://openstax.org/books/biology-2e/pages/35-5-nervous-system-disorders License: CC BY 4.0 DEED.

National Institute of Neurological Disorders and Stroke (NINDS) (n.d.). Deep brain stimulation (DBS) for the treatment of Parkinson's disease and other movement disorders. https://www.ninds.nih.gov/about-ninds/impact/ninds-contributions-approved-therapies/deep-brain-stimulation-dbs-treatment-parkinsons-disease-and-other-movement-disorders Public Domain.

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definition

implanting electrodes within areas of the brain. The electrodes produce electrical impulses that affect brain activity to treat certain medical conditions.

×Close definition

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10.9: Huntington's Disease

Huntingtons Disease

Huntington's disease (HD) is an inherited disorder which causes the death of select populations of neurons. The affected neurons are located in various areas of the brain, including those in the basal ganglia which help to control voluntary (intentional) movement.

Symptoms of HD

Symptoms of the disease, which gets progressively worse, include uncontrolled movements (chorea), abnormal body postures, and changes in behavior, emotion, judgment, and cognition. People with HD also develop impaired coordination, slurred speech, and difficulty feeding and swallowing.

HD typically begins between ages 30 and 50. An earlier onset form called juvenile HD occurs under age 20. Its symptoms differ somewhat from adult onset HD and include rigidity, slowness, difficulty at school, rapid involuntary muscle jerks called myoclonus, and seizures. More than 30,000 Americans have HD.

Huntington's disease causes disability that gets worse over time. Currently no treatment is available to slow, stop, or reverse the course of HD. People with HD usually die within 10 to 30 years following symptom onset, most commonly from infections (most often pneumonia) and injuries related to falls.

Causes of HD

Huntington's disease is caused by a mutation in the gene for a protein called huntingtin. The mutated gene includes an increased number of repeats of a select portion of it's normal genetic code. How these increased repeats lead to the disorder is still unclear. Each child of a parent with HD has a 50-50 chance of inheriting the mutated gene. A child who does not inherit the HD gene will not develop the disease and cannot pass it to subsequent generations. Since this is an autosomal dominant trait, a person who inherits the HD gene will eventually develop the disease. HD is generally diagnosed based on a genetic test, medical history, brain imaging, and neurological and laboratory tests.

Treatment of HD

There is no treatment that can stop or reverse the course of HD. The drugs, tetrabenazine and deuterabenazine can treat chorea associated with HD. Antipsychotic drugs may ease chorea and help to control hallucinations, delusions, and violent outbursts. Drugs may be prescribed to treat depression and anxiety. Side effects of drugs used to treat the symptoms of HD may include fatigue, sedation, decreased concentration, restlessness, or hyperexcitability, and should only be used when symptoms create problems for the individual.

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10.10: Multiple Sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system that involves **demyelination** and neurodegeneration. MS is the most common disabling neurological disease of young adults. Symptom onset generally occurs between the ages of 20 and 40 years. It affects about 2.5 million people worldwide. Symptoms of MS include muscle weakness (often in the hands and legs), tingling and burning sensations, numbness, chronic pain, coordination and balance problems, fatigue, vision problems, and difficulty with bladder control (**Figure 15**). People with MS also may feel depressed and have trouble thinking clearly (NINDS, 2023b).

Figure 15. Symptoms in Multiple Sclerosis include (clockwise from top right): white matter lesions, weakness and difficulties walking, spasms, Babinski sign (an abnormal toe reflex), incontinence, single-sided vision, blurred vision, double vision, tremor, and internuclear ophthalmoplegia (a gaze and eye movement abnormality).

MS involves the loss of **oligodendrocytes**, the glial cells that generate and maintain the myelin sheath in the central nervous system. Myelin makes up the brain's "white matter" and insulates axons for efficient transmission of action potentials. The loss of oligodendrocytes leads to myelin thinning or loss, and as the disease progresses, the axons themselves deteriorate (as do cell bodies in gray matter). Without myelin, a neuron loses its ability to effectively conduct electrical signals. During the early stages of the disease, a repair mechanism known as **remyelination** occurs, but the oligodendrocytes are incapable of fully restoring the myelin sheath. With each subsequent attack, remyelination becomes increasingly ineffective, eventually leading to the formation of scar-like plaques around the damaged axons. These plaques are visible using magnetic resonance imaging (MRI) and can be as small as a pinhead or as large as a golf ball. They most commonly affect the white matter in the optic nerve, brain stem, basal ganglia, and spinal cord (Compston & Coles, 2008). The symptoms of MS depend on the location and extent of the plaques, as well as the severity of inflammatory reaction.

Figure 16. In MS, the immune system cells that normally protect us from viruses, bacteria, and unhealthy cells mistakenly attack myelin in the central nervous system.

MS is considered an autoimmune disorder, in which the body's immune system, which usually defends against viruses, bacteria, and unhealthy cells, attacks part of the body as if it were a foreign substance. In MS, immune cells mistakenly attack the body's own oligodendrocytes. Apart from demyelination, another characteristic sign of MS is inflammation. Inflammation is caused by immune-system T cells that enter the brain after disruptions in the blood–brain barrier, often following infection. Beyond demyelination and inflammation, MS involves additional damage to neurons, and it is generally agreed that MS is driven by the interplay between immune response and neurodegeneration (Faissner et al., 2019; Pinel & Barnes, 2017).

MS affects people differently. A small number of people with MS will have a mild course with little to no disability, whereas others will have a progressive form that steadily worsens and increases disability over time. Most people with MS, however, have "relapsing-remitting MS" characterized by short periods of symptoms followed by long stretches of relative quiescence (inactivity). The disease is rarely fatal, and most people with MS have a normal life expectancy.

Epidemiology and risk factors. The exact causes of who gets MS are not fully known, but several environmental and genetic risk factors have been identified.

- Females are more frequently affected than males.
- Susceptibility may be inherited, and if one of your parents, siblings, or your twin had MS, you are at a higher risk. Dozens of genes are linked to vulnerability to MS, and most of these genes are associated with immune-system function.
- Certain infections are linked to MS, including Epstein-Barr, the virus that causes mononucleosis; note that only about 5% of the population has not been infected by Epstein-Barr, but they have a lower risk for developing MS.
- MS is more likely to develop in people with low levels of vitamin D (or who have very limited exposure to sunlight, which helps the skin produce vitamin D; Note: this is not a recommendation to sunbathe, due to significant skin-cancer risks). Researchers believe that vitamin D may help regulate the immune system in ways that reduce the risk of MS or autoimmunity in general.
- People from regions near the equator, where there is a great deal of bright sunlight, generally have a much lower risk of MS compared to people far from the equator, for example, in the U.S., Canada, and Europe.
- Finally, studies have found that people who smoke are more likely to develop MS and have a more aggressive disease course.

Treatments. Although MS has no cure, some conventional treatments can improve symptoms, reduce the number and severity of relapses, and delay the disease's progression. The initial approved medications used to treat MS were modestly effective, though were poorly tolerated and had adverse side effects. Several medications with better safety and tolerability profiles have been introduced, improving the prognosis of MS (McGinley et al., 2021), especially for relapse-remitting MS, but treatment of the progressive forms of the disease remains unsatisfactory (Faissner et al., 2019). Many people with MS try some form of complementary health approach, including yoga, exercise, acupuncture, dietary supplements, and special diets (such as a diet low in saturated fats and high in polyunsaturated fatty acids, such as fish oils) (NCCIH, 2019).

Despite extensive ongoing research into treatments and causes of multiple sclerosis, one take-home message is clear: myelin is critical for a properly functioning nervous system, and damaged myelin leads to major issues in neural function and wellbeing (Eagleman & Downar, 2016).

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definition

Damage or loss of the myelin sheath surrounding axons in the brain.

×Close definition

glial cells that generate and maintain the myelin sheath

×Close definition

Regenerative process by which the myelin sheath around a demyelinated axon is restored

×Close definition

the branch of medicine that investigates the incidence, causes, and possible control of diseases

×Close definition

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10.11: Neuroplasticity and Recovery After Brain Damage

Neuroplasticity

Bob Woodruff, a reporter for ABC, suffered a traumatic brain injury after a bomb exploded next to the vehicle he was in while covering a news story in Iraq. As a consequence of these injuries, Woodruff experienced many cognitive deficits including difficulties with memory and language. However, over time and with the aid of intensive amounts of cognitive and speech therapy, Woodruff has shown an incredible recovery of function (Fernandez, 2008, October 16).

One of the factors that made this recovery possible was **neuroplasticity**. Neuroplasticity refers to how the nervous system can change and adapt. Neuroplasticity can occur in a variety of ways including personal experiences, developmental processes, or, as in Woodruff's case, in response to some sort of damage or injury that has occurred. Neuroplasticity can involve creation of new synapses, pruning of synapses that are no longer used, changes in glial cells, and even the birth of new neurons. Because of neuroplasticity, our brains are constantly changing and adapting, and while our nervous system is most plastic when we are very young, as Woodruff's case suggests, it is still capable of remarkable changes later in life.

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11: LEARNING AND MEMORY

11.1: Memory Systems and Stages of Processing.
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11.1: Memory Systems and Stages of Processing.

Think back to your favorite birthday party. Where was it? Who was there? What did you do? Did you eat cake? Our ability to perform this task depends on creating, storing, and recalling memories. According to neuroscience, memory formation results from subtle changes among synapses distributed across several brain areas. Our capacity to learn new facts, recall recent events, or perform motor skills results from learning-induced neural plasticity.

The previous chapter covered neuroplasticity and how synaptic connections change with experience. This chapter explores how those changes translate into learning and memory. We'll examine different types of memory, stages of processing (encoding, consolidation, storage, retrieval), and the brain regions and specialized neurons involved. We review some recent trends in research on memory reconsolidation that can help stabilize memories or even help dampen maladaptive memories as in post-traumatic stress disorder (PTSD). The chapter concludes with a discussion of memory-related disorders.

Memory is the capacity to encode, store, and retrieve information (Squire, 2009). Memory is a broad concept that includes many distinct types of memory, stages of processing, and neural systems. Before we dig into the biological psychology of memory, we introduce some terminology and ways to categorize memory.

Scientists characterize memory in many ways. Scientists talk about types of memory (e.g., semantic, episodic, procedural) that differ in the type of information that is stored (see next section). Memory can also be categorized in terms of the time-frame that information remains available. An influential model proposes three stages of memory: sensory memory, short-term memory, and long-term memory (Atkinson & Shiffrin, 1968; Figure 1). **Sensory memory** acts as a buffer for information received through the senses; the duration is very short (milliseconds or seconds). To illustrate, close your eyes; you briefly "see" a detailed image of what you were looking at; that is a visual sensory memory. **Short-term memory** (STM) and working memory last seconds to minutes and have limited capacity—typically 7±2 separate items (Miller, 1956). Short-term memory and working memory hold information temporarily and either discard it or move it to long-term memory. You can think of it like the content on your computer screen: that information is saved to long-term memory (hard drive) or discarded (delete the document or close the web page). According to the three-stage model, information moves from STM (working memory) into the third stage of memory, **long-term memory** (LTM). Long-term memory has very large capacity and these memories can last days, years, or decades. When studying for an exam, you are trying to consolidate or solidify that information in long-term memory.

Memory **consolidation** (i.e., making a temporary memory more stable and long-lasting) is supported by structural and functional changes to the neurons. In addition to consolidation, memory involves different processes, including encoding, storage, and retrieval. **Encoding** involves the input of information into the memory system. **Storage** is the retention of the encoded information. **Retrieval** involves recovering stored information from memory back into awareness.

Image shows different stages of memory -- sensory, short-term, and long-term. Details in the text and caption.

Figure 1. Memory Duration. Memory can be characterized in terms of stages — the length of time that information remains available to us.

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definition

Short-term retention of incoming sensory information (e.g., sights, sounds, smells)

×Close definition

Temporary memory store that holds and processes information for a limited period of time

×Close definition

Memories that have become stabilized over an extended period of time (days, weeks, years).

×Close definition

Making a temporary memory more stable and long-lasting

×Close definition

The process of initially learning new information

×Close definition

Retention of encoded information

×Close definition

The process of accessing stored memories

×Close definition

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11.2: Types of Memory

Memory can be arranged in several broad categories based on the type of information stored (Figure 2). Two main types of long-term memory are declarative (explicit) and nondeclarative (implicit). Declarative memory involves consciously accessible information that you can "explicitly" declare and describe. **Declarative memory** can be divided into semantic memory (for facts) and episodic memory (for events). In contrast, **nondeclarative memory** (implicit) cannot be explicitly described or consciously accessed. It encompasses various forms of learning that alter behavior without requiring awareness, such as learning a new skill, conditioning, priming, and perceptual learning.

Figure 2. Different types of memory. Sensory memory, short-term memory, declarative memory, and nondeclarative memory are distinct. Sensory memory acts as a brief buffer for incoming sensory information. Working memory involves temporarily holding and manipulating a small amount of information. Declarative memories, also called explicit memories, are memories of information that can be stated explicitly. Declarative memories can be further subdivided into semantic memory (for facts), and episodic memory (for autobiographical events). Nondeclarative memories or implicit memories encompass memories learned and accessed without conscious awareness, including procedural memories ("knowing how"), priming, non-associative learning, and associative learning.

Declarative Memory (Explicit)

Declarative memories, also called explicit memories, are the pieces of information that can be consciously stated. Declarative memory can be subdivided into semantic memory and episodic memory. **Semantic memories** include memories for general knowledge about the world (e.g., concepts, facts), whereas **episodic memories** include memories of past personal experiences and events.

Semantic memories. Semantic memories reflect memories for general knowledge, facts, concepts, and information not directly linked to past personal experiences. Some examples of semantic memories include: 1. "Jupiter is the largest planet in our solar system." 2. "Rosalind Franklin discovered the double helix structure of a DNA molecule." 3. "The actor Keanu Reeves played the protagonist of the movie The Matrix.".

Episodic memories. An episodic memory, sometimes called an autobiographical memory, is the recollection of a moment in a person's life. It can be thought of as "mental time travel" or re-experiencing past personal events. The following are examples of episodic memories: "When I got home, I put my wallet and phone on the table." "I ordered pizza last night." "In 2019, I saw my favorite musicians perform live."

One important class of episodic memories are emotional memories, largely because emotional memories are often remembered more strongly than neutral memories (LaBar & Phelps, 1998; Kensinger, 2009; Sharot et al., 2004). For example, people tend to strongly remember emotionally-charged events, including positive events such as a high school graduation, or negative events such as throwing up in front of everyone at a wedding. It may feel intuitive that emotional events are better remembered than neutral events, but how do emotions enhance our memory? Researchers have begun characterizing neurobiological systems in the brain that may explain how emotions contribute to the stabilization of memories (see sections on memory encoding and memory consolidation).

Nondeclarative Memory (Implicit)

The other main category of long-term memory is nondeclarative or implicit memory. Unlike declarative (explicit) memory, implicit memory is acquired and used unconsciously. It affects thoughts and behaviors and results from experience-based neural plasticity. Different types of implicit memory include procedural memory, priming, non-associative learning, and associative learning.

Procedural memories. **Procedural memories** are unconscious and involve "knowing how" to perform actions. Unlike explicit memories, these cannot be consciously accessed or verbally described. They encompass skills and sequences of motor actions that, with practice, become automatic. Examples include riding a bicycle or an experienced musician playing scales. Procedural memory is sometimes colloquially called "muscle memory", even though the muscles do not store any actual memory!

Priming. **Priming** occurs when exposure to a stimulus implicitly shapes the response to a subsequent stimulus, without conscious or intentional learning. There are different types of priming, including perceptual priming and semantic priming. Perceptual priming occurs when perceptual properties (e.g., shape, sound, appearance) of a stimulus inform the response to a subsequent stimulus. For example, after seeing the word "WATER", individuals are more likely to complete the fragment "W_ _ _ R" with "WATER", rather than an alternative word like "WIDER". Semantic priming occurs when exposure to a stimulus activates associations with related concepts in memory, thereby making related stimuli more accessible. Semantic priming is captured in word association tasks. For example, after discussing "apples", individuals are more likely to mention related concepts like "fruit" or "red", rather than unrelated concepts.

Non-Associative Learning. **Non-associative learning**, a form of implicit memory, does not require learned associations and instead involves a change in behavior in response to repeated exposure to a single type of stimulus. Non-associative memories emerge from habituation and sensitization. In **habituation**, responses decrease after repeated stimulus presentation as the individual learns that the stimulus lacks meaning. For example, if someone pokes you in the back, you will initially jump in surprise. However, if someone repeatedly pokes you in the back over and over again, you will habituate—your response will decrease and you realize that the stimulus is meaningless. In **sensitization**, repeated exposure to a stimulus can result in increased sensitivity, or stronger responsivity to the stimulus. For example, a person who moves to a new city may initially show little responsivity to the sound of car horns. However, with repeated exposure to the sound of car horns, the person may become sensitized to the noise and exhibit a stronger response (e.g., startle).

Associative Learning. **Associative learning**, another form of implicit memory, involves learning associations between unrelated items and results in associative memories. One way we create associative memories is through traditional Pavlovian conditioning. For example, recall the classic experiment conducted by Ivan Pavlov in the late 1800s (Figure 3). Normally, the presentation of dog food, an unconditioned stimulus (US), causes a dog to salivate naturally, an unconditioned response (UR). Dogs are not particularly interested in the sound of a bell: this neutral stimulus will produce a minor response, such as a head turn and attentional shift toward the sound source, but not much more. However, when this stimulus is paired repeatedly with the presentation of food, dogs quickly learn to associate that the bell signals food. After multiple pairings, upon hearing the bell (a conditioned stimulus, CS), the dogs begin to salivate (a conditioned response, CR), independent of any food. Associative learning can also be measured with instrumental conditioning where a rodent, for example, learns to associate a response with a meaningful stimulus. For example, a rodent will learn to press a lever to access food.

Figure 3. Associative Learning. Initially, in the presence of an unconditioned stimulus (food) the dog will salivate; however in the presence of a neutral stimulus (a ringing bell), the dog will not salivate. During conditioning, the unconditioned stimulus is paired with the bell, causing the dog to salivate. Following conditioning, the dog will salivate from only the presence of the bell.

Working Memory

Compared to long-term memory, working memory has limited duration and capacity. Related to short-term memory, working memory has been described as the use of attention to manage short-term memory, or as the system that temporarily holds and manipulates information in short-term memory (Cowan, 2008). Working memory is necessary for complex cognitive tasks such as learning, reasoning, having a conversation or argument, and doing mental arithmetic.

Short-term memory is often tested using a forward digit-span task, where participants immediately repeat a list of numbers they hear. Working memory, which involves holding and manipulating information, is often tested with a backward digit-span task. In this test, participants hear a series of numbers and must repeat them *in reverse order*. Digit-span tests begin with short sequences and progressively increase in length until the participant can no longer correctly repeat or reverse the sequence. Performance on the backward digit-span correlates with fluid intelligence, reflecting its demand on cognitive resources (Cowan, 2008).

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definition

Memory that involves remembering events and facts. Also called explicit memory.

×Close definition

Memory for information that does not require conscious learning. Includes procedural memory, priming, non-associative learning, and associative learning.

×Close definition

Memory of factual information

×Close definition

Memory of an autobiographical event (e.g., personal experience)

×Close definition

Type of unconscious memory that allows for remembering procedures and performance of specific tasks

×Close definition

The presentation of one stimulus influences the response to a subsequent stimulus

×Close definition

Changes in behavior in response to repeated exposure to a stimulus

×Close definition

Decrease in response after repeated presentation of a stimulus

×Close definition

Increased responsivity after repeated exposure to the same stimulus

×Close definition

Association of a stimulus with a cue such as with classical Pavlovian conditioning or instrumental conditioning

×Close definition

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11.3: Brain Structures in Memory

Given the various types of memory and underlying processes, it's perhaps unsurprising that memory engages many brain regions. In this section, we present an overview of some brain structures involved in memory and their functions. We focus largely on the hippocampus, as it plays such an important and long-established role in memory. We also cover several other brain regions critical for different aspects of memory.

Memory Consolidation and Relational Memory—Medial Temporal Lobes including the Hippocampus

The main structures of the medial temporal lobes include the hippocampus, the entorhinal cortex, the perirhinal cortex, and parahippocampal cortex. Together, these structures are important in both consolidation and storage of declarative memories.

The hippocampus derives its name from the Greek word for "seahorse," reflecting its resemblance to the sea creature (Figure 4). It is located along the ventral and medial surface of the brain (Figure 5). The hippocampus is a critical structure in the limbic system, an evolutionarily ancient brain network involved in several functions, including emotions and memory.

picture of a hippocampus brain region on left and a seahorse on the right.

Figure 4. The hippocampus (left), a crucial brain structure for memory formation, derives its name from the Greek word for "seahorse" due to its resemblance to the marine creature (right).

Rotating gif showing the location of the hippocampus in the brain.

Figure 5. The hippocampi are located deep in the medial temporal lobes.

The hippocampus is involved in memory consolidation, binding information to spatial or temporal contexts (i.e., relational binding), and creating mental maps of our world. When we enter a new building for the first time and we search for a new classroom, the hippocampus facilitates spatial memory by binding distinct items (e.g., lockers) to the current spatial context (e.g., first floor). Further, the hippocampus supports temporal memory by binding these events to a timeline (e.g., Monday morning). Once these memories become stabilized or consolidated, retrieving the spatial context (e.g., first floor) or temporal context (e.g., Monday morning) can help cue our memory for where the classroom is located.

Patient HM

The most influential case study in the neuroscience of memory is the story of Patient HM, whose real name was Henry Molaison (1926-2008). HM grew up in a small Connecticut town. In his childhood, HM began having severe seizures, possibly the result of a head injury. In his teenage years, he started having tonic-clonic seizures, the most severe form of seizures that produces a loss of consciousness and convulsions. In his early adulthood, he was having a tonic-clonic seizure monthly and several minor seizures daily, preventing him from working a normal job or living a normal life, despite taking a cocktail of anti-epileptic medications.

Neurosurgeon William Scoville proposed a "frankly experimental operation" to treat HM. It was known that most epilepsy originates in patches of neurons of the medial temporal lobe, and HM's epilepsy was typical in this respect. Scoville suggested to surgically remove the medial temporal lobe. In 1953, Scoville removed about 8 cm (~3 inches) of the medial temporal lobe bilaterally, including part of the amygdala, and notably most of the hippocampus. The surgery succeeded at its primary goal: HM's seizures were less frequent and less severe. However, HM was left with an unusual and life-altering side effect: He was unable to create new declarative memories, a memory deficit called **anterograde amnesia**. "Antero" means going forward, so anterograde is an inability to form new memories going forward from (i.e., after) an event. In contrast, **retrograde amnesia** affects the ability to retrieve old memories; "retro" means backward, so retrograde affects memories backward from (i.e. before) an event. After the surgery, HM could not remember what he had eaten for lunch just minutes after finishing the last bite. It was as if he was permanently living in the present.

However, despite his pervasive memory deficits, HM did not display any deficits in intelligence. His language and speech were unaffected, and word recall was excellent, as he loved completing crossword puzzles and often did so successfully late in life with few spelling errors. He was also capable of recalling things from his early childhood, such as geography facts he had learned in elementary school.

HM's medial temporal lobe surgery disrupted some types of memories (e.g., memory for facts and new events) while others remained intact (e.g., motor skills). This inspired neuropsychiatrists to try to define different forms of memory. Much of the research was led by Dr. Brenda Milner, who conducted groundbreaking tests on HM to determine which memory types relied on the intact medial temporal lobe and which functioned without it.

Several tests concluded that HM had lost his ability to create new semantic memories. In one such study, HM was asked if a word was made up or real. For words with old origins, such as "shepherd" or "butcher," he performed as well as the control group. For words that were made up, such as "phlage" or "thweise", he also performed as well as the controls. However, when shown words that were added to the dictionary after his 1953 surgery, such as "granola" or "jacuzzi," he performed near chance, as if he never learned the meaning of these new words.

HM was also unable to create episodic (autobiographical) memories. When asked to recall one of his adult birthday celebrations, he couldn't give any significant details. Interestingly, HM's memories of his childhood were still intact. While HM displayed some retrograde amnesia (memory loss from before the surgery), it was much more evident for events shortly before the surgery. Thus, HM's retrograde amnesia was temporally graded, meaning that recent memories were more affected than older memories. Many of his memories for the two years before his surgery were completely lost, but memories from his youth and teenage years were intact.

From this observation, researchers concluded that the medial temporal lobe functions as a temporary storage site for memories, but after some years, those memories get relocated to other brain areas outside of the medial temporal lobe. Current scientific evidence supports this idea that over years, memory storage relies less on the hippocampus and more on distributed cortical networks (discussed below).

While HM lost the ability to create new declarative memories, he maintained a different class of memory—implicit memory, including procedural memory. The original test of procedural memory conducted by Dr. Brenda Milner was called the mirror tracing task. In this test, participants attempt to trace the outline of a star, but only based on seeing the mirrored reflection of their hand. This mirror tracing task is difficult, but over days of practice, people learn to complete it faster and more accurately. Over training, HM learned to finish the task ten times faster than initially. He retained these improved skills for up to a year, even without regular practice. Surprisingly, each day Milner examined HM, she would need to reintroduce herself and re-explain the task, since he had forgotten her and the task. HM couldn't form declarative memories about the experiment or people involved, but retained his ability to acquire procedural memories and motor skills for the task.

Based on the deficits seen in Patient HM and other experimental manipulations of the hippocampus, Dr. Milner and other scientists concluded that the hippocampus is strongly implicated in declarative memories and spatial navigation. Since some of HM's memory functions, such as procedural and working memory, were still intact, these functions were identified as largely independent of hippocampus function.

Hippocampal Function

The profound insights gained from studying patient HM significantly advanced our understanding of memory, establishing separate subtypes of memory and the crucial role of the hippocampus in declarative memory formation. Studying the hippocampus in animals such as rodents has established its pivotal role in other aspects of memory, including spatial memory, navigation, and binding together information.

Hippocampus: Item-Spatial Context. One spatial test often used in rodents is the Morris water maze (Figure 6). In this test, a shallow pool is filled with an opaque liquid, making it difficult to see through. Hidden somewhere in this pool is a clear plexiglass platform, and surrounding the pool are different items (i.e., navigational cues) that can be seen from the surface of the water. The water is deep enough that when a rodent is put into the Morris water maze, they must swim to stay afloat. The rodents swim around aimlessly until they find the platform. Researchers record the time it takes to find the platform. Over additional trials, the animals learn that the platform is located near certain navigational cues. In future trials, they spend more time near those items and find the platform more quickly. When their hippocampus is surgically inactivated or removed, rodents perform poorly in the Morris water maze.

So the hippocampus plays an important role in navigation and spatial learning. More specifically, researchers have proposed that the hippocampus binds the navigational cue items to the spatial contexts of the pool. This hippocampal "relational binding" is thought to support the development of a stable memory representation of the water maze, and allows successful navigation.

A Morris water maze is used to test spatial navigation and hippocampal function. Details in caption and text.

Figure 6. The Morris water maze tests rodents' spatial memory. In an opaque-filled pool with a hidden platform, rodents swim to find escape. Visual cues surround the pool. A camera tracks the rodent's path, and researchers record the time taken to find the platform. Over multiple trials, rodents learn to use the navigational cues, reducing their search time to find the platform.

Hippocampus: Item-Temporal Context. Similar to how items can be bound to a spatial context in memory, items can also be bound to a temporal- or time-context in memory. Temporal context in memory refers to how memories are shaped by the timing and sequence of events. For example, if someone asks "what did you do last weekend?", it's likely that retrieving the temporal context (e.g., Saturday) will help cue your memory for events. The landmark temporal context model describes how retrieving the temporal context of an event helps memory retrieval (Howard & Kahana, 2002). Here, the temporal context is represented as a timeline of when events were experienced. The temporal context model includes principles of contiguity and recency (Howard & Kahana, 2002). The contiguity effect refers to the finding that items that occur closer together in time become associated. For example, when recalling a list of words, recalling one word can trigger or cue memory of temporally adjacent words (Solway et al., 2012). The recency effect shows that memory is stronger for recent items. As time passes or more intervening items appear, memory typically weakens. For instance, in a word list, you're more likely to remember the last few words than earlier words. The temporal context model explains this observation by proposing that the temporal context for recently encountered items is more similar to the current temporal context, which makes the more recently encountered items more readily accessible in memory (Howard & Kahana, 2002).

Hippocampus: Item-Context Binding. Although early perspectives of the hippocampus in memory focused on its role in encoding spatial maps or temporal sequences, some newer memory models propose that the hippocampus may instead serve a more general computational role by binding relations associated with an item (Davachi, 2006; Eichenbaum et al., 2007). A memorable item or event consists of multiple elements and is associated with various contexts, including spatial, temporal, and other associated details. In a relational binding framework, the hippocampus binds together item and contextual information from other regions of the brain. Successful memory retrieval relies on retrieving the context associated with the item (Yonelinas et al., 2019). Recent fMRI studies in humans and neurophysiological studies in rodents and monkeys show that hippocampal subregions and other subregions of the medial temporal lobes (e.g., perirhinal and parahippocampal cortex) make distinct contributions to encoding and binding items, contexts, recollection, familiarity, etc. (see Davachi, 2006; Eichenbaum et al., 2007 for details). In sum, the hippocampus binds items with their associated contexts, and this item-context binding function is essential for forming, storing, and recalling complex memories of information and experiences.

Declarative Memory—Cortex

In addition to the hippocampus, several other brain regions are involved in processing memory, and early studies established the role of the cortex. In the 1950's, the scientist Karl Lashley was interested in finding a location in the brain where memories were stored. His experiments searched for the location within the cortex of what he called an "**engram**" or memory trace. He trained rats to run in a complex maze to reach a food reward. After the animals learned to run the maze successfully, Lashley would lesion different areas of the rat cortex and then test the rats in the maze again. He found that regardless of where the cortex was lesioned, the lesions impaired their ability to run the maze and remember the food's location. Instead of finding a specific cortical area where the memories were stored, Lashley discovered that the size of the lesion corresponded to the amount of memory deficit in the animal. This demonstrated that the memory trace (engram) was widely spread across the cortex.

Lashley's work from the 1950's nicely predicted some current understanding of how memory features are encoded in several primary and associative cortical regions. Various features of an experience are encoded in widespread cortical areas. According to a standard consolidation model of memory (see below), information across these distributed cortical regions is coordinated or integrated by the hippocampus. As the memory is consolidated (strengthened) over time, the connections between cortical regions strengthen and these memories become more independent of the hippocampus (Frankland & Bontempi, 2005).

Working Memory—Prefrontal Cortex

The prefrontal cortex is involved in higher-order cognitive processing, decision making, and personality (Figure 7). In the context of memory, neural circuits in the prefrontal cortex are important for short-term and working memory (the memory system involved in temporarily storing and manipulating information for cognitive tasks).

Both animal and human studies have demonstrated the prefrontal cortex's crucial role in working memory. In a delayed-response task, a monkey observes food placement in a randomly selected compartment, which is then concealed. After a delay, the monkey must locate the food. This task depends on prefrontal cortex activity; monkeys with prefrontal lesions perform worse than those

with intact prefrontal cortices.

Human patients with injuries to their prefrontal cortex after stroke, tumors, or aneurysm, performed worse on a variety of working memory tasks such as the backward digit span test. Additionally, people with frontotemporal dementia, a neurodegenerative disorder characterized by a degradation of the frontal lobe, often have difficulty with working memory.

The prefrontal cortex is located in the anterior portion of the frontal lobe. Details in caption and text.

Figure 7. Prefrontal Cortex. The prefrontal cortex, shown in blue in an external view of the brain, is located in the anterior portion of the frontal lobe.

Habit or Procedural Memory—Striatum

The striatum (Figure 8), made up of the caudate nucleus and putamen, is important for habit or procedural memory and reward in learning. A T-maze is used to test procedural learning (Figure 9). In this task, a rodent is placed at the bottom of the T in the maze. The animal is trained to turn either left (with one tone) or right (with a different tone) once they reach the cross of the T. If the animal completes the task successfully, they are rewarded with a treat. The ability of the animal to learn this task depends on activity within the striatum. Animals with striatal lesions have impaired performance on the T-maze, but not on tasks that rely on other types of memory.

Rotating gif showing the location of the striatum in the brain.

Figure 8. Location of the striatum (in red), which is involved in procedural memory.

Figure 9. A T maze is used to test procedural memory and reward in learning. In this task, a rodent is placed at the area of the maze that corresponds to the bottom of the T. The animal is trained to turn either left or right. If the animal completes the task successfully, they are rewarded with a treat.

Emotional Memories—Amygdala

The amygdala plays a well-known role in processing emotions like fear and aggression, and is also involved in forming and storing memories, especially of emotionally arousing experiences. For example, Josselyn (2010) demonstrated the amygdala's role in storing fear memories in a study with rats. The researchers conditioned rats to fear a tone by pairing it with foot shocks. After conditioning, the rats would freeze upon hearing the tone, indicating they remembered the tone-shock association. When researchers induced cell death in the rats' lateral amygdala, this fear memory faded. Conditioning and implicit memory are also impaired in humans with amygdala damage (Bechara et al., 1995).

In addition to fear conditioning and implicit learning, the amygdala is also involved in encoding and storing emotional events. Emotional experiences form strong memories, with the amygdala playing a crucial role. The basolateral amygdala (BLA) is particularly important, as stress hormones and neurotransmitters, especially noradrenaline, in this region enhance the consolidation of emotional memories. Noradrenaline is released in response to emotional or stressful events. In experiments with rodents, noradrenaline injections into the BLA, but not adjacent parts of the amygdala, enhanced consolidation of emotional memories. This enhancement occurred by stimulating cAMP-dependent cell signaling and increasing neuroplasticity (Roozendaal et al., 2009). Noradrenaline plays a crucial role in synaptic plasticity in the amygdala and interconnected regions, including the hippocampus and neocortex. These mechanisms typically help form strong emotional memories, but under traumatic or chronic stress conditions, they can contribute to anxiety and the retention of traumatic memories, as seen in PTSD.

A coronal slice of the brain showing the location of the amygdala.

Figure 10. Illustration of a coronal slice of the human brain from Gray's Anatomy of the Human Body (1918), showing the amygdala in purple pointed to by the arrow. The amygdala is important for processing emotional memories.

Interim Summary

This section highlights several brain structures involved in memory. We focus largely on the hippocampus for its well-established role in declarative memory. We cover other brain regions involved in memory, including distributed cortical networks that store long-term memories, prefrontal cortex that processes working memory, the striatum for procedural memory, and the amygdala for emotional memories. This list of brain structures involved in memory is certainly not exhaustive. For example, the cerebellum is involved in procedural memory; the orbitofrontal cortex plays a role in positive emotional memories; and sensory cortices are important for storing aspects of memories processed in those areas. A single memory could be stored in several brain areas,

much like a mosaic.

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definition

Inability to create new declarative memories

×Close definition

Inability to retrieve memories from one's past

×Close definition

memory trace, or a hypothetical construct that represents the physical changes in the brain that constitute memory.

×Close definition

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11.4: Synaptic Mechanisms of Long-Term Memory

Learning Objectives

By the end of this section, you should be able to

- Describe the similarities and differences between LTP and LTD.
- Explain how LTP is demonstrated in a lab.

We have now learned about several brain regions that are important for memory encoding. But, what neural mechanisms within those regions are necessary for long-term memory? Decades of research, most of which used animal models, has supported the hypothesis that the long-term storage of information relies on changes in the strength of synaptic connections, in other words, changes in the ability of the presynaptic neuron to elicit a response (EPSP) in the postsynaptic neuron. Long-term changes in synaptic strength last hours, days, or weeks, which makes it tempting to link these changes in synaptic strength with memory. Currently, such long-lasting synaptic strength changes are the best supported mechanism for learning and memory, though the link between synaptic plasticity and memory is still under debate. In this section, we will learn about the molecular mechanisms by which synaptic connections can be changed to support memory formation.

Long-term potentiation and depression

There are two types of long-term synaptic plasticity: long-term potentiation (LTP) and long-term depression (LTD). LTP refers to a long-term increase in synaptic strength, where LTD refers to a long-term decrease in synaptic strength. Both types of plasticity are equally important for dynamically adjusting synaptic strength based on synaptic activity.

Our current understanding of the molecular mechanism of memory has its foundation in ideas first proposed over 70 years ago. In 1949, Dr. Donald Hebb suggested that memory might rely on simultaneous activity of the presynaptic and postsynaptic neuron, in other words “neurons that fire together, wire together”.

It wasn’t until 1973 that an experiment was done to test Hebb’s postulate. The Norwegian scientists, Drs. Bliss and Lomo, conducted an experiment where they recorded from and stimulated the hippocampus. To understand the experiment that Bliss and Lomo performed, we must first learn more about the unique circuitry of the hippocampus. The hippocampus is organized in a vastly different way than other brain structures. While different regions of the neocortex are reciprocally connected, receiving and sending input to the same brain areas (Felleman & Van Essen, 1991), regions of the hippocampus are connected through a series of excitatory glutamatergic pathways known as the trisynaptic loop (Figure 18.20).

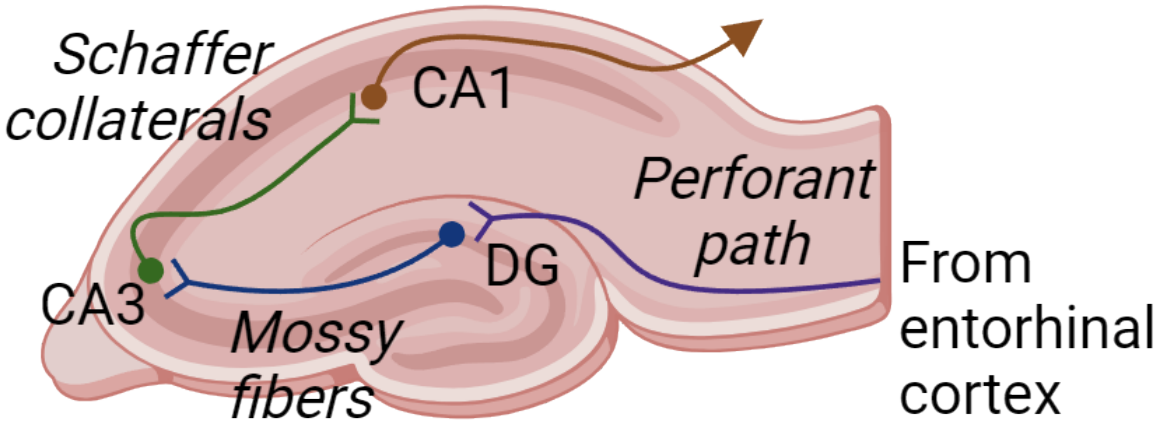


Figure 18.20 Hippocampal trisynaptic circuit

The first synapse is via the perforant path, which consists of axons from principal neurons whose cell bodies are located in the entorhinal cortex and terminate in the dentate gyrus. The second synapse is via the mossy fiber pathway, which consists of axons from principal cells in the dentate gyrus that send axon terminals to CA3. The third synapse is via the Schaffer collateral pathway, which consists of axons from principal cells in the CA3 that send axon terminals to CA1. There are other connections that course through the hippocampus, as well as an extensive network of inhibitory neurons that modulate the activity of the principal cells. As you will read below, this trisynaptic circuit in the hippocampus is where Bliss and Lomo first discovered the synaptic plasticity known as LTP (Anderson, 2007).

Bliss and Lomo's original experiments demonstrating LTP were performed by recording from the dentate gyrus in anesthetized rabbits (Figure 18.21). Specifically, they used an extracellular electrode to record the amplitude of the field/population EPSP (pEPSP), which reflects the summed activity of numerous simultaneously active neurons (see Methods: Electrophysiology). To get a baseline response, they first gave a test stimulation to the pathway of axons that provides input to the dentate gyrus, called the perforant path, and measured the amplitude of the pEPSP. They then delivered high frequency stimulation, called a tetanus, of the perforant path. Next, they delivered test pulses every few seconds and measured the pEPSP amplitude.As shown in Figure 18.21, the pEPSP amplitude increased by 300% after the tetanus and stayed elevated for at least 6 hours.

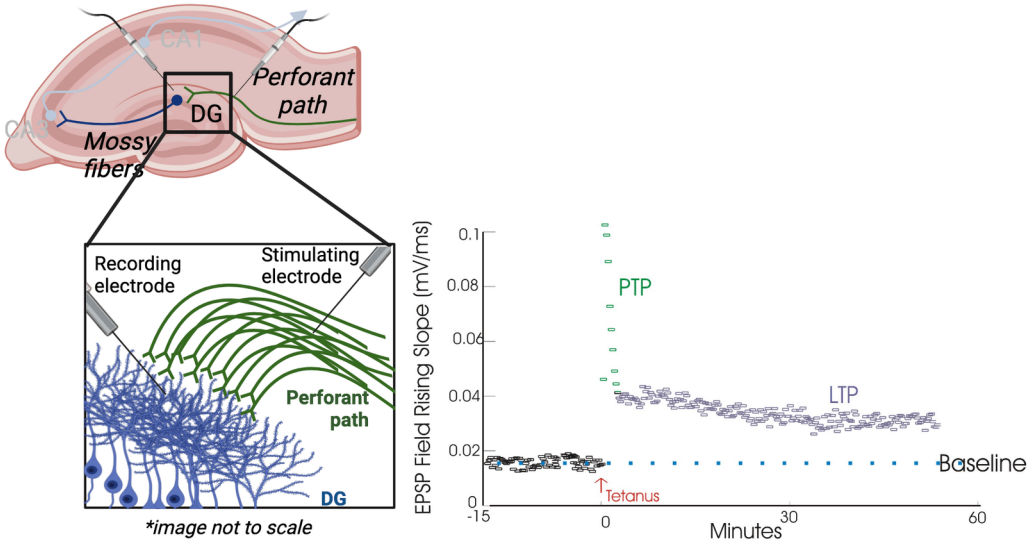


Figure 18.21 Bliss and Lomo experimental set-up This graph shows an example of long-term potentiation. The test stimulus leads to a small field EPSP at the start. After tetanus, field EPSP in response to the test stimulus is about 2x greater than before tetanus. Image credit: modification of work by Synaptidude at English Wikipedia. CC BY-SA 3.0, https://commons.wikimedia.org/w/inde...p?curid=886855

Following the findings of Bliss and Lomo, there were a number of follow up studies that contributed to the understanding of LTP. Bliss and Gardner-Medwin (1973) found that LTP lasts many weeks. Douglas and Goddard (1975) used theta-burst stimulation, a more physiologically-relevant stimulation, instead of a high-frequency tetanus to induce LTP. Other studies eventually showed that LTP is not something that only happens in one synapse at a time. While LTP can be homosynaptic (one pathway), it can also be associative (more than one pathway). In associative LTP, a weak synapse becomes stronger when it is stimulated simultaneously with a strong synapse. Stimulation of either synapse alone does not result in potentiation of the weak synapse; it's the combination of weak and strong firing together that makes LTP possible for the weaker synapse.

One could argue that decreases in synaptic strength are just as important as increases, thus the need for LTD. In LTD, synaptic strength decreases, rather than increases. There are two main reasons LTD is needed. First, being able to reduce synaptic strength prevents saturation and thus reaching a plasticity ceiling that would block further synaptic strengthening. Second, LTD is necessary to prevent network instability due to hyperexcitability, especially for structures like the hippocampus that are susceptible to seizures. Like LTP, LTD can either be homosynaptic or associative. The induction protocol for LTD is almost identical to the induction protocol for LTP, with one important difference: instead of high-frequency stimulation, LTD is induced by low-frequency stimulation. Low-frequency stimulation delivered to an already-potentiated synapse causes the synaptic strength to decrease to pre-potentiated levels, a term called depotentiation. By contrast, low frequency stimulation delivered to naive synapses leads to a decrease in synaptic strength below baseline. Both LTP and LTD are diagrammed, along with some of the molecular mediators that we will learn about, in Figure 18.22.

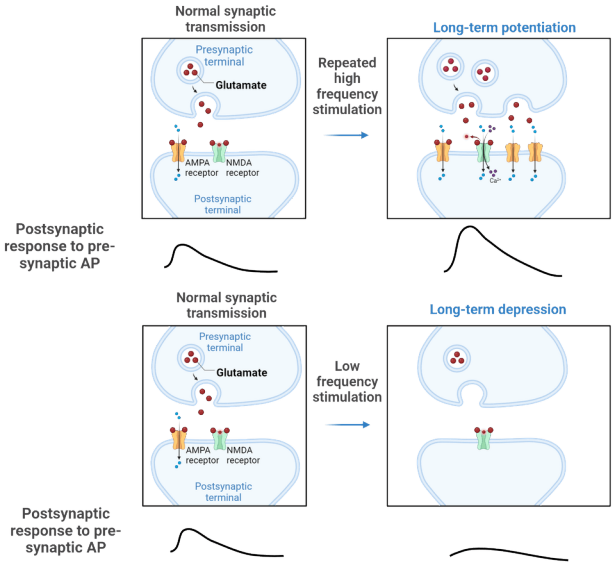


Figure 18.22 LTP vs LTD

Mechanisms of LTP and LTD

When Bliss and Lomo first described LTP in the 1970s, it was not clear how this could happen. What are the molecular changes that make a postsynaptic cell respond differently to the same presynaptic firing input? In 1983, a first clue was found when it was discovered that NMDA receptor antagonists blocked LTP induction, but did not affect LTP once it was induced (Collingsridge et al., 1983). Recall that NMDA receptors are nonspecific cation channels that, unlike AMPA receptors, are permeable to calcium. In addition, calcium chelators that prevent a rise in internal calcium in the CA1 pyramidal cells blocked LTP. Together, these studies suggested that LTP results from postsynaptic changes and requires calcium.

In addition to changes at the synapse, further evidence suggests that protein synthesis is required for at least some types of LTP. Frey et al., 1993 discovered that protein synthesis inhibitors caused LTP to decay to baseline levels 3-4 hours after LTP induction. This finding suggests that there is a form of LTP, called early LTP, that depends on changes in the synapse and is independent of protein synthesis and a form of LTP, called late LTP, that is dependent on protein synthesis. In other words, early LTP is the strengthening of an existing synapse whereas late LTP is the creation of new synapses. We will next discuss the mechanisms of each of these sequentially.

Early LTP and LTD

To understand the molecular mechanism of early LTP, one must first appreciate the unique nature of the NMDA receptor, which we established above is critical to LTP. NMDA receptors, like AMPA receptors, are ionotropic glutamate receptors that are present on the postsynaptic membrane of many excitatory synapses and allow entry of positive ions when activated (Figure 18.23). You might therefore be wondering why NMDA receptors are necessary for LTP if glutamate binding to AMPA receptors causes a depolarization in the postsynaptic neuron. The answer is the NMDA receptor/channels have 2 key features that distinguish them from AMPA receptors.

A reminder from chapter 3

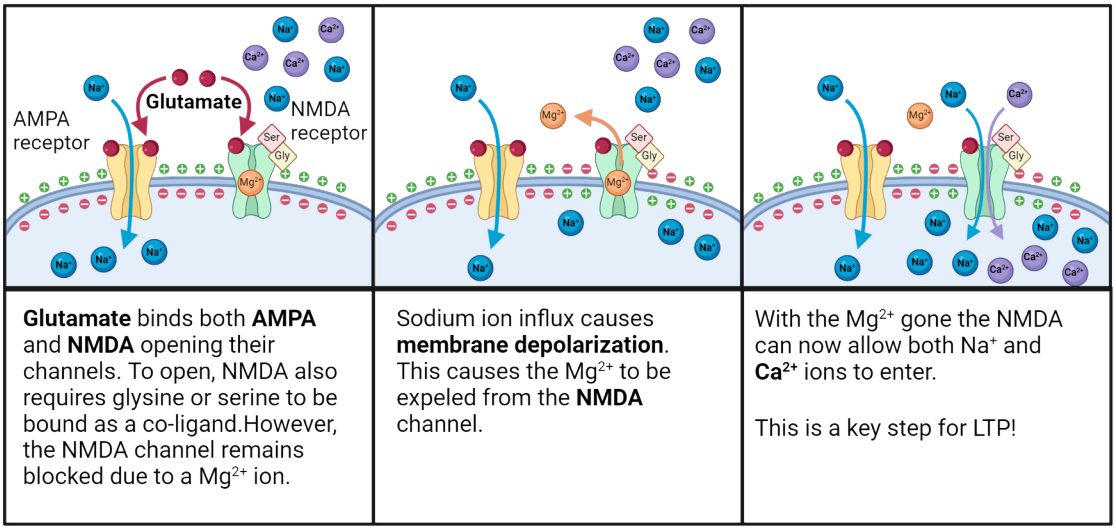


Figure 18.23 Reminder of AMPA/NMDA receptor functions

The first key feature is that NMDA receptors conduct not only sodium and potassium, but also calcium ions. Thus, activation of NMDA receptors leads to an increase in calcium concentration in the postsynaptic neuron. The early experiments mentioned above, showing that calcium was critical for LTP, therefore help further point us towards NMDA receptors as key in the LTP process. The increase in calcium concentration after NMDA channel opening leads to the activation of intracellular signaling pathways that are responsible for enhancing the response of the postsynaptic neuron to glutamate.

What are these changes that enhance response? It turns out that much of the enhancement comes from AMPA channels. We now know that when calcium enters through the NMDA channel, it binds to the enzyme calcium-calmodulin dependent protein kinase II (CAMKII), which either directly phosphorylates the existing AMPA receptors, causing them to be more permeable to sodium, or activates other enzymes which add new AMPA receptors to the postsynaptic membrane. Several lines of data support this model for early LTP induction. For example, LTP induction is prevented in CAMKII knockout mice, and direct addition of CAMKII to the postsynaptic membrane (thereby bypassing the need for AMPA and NMDA receptor activation) induces LTP.

From the above, it is clear that NMDA receptors are critical for the calcium entry that stimulates increased AMPA receptor conductivity (and therefore synaptic potentiation). But what makes this process sensitive only to high levels of input, like that from a tetanus in a classic LTP experiment? To understand this, we need to think about the second key feature of NMDA receptors that distinguishes them from AMPA receptors. While AMPA receptors open in response to glutamate alone, the NMDA channel is a molecular coincidence detector; there is a magnesium ion blocking the channel pore when the neuron is at its resting membrane potential, thus requiring not only glutamate for its activation, but also a membrane depolarization (Mayer et al., 1984; Nowak et al., 1984). Consequently, the postsynaptic membrane must be depolarized at the same time that glutamate is released from the presynaptic neuron. AMPA receptors work synergistically with NMDA receptors to activate this coincidence detector system. Specifically, glutamate activation of AMPA receptors provides the depolarization that is required for activation of the NMDA receptors. The AMPA channel activation has to be large enough to cause enough depolarization to kick out the magnesium block in the NMDA channels.

This process of AMPA-induced depolarization leading to NMDA channel unblocking is diagrammed in Figure 18.23. The steps for how that change contributes to LTP at the synaptic level are diagrammed in Figure 18.24. That threshold for NMDA unblocking is what makes the process sensitive to how strong the presynaptic firing is. More pre-synaptic firing in quick succession (like in a

tetanus stimulus) causes glutamate to build up in the synapse, opening many AMPA channels to create enough depolarization to "unclog" the NMDA channels and allow calcium to enter.

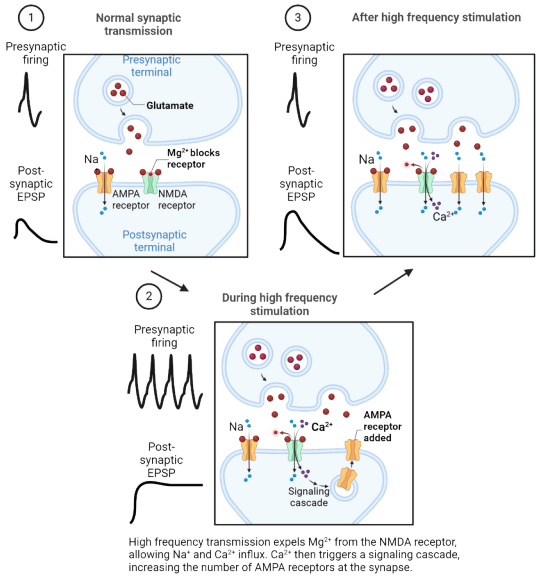


Figure 18.24 LTP

As you might guess, the mechanisms of LTD are opposite those of LTP (Figure 18.24). Postsynaptic AMPA receptors are downregulated, or removed from the synapse. AMPA receptors also show decreased conductance after LTD due to dephosphorylation by protein phosphatase. Although it might be tempting to think that LTD is a result of reduced postsynaptic calcium, both LTP and LTD have been shown to rely on increases in postsynaptic calcium. Whether LTP or LTD is induced depends on whether there is a large or small increase in calcium concentration, respectively.

Silent synapses reveal mechanisms of early LTP

One of the key discoveries that helped researchers figure out how LTP is induced actually came from finding synapses that don't work. In trying to better understand excitatory synapse LTP, researchers stumbled on synapses that are devoid of AMPA receptors, thus rendering them silent synapses—synapses that are unable to be potentiated. Can silent synapses be unsilenced? Two research groups conducted experiments to test this question. In both experiments, it was found that LTP induction caused an enhancement of the postsynaptic response to glutamate for AMPA, but not NMDA receptors, suggesting that unsilencing relied on a change in the postsynaptic response of AMPA receptors to glutamate (Kauer, Malenka & Nicholl, 1988; Liao, Hassler & Malinow, 1995). What properties of the postsynaptic neuron changed to allow this unsilencing? Two possibilities could have contributed to the increase in AMPA receptor conductance following LTP induction: either AMPA receptors were added to the postsynaptic membrane or existing AMPA receptors increased their conductance.

Late LTP

As mentioned above, LTP has two phases: an early phase which lasts 1-3 hours and a late phase that can last days or even weeks. Late LTP relies on the transcription factor, cAMP response element binding protein (CREB), which is responsible for synthesizing new proteins that are involved in the formation of new synapses. Experimental evidence supporting the idea that late LTP requires protein synthesis comes from studies showing that protein synthesis inhibitors (the same types of drugs that impair consolidation) disrupt late LTP (Frey et al., 1988). Furthermore, Engert and Bonhoffer (1999) used two-photon imaging to monitor hippocampal dendritic spines before and after LTP induction. They showed that after the LTP induction protocol, new dendritic spines emerged on the postsynaptic membrane. In summary, early LTP involves changes to existing synapses to increase their strength, whereas late LTP involves the growth of new synapses.

Do long-term changes in synaptic plasticity underlie learning and memory?

It is tempting to conclude that long-term changes in synaptic plasticity is the underlying cellular mechanism for memory. What is the experimental evidence that supports this idea? One of the first research groups to investigate the relationship between LTP and learning and memory was that of Dr. Edvard Moser. Dr. Moser's lab recorded synaptic potentials from the dentate gyrus in response to stimulation of the perforant path as rats explored a novel environment. The hypothesis was that as the rat learned the new environment, the synaptic potentials would increase in size, indicative of LTP. As predicted, the synaptic potentials increased in size, especially early in the session (Moser et al., 1993). Even stronger evidence came from research groups who demonstrated the manipulations that block NMDA receptors, for example with NMDA receptor antagonists, also disrupt learning and memory (Davis, Butcher, and Morris, 1992). Conversely, genetically altering rats to overexpress one of the subunits that comprise the NMDA receptor, NR2B, resulted in improved memory on a variety of memory tasks (Wang et al., 2009; Tang et al., 1999). Other studies support the idea that LTD is also critical for learning and memory. For example, Nicholls et al. (2008) found that by genetically altering mice so that they could not express LTD, they could disrupt behavioral flexibility in two different tasks. The authors suggested that weakening of synapses allows for behavioral flexibility by weakening old memories when new information is learned. Together, these studies strongly support the hypothesis that LTP and LTD are the neural substrates for learning and memory.

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11.5: Special Types of Neurons

A memory is distributed across several different parts of the brain. However, a few special types of neurons mainly in the medial temporal lobe contribute to highly specific types of memories.

Place Cells

Place cells are a special population of pyramidal cells of the hippocampus (Figure 11). These neurons increase their firing rates when the animal occupies a specific location in its environment. Figure 11 illustrates this phenomenon, showing a rat navigating a maze while its hippocampal place cells are recorded. The colored dots represent the rat's position on the maze when each place cell fires, with each color corresponding to a unique cell. This visualization demonstrates that individual place cells consistently fire when the rat occupies a particular spatial location. The place cells, when firing at the right times, help the animal create a spatial map of their surroundings.

Interestingly, these spatial maps are consolidated during sleep. When the rat sleeps after learning to run a particular maze during the day, their place cells fire in a sequence consistent with the spatial layout of the maze (even though they are not moving to these locations while asleep). This suggests that they are "replaying" their experience during sleep to learn and consolidate the spatial memory (Klinzing et al., 2019; see section on memory reactivation during sleep).

Picture of a rat going into a maze. colored dots depict the rat's location where certain place cells fire. Details in caption and text.

Figure 11. Place Cells. Place cells, a special population of neurons in the hippocampus, fire action potentials when an animal is in a specific location and are important in navigational memory. Here a rat is placed in a maze and place cells in its hippocampus are recorded. Where each place cell fires is indicated on the maze with colored dots. Dots of the same color indicate firing of the same place cell.

Grid Cells

Grid cells are located in the entorhinal cortex, the main input structure to the hippocampus. Closely related to the place cells, grid cells increase their firing periodically when an animal is at an intersection of a "grid" in a wide-open, previously-explored environment. The grid itself is roughly hexagonal and spans the whole environment an animal is in (Figure 12). The overlap of multiple grids gives the animal an idea of the surroundings. The scientific description of place cells and grid cells earned three scientists, Edvard Moser, May-Britt Moser, and John O'Keefe, a Nobel Prize in Physiology or Medicine in 2014.

Grid cells in the entorhinal cortex fire when in a specific area of a grid within a previously explored environment. Details in caption and text.

Figure 12. Grid cells are a special population of neurons located in the entorhinal cortex, which serves as the main input structure to the hippocampus. Similar to place cells, grid cells fire when an animal is at an intersection of a "grid" in a wide-open, previously-explored environment. These images on the left show the movement of a rat through a square environment depicted by a black line. The red dots indicate locations within the environment where a specific entorhinal grid cell fired. The images on the right show a spatial autocorrelogram that corresponds to the neuronal activity of the grid cell from the figures on the left.

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- Grid cells © Lisa M. Giocomo, May-Britt Moser, Edvard I. Moser adapted by Valerie Hedges is licensed under a CC BY (Attribution) license

definition

Specialized cells in the hippocampus that code specific locations in an environment. Important for establishing cognitive maps of different environments

×Close definition

Specialized cells in the entorhinal cortex that fire at consistent intervals as an animal moves through space. Important for establishing cognitive maps of different environments.

×Close definition

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11.6: Stages of Memory

This section gives a brief overview of memory processing stages, including encoding, consolidation, and retrieval.

Memory Encoding

Encoding refers to the process of converting incoming information into a mental representation that the brain can retain. In real life, you are presented with countless stimuli simultaneously. Imagine walking down a busy street, and the number of different sights, smells, and sounds you experience. Storing memories is an energetically costly process, and we are limited in the fact that all of our sensory inputs cannot possibly get encoded. Instead, our memory systems have evolved to adaptively encode the most salient information, such as environmental cues associated with threatening or rewarding experiences.

Decades of research have established that emotional memories are more strongly and vividly remembered than neutral memories, which may be partially driven by the preferential encoding of emotional events. The neurobiological mechanisms that prioritize emotional events include arousal from stress hormones (e.g., noradrenaline), fight-or-flight-related neurotransmitters (e.g., norepinephrine), and increased recruitment of the amygdala. These may drive the enhanced encoding of the most salient features of emotional events (Clewett & Murty, 2019; Mather & Sutherland, 2011).

Memory Consolidation

Memory consolidation refers to the process where short-term memories are transformed into long-term memories. While many theories have addressed how memories are stabilized over time, systems consolidation theory has emerged as the dominant perspective. Systems consolidation theory suggests that memories are stabilized as a result of interactions between the hippocampus and different regions of the neocortex (Alvarez & Squire, 1994; McClelland et al., 1995; Cowan et al., 2021). More specifically, the hippocampus is initially crucial for storing and retrieving memories; but over time, these memories become less dependent on the hippocampus and shift to being stored in the neocortex (Figure 13). Systems consolidation aligns with Patient HM's memory capacity. Recall HM's temporally graded retrograde amnesia, where he lost memories from the two years before his surgery, but maintained memories from his more distant past. The memories from shortly before the surgery still depended on the hippocampus, so were lost when his hippocampi were removed. Conversely, his childhood memories had fully transferred to the neocortex and no longer involved the hippocampus, so they were maintained after removing the hippocampus.

Two panels showing connections between cortical modules and hippocampus for new memories. Over time, the connections between cortex and hippocampus weaken, and the connections within cortex strengthen for consolidation in long-term memory.

Figure 13. Standard consolidation model. New memories are encoded across areas of cortex that represent the memory's features (e.g., sights, sounds, associations of the item and context); the hippocampus integrates and binds together that information. Over time, the hippocampal-cortical connections weaken and cortico-cortical connections strengthen until the memory is transferred to cortex (independent of the hippocampus) for long-term storage (consolidation). [Image adapted from Frankland & Bontempi, 2005]

Memory Retrieval

The process of accessing and recalling information previously encoded and stored in memory is known as retrieval. Memory retrieval is crucial for allowing people to use past information, knowledge, and skills in everyday life and to integrate learning of new information. Although memory retrieval is typically thought of as the conscious retrieval of stored facts and life events (i.e., declarative memories), retrieval also happens with procedural memories, as when you recall or perform a skilled action. Memory retrieval can be differentiated from memory encoding using a cued word-recall test. Imagine being given a list of 50 words to memorize, where the words belong to a few different conceptual categories (such as cinnamon, pepper, and curry, which fall under the category 'food flavors'). In a free-recall test, where you're asked to write down as many words as possible from memory, you might remember about 30% of the words. However, in a cued-recall test, where you're cued with categories (like 'food flavors'), you'd likely perform much better, possibly recalling 75% of the words. Higher scores in cued-recall show how retrieving information is helped by cues that activate contexts and associations between items encoded in memory.

State- and context-dependent memory. State-dependent memory refers to the phenomenon where memory retrieval is most effective when a person is in the same state of consciousness as when the memory was formed. This applies to states induced

by psychoactive substances like alcohol, as well as moods or other internal conditions. Context-dependent memory is related but instead of internal conditions, it involves external environments—memory retrieval is most effective when the person is in the same external environment as when the memory was formed. For example, in state-dependent memory, information studied while caffeinated is best retrieved in a similar state of caffeination. Whereas in context-dependent memory, information studied in one room is best retrieved in that same room. Biologically, memories are encoded through changes in synaptic strength and stored as spatiotemporal patterns of activity across neuronal networks. Being in the same state or context activates part of the neuronal pattern associated with the memory, facilitating full activation of the memory trace for retrieval.

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11.7: Memory Reconsolidation—New Views and Applications

Early perspectives of memory believed that memory storage was a singular and linear process, such that each time we remembered a prior experience, the original memory trace was retrieved (Alberini & LeDoux, 2013). However, recent work suggests that memories are susceptible to change, and as a result, memories can be distorted each time they are retrieved. In other words, it's possible that each time we recall a memory of a past event, it might change a little. Our memories are not fixed recordings of an event, but rather, dynamic reconstructions that evolve. This process is known as **memory reconsolidation**. Below, we briefly discuss current perspectives on reconsolidation and how researchers leverage reconsolidation to selectively update memories.

Memory Reactivation

Although it's well-established that memories become consolidated or stabilized over time, scientists are actively investigating the neural mechanisms underlying memory consolidation. Neuronal firing patterns present during encoding are repeatedly reactivated during 'offline' periods of post-encoding rest (e.g., sleep, awake rest) (McCleland et al., 1995; Alvarez and Squire, 1994; Tambini & Davachi, 2019). Indeed, landmark animal research revealed that place cells within the hippocampus that were active during recent exploration were preferentially reactivated during subsequent sleep (Pavlides & Winson, 1989; Wilson & McNaughton, 1994). Place-cell activation patterns observed during exploration and subsequent sleep were absent in pre-exploration sleep. Thus, the neuronal reactivation after exploration represented a replay of waking experiences. Critically, memory reactivation during sleep is linked with improved memory the next day.

Although early rodent research focused on reactivating spatial memories, recent human research has demonstrated memory reactivation of nonspatial, episodic experiences (Tambini & Davachi, 2019). In an fMRI study, participants learned pairs of items that consisted of an object and a picture of a scene. Researchers analyzed brain activation in the medial temporal lobe while participants encoded the pairs and while they rested after encoding. Participants were later tested if they remembered the object that was paired with a scene. Results showed that brain activation during encoding and rest was highly similar for remembered pairs; whereas brain activation during encoding and rest was dissimilar for forgotten pairs (Staresina et al., 2013). These results show that memory reactivation occurred during the post-encoding rest period, and was linked to subsequent memory performance.

Researchers have begun examining when memory reactivation most likely occurs. Reactivation of neuronal sequences are most pronounced during a brain state that can be measured with EEG, called high-frequency oscillatory events or sharp wave ripples (SWRs) (Skaggs & McNaughton, 1996). Although SWRs can occur during periods of awake rest, they primarily occur during slow-wave-sleep, also known as non-rapid-eye-movement (NREM) sleep, which is thought to be the most restorative stage of sleep. Several studies have shown that disturbances to SWRs can impair learning and later memory (Tambini & Davachi, 2019). These memory impairments likely stem from disrupted memory reactivation. In sum, given the mounting evidence connecting reactivation to later memory performance, researchers increasingly view neural reactivation as a key mechanism underlying memory consolidation in humans.

Targeted Memory Reactivation

Targeted memory reactivation (TMR) is a noninvasive technique to selectively strengthen or weaken memories during sleep or awake rest (Oudiette & Paller, 2013). In TMR studies, sensory cues (e.g., sounds or scents) are paired with items (e.g., words or pictures) during a learning session. During subsequent sleep, the same sensory cues are presented to trigger the reactivation of the associated memory and thereby strengthen the memory for specific items (Hoffman et al., 2024) (Figure 14). Indeed, several TMR sleep studies have reported enhanced memory for items that were cued during sleep compared to items that were not cued (Rasch et al., 2007; Rudoy et al., 2009). Critically, this memory benefit is attributed to the memory reactivation processes described in the section above. A recent meta-analysis reviewed 90 TMR studies and found general support for TMR-related memory benefits and that the effects of TMR are most pronounced during non-rapid-eye-movement stages of sleep, and particularly slow-wave-sleep (Hu et al., 2020).

Image shows 3 panels: encoding (or studying); consolidation during sleep; retesting or retrieval without sensory cues. Details are presented in the text and caption.

Figure 14. Targeted Memory Reactivation (TMR) involves pairing sensory cues (e.g., sounds) with items to be remembered (e.g., words) during a learning session (encoding). During subsequent sleep, the sensory cues are presented to trigger the reactivation of the associated memory (consolidation). After waking up, retrieval for memory that was targeted and reactivated is stronger (without presenting the sensory cue). [Image adapted from: Carbone & Diekelmann, 2024]

TMR has been shown to be effective across different types of memory, including declarative and procedural memory. Given the compelling experimental findings, researchers have begun examining applications of TMR to improve people's lives. For example, recent TMR studies on vocabulary and grammatical learning have found TMR-related memory benefits (Batterink et al., 2017). Thus, using cues to reactivate memories during sleep could support language acquisition in educational contexts. Moreover, given the relationship between TMR and procedural memory, TMR could be leveraged to support motor skill development (Cousins et al., 2014). This might be applied to improve athletic or musical performance, or to clinical disorders related to motor impairments. Finally, TMR is not only applied to strengthen memories, but several studies have explored using TMR to weaken specific memories (Simon et al., 2018; Schectman et al., 2020). Thus, TMR has been proposed to be a psychotherapeutic instrument for weakening memories related to traumatic events, which is especially relevant for anxiety or post-traumatic stress disorder (PTSD). However, the relationship between TMR and emotional memories remains mixed—one study showed that TMR-related memory benefits appeared for neutral, but not emotional memories (Groch et al., 2016), whereas another study showed that TMR was indeed effective for dampening emotional memories (Lehmann et al., 2016). Targeted memory reactivity (TMR) is an exciting and rapidly evolving area of research with potentially impactful applications.

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definition

The process in which reactivated memories become transiently sensitive to modifications

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11.8: Memory-Related Disorders

Memory is fundamental to our daily functioning and sense of self, yet it can be fallible and fragile. Memory disorders represent a diverse group of conditions that disrupt our ability to encode, store, or retrieve information. Memory disorders can range from mild forgetfulness to severe impairments that profoundly affect an individual's quality of life.

Memory impairments are prevalent across many clinical conditions, including amnesia, traumatic brain injury, and neurodegenerative conditions such as Alzheimer's disease. Cases of amnesia, such as Patient HM after surgical removal of his hippocampi, are among the earliest documentations of brain-related memory dysfunction. Traumatic brain injuries and concussions have also been shown to be related to memory impairment, particularly short-term memory loss (McDowell et al., 1997; Malojcic et al., 2008; Covassin & Elbin, 2010). Neurodegenerative conditions, such as Alzheimer's disease, can also be characterized by short-term and long-term memory degradation. Researchers have been working intensely to understand how disruptions to neural, genetic, and vascular systems may give rise to different types of memory dysfunction (Morely & Farr, 2014; El Haj et al., 2016; Religa et al., 2013). As our population ages and the prevalence of memory disorders such as dementia and Alzheimer's increases, understanding these disorders will be increasingly relevant to society.

Another memory-related condition that may affect younger adults and is interesting to students is Korsakoff's syndrome. This section concludes with an examination of Korsakoff's syndrome, exploring its effects and neurobiological underpinnings.

Korsakoff's Syndrome

Korsakoff's syndrome is a disorder resulting from a severe deficiency of thiamine. Thiamine (vitamin B-1) is essential for metabolic processes, such as producing energy from glucose. Dietary thiamine is found in whole grains, legumes such as beans and peas, and some meats and fish. Healthy people with a well-balanced diet get sufficient thiamine, however, gastrointestinal illnesses can cause an inability to absorb thiamine properly. The body's ability to absorb thiamine is also disrupted by chronic alcohol misuse. Alcohol misuse, in addition to its toxic effects on brain cells, can cause Korsakoff's syndrome. While chronic alcohol consumption is the primary cause of Korsakoff's syndrome, malnutrition, eating disorders, and genetic factors can also increase susceptibility to the condition.

People with Korsakoff's syndrome experience several kinds of cognitive and memory impairments. They can have both retrograde and anterograde amnesia, as well as severely impaired short-term memory. The patients may confabulate or make up information they can't remember. People who confabulate do not consciously recognize that their statements are untrue, and are not intentionally trying to deceive others, which is why it is sometimes called "honest lying." Generally, confabulation only happens as a person is trying to recall recent autobiographical memories; their semantic and procedural memories are less susceptible to confabulation. Scientists propose that individuals with retrograde amnesia confabulate to fill memory gaps.

Korsakoff's syndrome leads to decreased glucose metabolism in the brain, reducing its primary fuel source, and causes destruction of both neurons and glial cells. As a result of this cell loss, there is often shrinkage of the cortex, thalamus, cerebellum, and hippocampus. Korsakoff's syndrome can be treated by giving thiamine supplements and eliminating alcohol consumption. If treated within days after the onset of brain damage, people generally recover completely. However, one of the major challenges is making a proper diagnosis, since the symptoms of Korsakoff's syndrome present similarly to other disorders.

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definition

A condition of the central nervous system caused by severe deficiency of thiamine (vitamin B-1) that primarily affects the memory system.

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12: HUNGER, EATING, AND HOMEOSTASIS

12.1: Principles of Homeostasis
12.2: Neural Control of Feeding Behavior
12.3: Food Intake Disorders

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12.1: Principles of Homeostasis

Learning Objectives

By the end of this section, you should be able to

- Describe the major principles of homeostasis including set points and negative feedback mechanisms.
- Explain the components of a generic homeostatic system including sensors, control systems, and effectors.

Animals maintain a stable internal environment using multiple homeostatic systems that each regulates a distinct, life-sustaining factor. For example, the neurons and organs that regulate hunger and energy balance are distinct from those that regulate thirst and water balance. Although distinct, these homeostatic control systems all utilize the same fundamental principles.

Homeostatic systems maintain life-sustaining factors at optimal set points

Animals maintain homeostasis for a particular biological parameter by maintaining values at an optimal set point. For example, most humans maintain a blood oxygen level of 75-100 mmHg (the partial pressure of oxygen in the bloodstream), a core body temperature of 37 °C, a caloric intake of 2000-2500 calories per day, and a blood osmolarity of 300 mOsm/L (the concentration of solutes in fluids). Set points are not necessarily a specific value, but rather a narrow range of values by which an animal can survive in good health. Individuals within a species may have slightly different set points based on their genetics and their environment.

Set points for specific factors can change over a 24-hour circadian period. For example, human core body temperature is approximately 36.5 °C at night when we are sleeping compared with 37.5 °C during the day when we are more active. Set points can also change throughout the life of an animal. For example, as animals develop from juveniles to adults (such as humans during puberty), they require a much higher caloric intake than when they were younger. Later in life, as animals age, metabolism slows down and daily caloric needs decline.

Sometimes, during certain environmental challenges, it is temporarily beneficial to maintain factors outside normal set point values. Allostasis (from the Greek root allo, meaning “other”) is the temporary maintenance of internal physiological conditions outside the normal range. These changes in set points allow an organism to respond to an immediate threat to survival. For example, when we are sick, one response is to develop a “fever” in which our set body temperature increases by 1-2 °C to combat the infection (Figure 16.3). When we experience a stressful environmental condition, such as taking an exam, speaking in front of an audience, or undergoing something truly life-threatening, we undergo a temporary elevation in body temperature and heart rate while simultaneously undergoing a temporary decrease in hunger and thirst. While these allostatic responses help to temporarily persevere against short-term challenges, it is not optimal to be in a state of allostasis for too long. For example, being in a state of chronic stress can ultimately lead to cardiovascular disease and aberrations in body weight.



Figure 16.3 Allostasis example: Fever An increased body temperature can help fight infection, an example of allostasis. Image credit: CDC - www.cdc.gov/vhf/ebola/resour...ographics.html, Public Domain, https://commons.wikimedia.org/w/inde...curid=41517131

Homeostatic systems maintain set points using negative feedback mechanisms

Animals maintain set points by utilizing negative feedback mechanisms. In these systems, a deviation from a set point causes a response that counteracts the change, thereby restoring optimal set point values (Figure 16.4). There are three components of a negative feedback loop: A sensor detects the initial deviation from the normal set point. A control system receives and processes information from the sensors, ultimately causing an effector system to produce a response that counteracts the change.

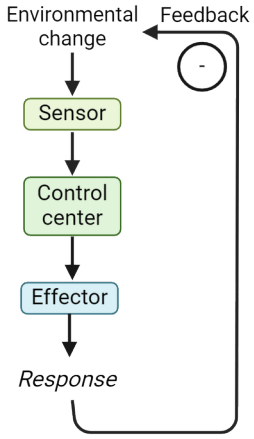


Figure 16.4 Homeostatic negative feedback loop

A familiar example of a negative feedback mechanism is the cooling system of a laptop computer (Figure 16.5). If a laptop becomes too hot, the high temperatures could damage the circuits and hardware. Small thermometers within the laptop serve as sensors, detecting temperatures higher than an optimal value. These thermometers signal to the central processing unit that the computer is too hot. The central processing unit then turns on an effector system—fans within the computer—to blow out the hot air. Once the computer cools down, the thermometers detect the cooler temperatures, the central processing unit turns off the fans, and an optimal temperature is achieved.

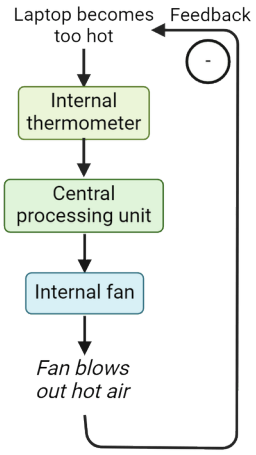


Figure 16.5 Unidirectional negative feedback loop

A computer fan is an example of a unidirectional homeostatic system, a feedback mechanism in which a factor is regulated in only one direction—in this case, whether the computer becomes too hot (but not if the computer becomes too cold). In contrast, bidirectional homeostatic systems regulate deviations from a set point in two directions. For example, consider a home thermostat system that maintains an optimal temperature range so that a home does not become too hot or too cold (Figure 16.6). An increase in temperature is sensed by a thermometer inside the home and is relayed to the control system, the thermostat. The thermostat then causes an effector system, an air conditioner, to blow cool air into the home to decrease the temperature. If the home becomes too cold, this decrease is also detected by a thermometer and relayed to a thermostat. The thermostat responds to this change by turning on the home furnace to increase heat. Therefore, the home thermostat system functions as a bidirectional homeostatic system to keep the temperature within a narrow range.

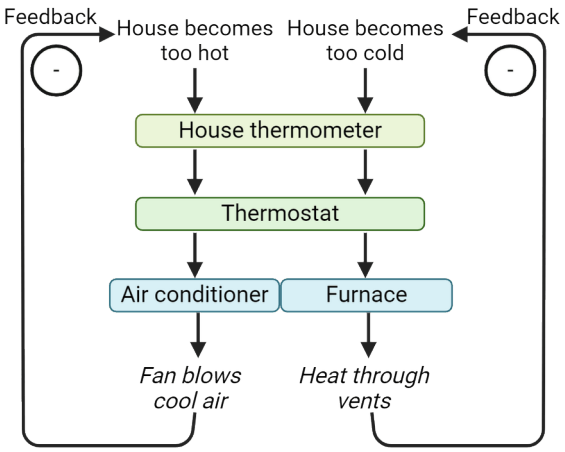


Figure 16.6 Bidirectional negative feedback loop

Just as engineers design unidirectional and bidirectional homeostatic mechanisms in computers, home thermostats, and other technology, animals have evolved homeostatic mechanisms of their own that work in the same way. Instead of electrical circuits in wires, these homeostatic mechanisms depend on neural circuits throughout the brain and body to precisely sense a deviation from a set point, to integrate and process these changes in control systems, and to effect physiological and/or behavioral effector systems to counteract the change.

The nervous system regulates homeostasis using different effector systems

Many homeostatic systems throughout the body, such as those that regulate blood oxygenation levels, body temperature, caloric intake, and fluid intake, are regulated by the nervous system. The challenge for neuroscientists interested in studying the neurobiology of homeostasis is to understand the biological substrates of these homeostatic mechanisms. How do animals sense changes in their internal environments, integrate this information within control centers, and ultimately cause changes in physiology and behavior to maintain homeostasis? What and where are the relevant neurons and cell types, and how do they communicate information with each other?

The nervous system detects changes in set points via sensory cells within the central and peripheral nervous systems (Figure 16.7). These specialized cells express unique ion channels and membrane-bound proteins to detect changes in blood chemistry, body temperature, stretch of visceral organs, blood osmolarity, and hormones released throughout the body. In response to deviation from a set point, these sensory cells communicate with other cells in the brain, typically in the brainstem or hypothalamus, that function as control centers. These control centers integrate information and regulate effector systems that counteract the deviation from the set point.

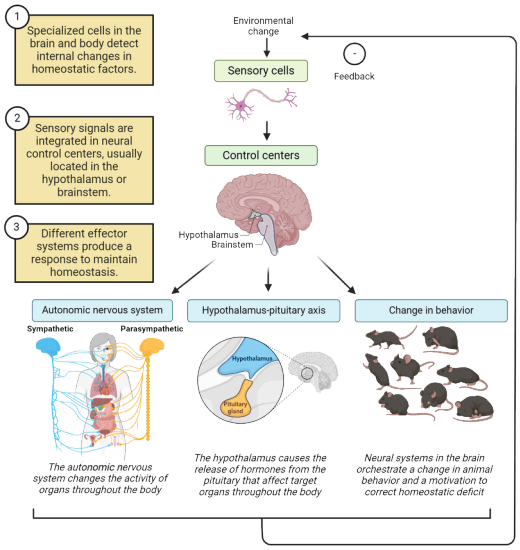


Figure 16.7 Neural mechanisms of homeostasis

In general, these effector systems modulate changes in life-sustaining factors in one of three ways (Figure 16.7):

- Some effector systems cause a physiological change via the autonomic nervous system. The autonomic nervous system regulates physiological functions, such as heart rate or respiratory rate, that are typically not under conscious control. The autonomic nervous system can be anatomically and functionally divided into the sympathetic nervous system and the parasympathetic nervous system, two distinct neural networks that often cause opposing effects on target neurons. The sympathetic division typically facilitates an increase in activity necessary for a “fight or flight” response in which an animal is alert and active. For example, when the sympathetic nervous system is preferentially activated, heart rate increases and digestive functions decrease. In contrast, the parasympathetic nervous system typically facilitates a non-emergency, energy-replenishment state that can be characterized as more of a “rest and digest” response, for example by decreasing heart rate and increasing digestion. Therefore, the autonomic nervous system can cause changes in physiological states that affect the maintenance of homeostasis for physiological factors. These changes are often involuntary and automatic, occurring without any conscious realization by the animal undergoing these changes.
- Some effector systems cause a physiological change via the neuroendocrine system. This system causes the release of hormones that affect target organs throughout the brain and body. Most of these hormones are released via the hypothalamus-pituitary system, a parallel series of fibers that originate from the hypothalamus and cause hormone release from the pituitary gland. Like regulation by the autonomic nervous system, homeostatic regulation by the neuroendocrine system is involuntary and unconscious.
- Some effector systems regulate homeostasis by changing motivational drive and animal behavior. For example, if there is insufficient calories/nutrients or insufficient water within an animal, the nervous system can correct for these deficiencies by

increasing the drive for food or water. We describe these increases in motivation as “hunger” and “thirst,” and they ultimately cause a change in behavior that can maintain homeostatic set points. Unlike regulation by the autonomic nervous system and neuroendocrine systems, behavioral responses are voluntary and conscious. Although an animal cannot voluntarily choose to be hungry or thirsty, an animal can choose how to behave during these motivational states. However, the longer the animal goes without eating or drinking, the stronger the motivational drive, and animals gradually feel more uncomfortable until they ultimately act on their homeostatic needs.

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12.2: Neural Control of Feeding Behavior

Learning Objectives

By the end of this section, you should be able to

- Describe the reasons why animals need to maintain homeostasis for calories and energy balance.
- Describe the neural components of homeostatic systems that regulate hunger and satiety.

People typically celebrate major milestones (e.g., birthdays, promotions) or holidays (e.g., Thanksgiving, Independence Day), with a large, delicious meal. Think about the last time you gathered with friends or family for such an event. In the morning and early afternoon, you might only have had a light breakfast or lunch in anticipation of all the good food to come. By the time dinner starts, you are hungry and can't wait to eat. This hunger is palpable—your stomach might gurgle and feel "empty," and you think about food more and more. Perhaps you even start to feel "hangry"—emotionally upset because of your growing appetite. Once you finally start eating, your hunger dissipates, and you enjoy the meal. However, in the moments to come, another interesting process starts to occur—you eat so much that, not only are you satiated, you start to feel full. In fact, on holidays like Thanksgiving, people typically overeat to the point that they feel uncomfortably full and can't eat another bite.

This process of transitioning from a hungry state to a full state presents an interesting neurobiological question. At one moment in time, food is rewarding, and you are highly motivated to eat. But then, just 20-30 minutes later over the course of a meal, food no longer seems rewarding to consume—in fact, it becomes aversive. When you feel full, you wouldn't consume even the most delicious dish. How does the nervous system change the rewarding and aversive properties of food? How does the brain ensure that you consume enough food but not too much such that it overwhelms the digestive system?

Eating food is ultimately about maintaining an optimal caloric intake. All animals need to consume calories for energy and nutrition—and the only way to acquire calories is to seek food. Therefore, energy homeostasis requires that an animal's nervous system sense its caloric need and produce an appropriate motivational state to consume food, what we call being hungry or full. If we don't consume sufficient calories, we might become undernourished and lose weight to an unhealthy degree. In contrast, if we consume too much food, we store excess calories as body fat that could cause further health problems. Fortunately, our energy homeostasis systems work so well that the average person doesn't fluctuate in body weight more than 1-2 pounds over the course of a year. Like all homeostatic processes, various populations of cells serve as sensors, control centers, and effectors for driving and halting food intake to maintain energy homeostasis.

Hormonal and neuronal sensors of caloric intake

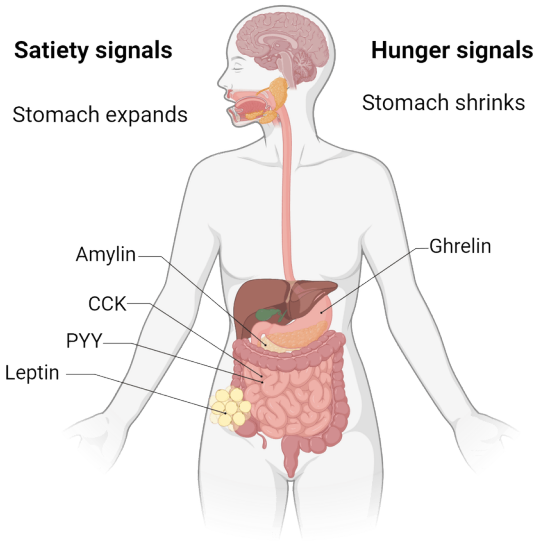


Figure 16.15 Hormonal indication of food intake

The nervous system measures caloric need using neural and hormonal mechanisms (Figure 16.15). The initial ingestion of food is sensed by the degree to which the stomach expands. The stomach is composed of elastic smooth muscle fibers that can stretch upon the ingestion of foods and liquids. Sensory fibers from the vagus nerve (the 10th cranial nerve) surrounding the stomach increase activity the more the stomach is stretched (Figure 16.16). Therefore, relatively high activity in these fibers indicate that the stomach is becoming more full, while relatively low activity in these fibers indicate that the stomach is empty. The amount of activity in these neurons indicates the degree to which an animal should feel full. (This is why drinking a large amount of water can temporarily make you feel full—the stomach is stretched in response to the water even though there are no calories). (See Studying the effect of digestive organ stretch on neural activity.)

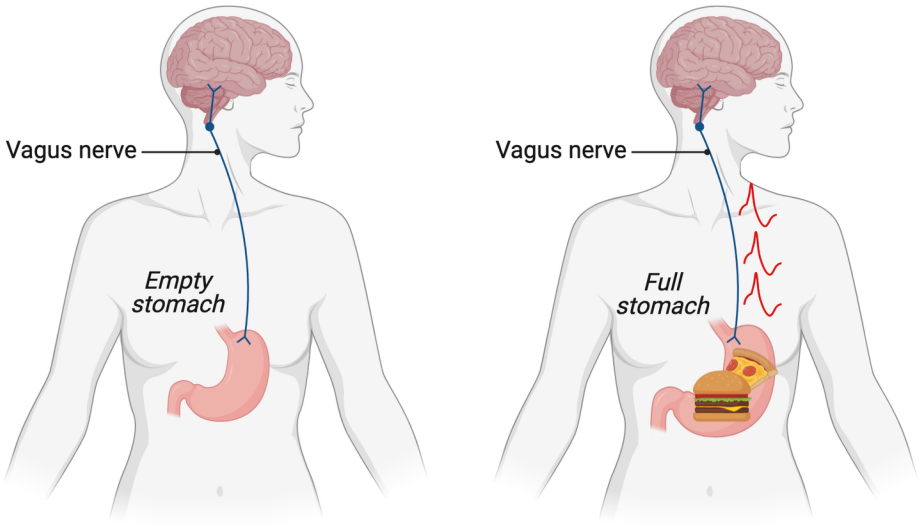


Figure 16.16 Stomach fullness as a satiety signal Stretch of the stomach muscles causes sensory fibers of the vagus nerve to fire.

Caloric need is also sensed by cells throughout the digestive tract that release a variety of hormones to indicate that an animal has recently ingested food. Many of these hormones are anorexigenic, meaning that they ultimately cause a reduction in feeding. For example, in response to food passing from the stomach into the gut, specialized cells in the pancreas release amylin. Cells in the intestines release cholecystokinin (CCK) and peptide YY (PYY). Levels of these hormones correlate with the amount of food recently consumed—they are relatively low just before a meal and relatively high during and just after a meal (Figure 16.17). The presence of these hormones in the bloodstream indicate that an animal has just consumed a meal and ultimately cause an animal

to feel satiated. In contrast, prior to a meal, cells in the stomach release the orexigenic hormone ghrelin (Figure 16.17). Elevated ghrelin levels indicate an absence of food and cause an animal to feel hungry.

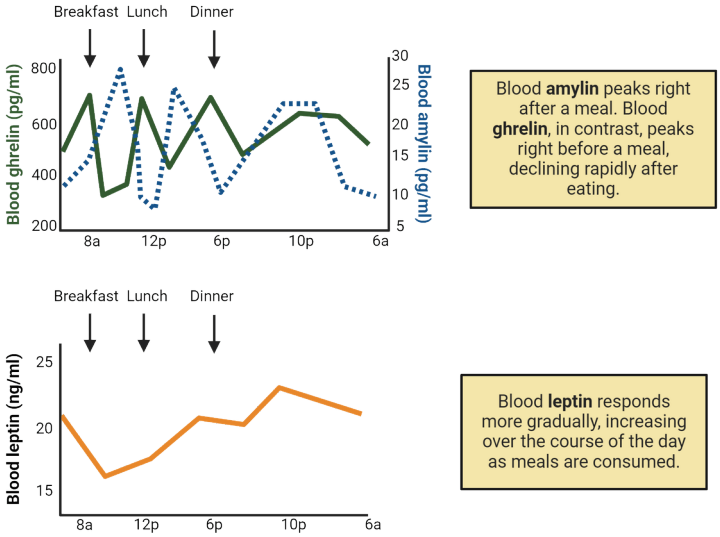


Figure 16.17 Variation in blood hormones after a meal Ghrelin and leptin data based on findings of: Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. 2001 Aug;50(8):1714-9. doi: 10.2337/diabetes.50.8.1714. PMID: 11473029. Amylin data based on: Kruger DF, Gatcomb PM, Owen SK. Clinical Implications of Amylin and Amylin Deficiency. The Diabetes Educator. 1999;25(3):389-397. doi:10.1177/014572179902500310

Food intake is also regulated in a more long-term manner through the release of the hormone leptin (Figure 16.17). Leptin is released by adipocytes in white adipose tissue (WAT) in proportion to their size. Therefore, an animal with relatively low body fat will not release as much leptin as compared to levels if the same animal gains weight and accumulates more body fat. The larger the fat mass, the more leptin is released, which ultimately causes an animal to feel less hungry.

Therefore, if you have not eaten recently and are just about to start a meal, your stomach is likely to be in a contracted state, your blood concentration of ghrelin is relatively high, and your blood concentration of amylin, CCK, and PYY is relatively low. As you eat a meal, your stomach expands, ghrelin levels decrease, and concentration of amylin, CCK, and PYY increase. These signals are ultimately integrated within the brain.

Neuroscience in the Lab

Studying the effect of digestive organ stretch on neural activity

When you eat a meal, your stomach expands, holding and mixing the ingested food with enzymes and acids for 2-4 hours before slowly releasing it into the intestines. This stretch of the stomach is sensed by specialized nerve endings from the vagus nerve that transmit information to the brain about an increase in stomach volume. In fact, vagal nerve endings also sense stretch of the intestines as digested food passes through.

In the lab, it is possible to study the effects of stomach and intestinal stretch on neural activity by artificially inflating the stomach or intestines of an anesthetized laboratory animal with a small balloon (Figure 16.18). A sterile latex balloon is inserted into the stomach or intestines and inflated to a precise volume via a small catheter. Scientists can then inflate or deflate the balloon while simultaneously measuring neural activity in peripheral or central neuron populations.

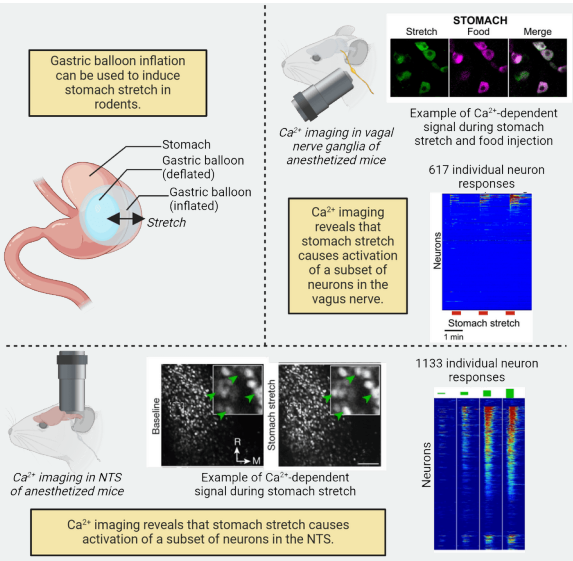


Figure 16.18 Neural activation by stomach stretch Vagus nerve Ca^{2+} imaging data reprinted from: Williams EK, Chang RB, Strochlic DE, Umans BD, Lowell BB, Liberles SD. Sensory Neurons that Detect Stretch and Nutrients in the Digestive System. Cell. 2016 Jun 30;166(1):209-21. doi: 10.1016/j.cell.2016.05.011. Epub 2016 May 26. PMID: 27238020; PMCID: PMC4930427. (C) 2016 with permission from Elsevier. NTS Ca2+ imaging data from: Ran, C., Boettcher, J.C., Kaye, J.A. et al. A brainstem map for visceral sensations. Nature 609, 320–326 (2022). https://doi.org/10.1038/s41586-022-05139-5 CC BY 4.0

Using this technique, recent studies have identified the exact neural populations that sense stomach and intestinal stretch using calcium imaging (see Methods: In Vivo Calcium Imaging). For example, a recent experiment (Williams et al., 2016) increased stomach or intestinal volume while measuring neural activity in different populations of vagus nerve sensory neurons (Figure 16.18). A small subset of vagus nerve neurons that express a distinct genetic marker, *Glp1r*, were found to innervate the stomach and intestines. Consistently, these neurons increased neural activity during artificial inflation of the stomach and intestines. Interestingly, other populations that expressed other genetic markers were found to innervate other peripheral organs.

Glp1r-expressing vagus neurons synapse onto neurons in the nucleus tractus solitarius (NTS). Another experiment (Ran et al., 2022) measured activity in the NTS during stomach and intestinal stretch, finding that NTS neurons are topographically organized based on the region being stretched. NTS neurons that increase activity in response to stomach stretch are located more dorsolaterally, while NTS neurons that increase activity in response to intestinal stretch are located more medially.

Taken together, these studies identified a genetically-defined anatomical pathway from the digestive tract to the brain that signals stomach and intestinal volume within the NTS. Future research will identify how this increase in volume along the digestive tract ultimately causes satiety and the perception of feeling full.

Central integration and regulation of food intake

Neural and hormonal signals from the digestive tract and adipose tissue are integrated in the central nervous system. Although there are multiple parts of the brain that regulate food intake, the two areas that seem to directly detect neural and hormonal signals from the periphery are the hypothalamus and brainstem.

The hypothalamus has several groups of neurons located along circumventricular organs, areas where the blood brain barrier is relatively diminished such that hormones and other substances can easily pass from the blood to the extracellular environment (Figure 16.19). These regions include the organ vasculosum of the lateral terminalis (OVLT), the median eminence, the neurohypophysis in the pituitary, the subfornical organ (SFO), the pineal gland, and the subcommissural organ. These brain regions play roles in multiple homeostatic processes.

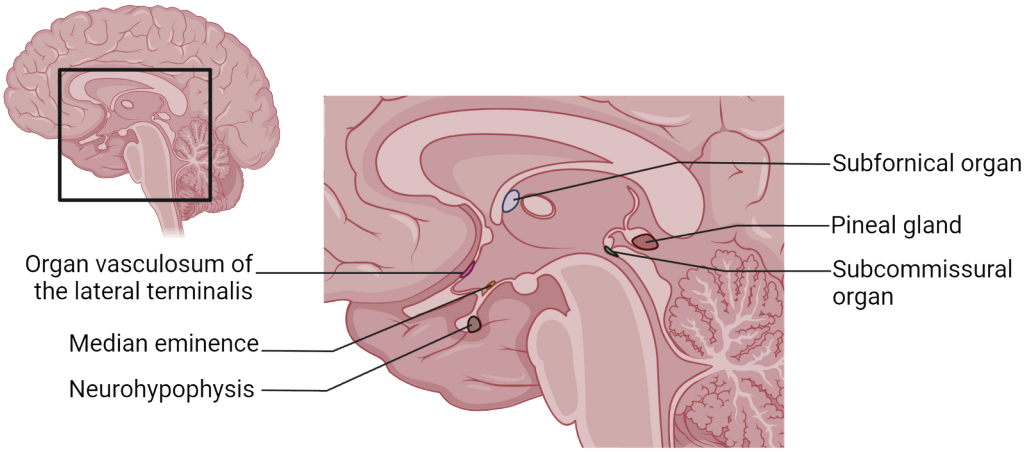


Figure 16.19 Circumventricular organs

In the case of caloric regulation, neurons in a region of the hypothalamus called the arcuate nucleus, which sits adjacent to the median eminence, have receptors for hormones that regulate feeding. The arcuate nucleus can be subdivided into two antagonistic populations of neurons: those that express the neuropeptide agouti-related peptide (AgRP) and those that express pro-opiomelanocortin (POMC) (Figure 16.20).

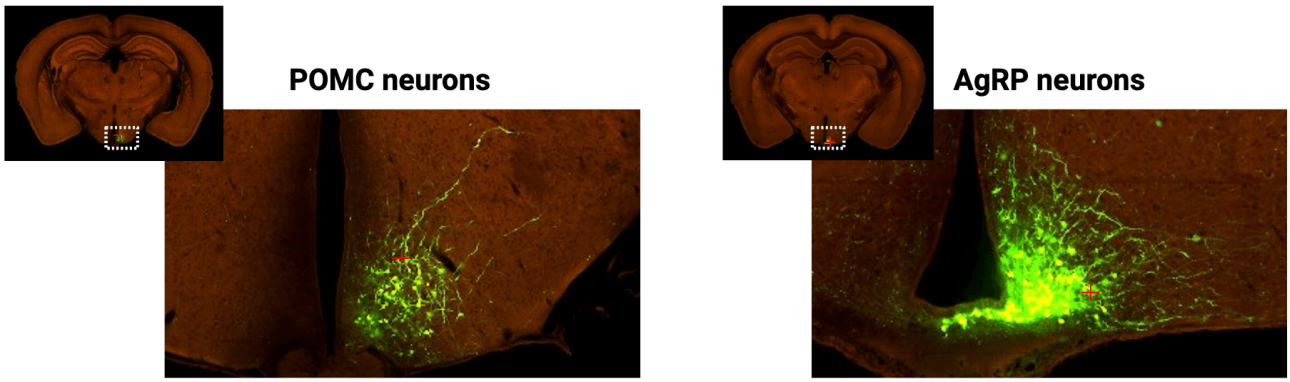


Figure 16.20 Acruate nucleus neuron tracing Green fluorescent tracers reveal POMC and AgRP cell bodies and axons. Image credit: POMC-Cre anterograde tracing. AgRP-IRES-Cre anterograde tracing. Allen Brain Atlas.

AgRP neurons increase activity in response to orexigenic hormones, such as ghrelin, and are inhibited by anorexigenic hormones. In contrast, POMC neurons increase activity in response to anorexigenic hormones and are inhibited by orexigenic hormones (Figure 16.21). Therefore, AgRP and POMC neurons are like two sides of a balance beam—the relative activity within AgRP and POMC neurons correspond with the homeostatic feeding state of an animal, with AgRP neurons preferentially activated the longer an animal goes without feeding, and POMC neurons activated when an animal consumes a meal (see feature box on studying the regulation of food intake by the hypothalamus).

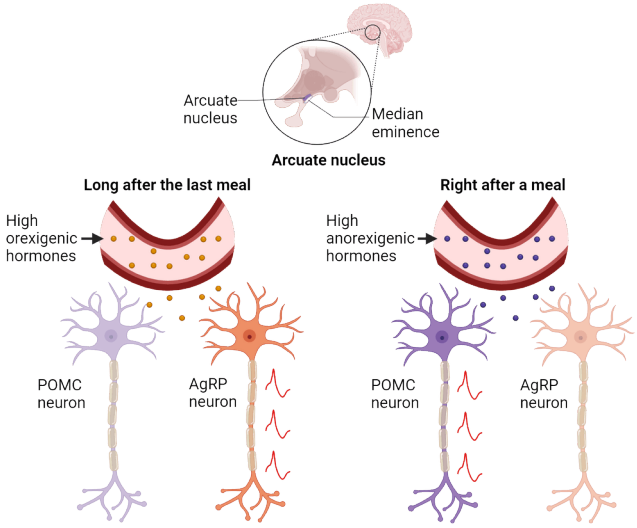


Figure 16.21 Hunger signaling in the brain

AgRP and POMC neurons therefore serve as control centers that integrate neural and hormonal information from the body about feeding. They also integrate information from other sources—for example, sensory information from visual, olfactory, and even auditory stimuli that can inform animals of feeding opportunities. AgRP and POMC neurons, in turn, affect several downstream populations of neurons that ultimately control hunger and satiety (Figure 16.22). Some downstream areas directly generate the emotional states of being hungry or full. Some downstream areas inhibit competing behaviors such as pain, itch, sex, and sleep to ensure that animals prioritize food seeking depending on homeostatic need.

Flowchart of central regulation of caloric balance. Caloric need -

Figure 16.22 Central regulation of food intake by the hypothalamus

Feeding is also directly regulated by neurons in the brainstem (Figure 16.23). These neurons seem to function in satiety and the feeling of being unpleasantly full after a meal. For example, when the stomach becomes relatively full and enlarged, neurons from the vagus nerve transmit this information to a population of neurons in the brainstem called the nucleus tractus solitarius (NTS). Increased stomach stretch causes increased NTS neural activity (see feature box on studying the effect of digestive organ stretch on neural activity). These neurons also have receptors for several anorexigenic hormones, including amylin, CCK, and PYY. The NTS sends axonal projections to other areas of the brain, especially parts of the limbic system (such as the amygdala) that seem to mediate feelings of satiety and the uncomfortable aspects of feeling full.

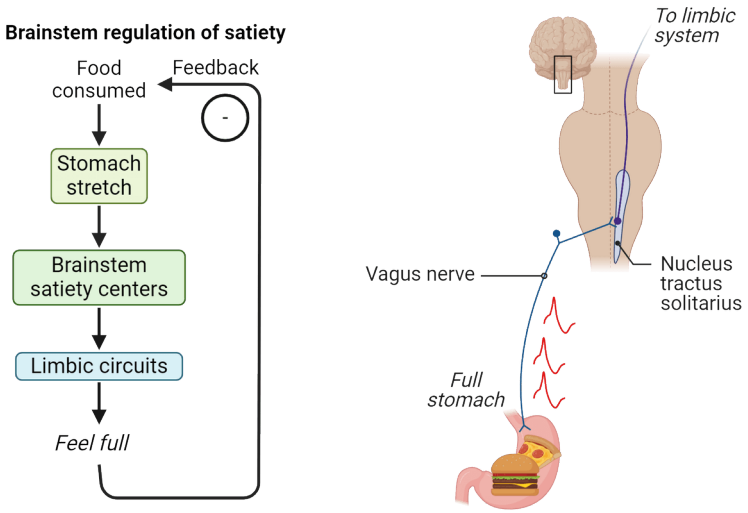


Figure 16.23 Central regulation of food intake by the brainstem

Dysfunction of hypothalamic and brainstem populations, as well as their upstream and downstream connections, can lead to food intake disorders including obesity and eating disorders (see next section).

Neuroscience in the Lab

Studying the regulation of food intake by the hypothalamus

How do neuroscientists study the neurobiology of homeostasis, such as the neural regulation of feeding behavior? Many food intake studies are performed in human subjects. However, these studies are limited by the fact that it is impossible to study specific cell types in a living person. To study and perform experiments to elucidate the neural basis of feeding, many neuroscientists turn to rodent models, especially mice. Because mice have homologous brain structures as humans, it is possible to perform experiments that are impossible in humans.

For example, in recent years, most of our understanding of the role of AgRP and POMC neurons has come from studies in mice. Using techniques like optogenetics (see Methods: Optogenetics) and chemogenetics (see Methods: Chemogenetics), it has been possible to artificially stimulate each individual population of neurons and observe behavior (Figure 16.24). For example, stimulating AgRP neurons using optogenetic activation of channelrhodopsin-2 causes a rapid behavioral response in animals in which animals consume much more food than normal (Aponte et al., 2011). In contrast, stimulating POMC neurons causes a reduction in feeding.

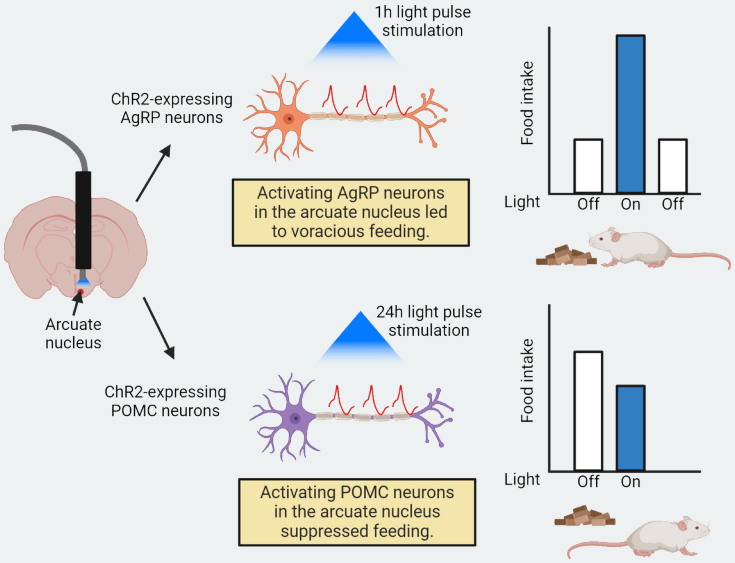


Figure 16.24 Optogenetic activation of AgRP and POMC neurons Based on data from: Aponte, Y., Atasoy, D. & Sternson, S. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. Nat Neurosci 14, 351–355 (2011). https://doi.org/10.1038/nn.2739

By expressing a fluorescent reporter molecule in AgRP or POMC neurons, it is possible to visualize where each of the axons travel throughout the brain. Current research is aimed at identifying the role of each downstream projection to more fully dissect how AgRP and POMC neurons orchestrate a behavioral state of hunger or satiety.

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12.3: Food Intake Disorders

Food intake disorders

Dysregulation of the hormones and neurons that regulate food intake can cause severe problems in body weight regulation leading to obesity or various eating disorders. Because modern day society is very different from natural conditions faced by animals in the wild, humans encounter environmental stimuli (a surplus of highly palatable and calorically-dense food, extreme societal pressure to maintain a certain body weight, etc.) that contribute to food intake disorders that are often difficult to reproduce in animal models of disease.

Obesity is a complex and multifactorial disorder characterized by an excessive accumulation of body fat. The neurobiology of obesity is complex, with many potential underlying causes. Obesity is ultimately caused by consuming too many calories relative to metabolic activity and caloric expenditure.

Why don't homeostatic systems prevent obesity? Consuming high calorie foods and gaining body weight likely causes dysregulation of the hormones and neurons that regulate food intake in the hypothalamus. For example, individuals with obesity often exhibit a state of leptin resistance, in which neurons in the hypothalamus downregulate leptin receptors and become insensitive to the satiety hormone. This leptin resistance results in increased appetite and decreased energy expenditure. Additionally, chronic overconsumption of high-calorie, high-fat foods can cause changes in the reward pathways of the brain, resulting in a decrease in the perceived pleasure of healthier, lower calorie foods.

Like obesity, eating disorders are complex psychiatric conditions characterized by altered eating behavior. These disorders often manifest with excessive and unrealistic body image perception. For example, anorexia nervosa is a disorder in which an unwarranted fear of gaining weight causes an individual to engage in too much fasting or exercising such that they manifest an abnormally low body weight. Bulimia nervosa is characterized by bouts of overeating followed by self-induced vomiting or extreme exercise to avoid absorbing calories.

Because eating disorders are intertwined with body image perception, these disorders do not seem to be caused by dysfunction of the neural systems and circuits that maintain caloric homeostasis. Indeed, individuals with food disorders are often very hungry and intentionally suppress the homeostatic motivation to consume food to correct for low body weights. Therefore, brain regions implicated in the pathophysiology of eating disorders seem to be located in areas that regulate cognition and perception, such as the cerebral cortex. The insular cortex regulates the conscious perception of taste, hunger, and satiety, and likely contributes to the etiology of eating disorders. Additionally, the prefrontal cortex is involved in executive functions such as decision making and impulse control. Neurons in the prefrontal cortex likely suppress homeostatic signals from the hypothalamus and brainstem to cause dysregulated food intake.

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13: THE NEUROENDOCRINE SYSTEM, SEX, AND SEXUAL BEHAVIOR

13.1: Hormones, Communication, and Behavior
13.2: Sexual Differentiation
13.3: Biological Mechanisms of Sexual Determination and Differentiation
13.4: Sex Differences in Psychology and the Brain
13.5: Neural Mechanisms of Sexual Behavior
13.6: Hormones, Aggression, and Parental Behaviors
13.7: Sex, Gender, and Sexual Orientation

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13.1: Hormones, Communication, and Behavior

This section explores the relationship between hormones and behavior. Hormones can influence various behaviors. For example, sex-hormone concentrations in the blood increase during puberty and decrease with age, particularly after 50, mirroring trends in sexual behavior. Overuse of anabolic steroid hormones is associated with aggression. While many hormones affect a range of behaviors, and many behaviors influence hormone levels, this chapter focuses on a few illustrative examples.

To understand the hormone-behavior relationship, it is important to describe hormones. **Hormones** are organic chemical messengers produced and released by specialized **endocrine glands**. Major hormone-producing structures include the pituitary, pineal, thyroid, and adrenal glands, the hypothalamus, and the gonads (male testes and female ovaries). Hormones are released from these glands into the blood, where they may travel to act on target structures at some distance from their origin. Hormones are chemical messengers similar in function to **neurotransmitters**, however, hormones can operate over a greater distance and longer time than neurotransmitters (**Focus Topic 1**).

Major classes of hormones are steroid hormones and protein or peptide hormones. Steroid hormones are generally synthesized from cholesterol in the gonads and adrenal glands. Examples include **testosterone** (a common type of androgen), estradiol (a common type of estrogen), **progesterone** (a common type of progestogen), and cortisol (a common type of glucocorticoid) (see Table 1, A-B). Protein hormones and peptide hormones are chains of amino acids; prominent examples include **oxytocin**, vasopressin, **prolactin,** and leptin.

Focus Topic 1:Neural Transmission versus Hormonal Communication

Although neural and hormonal communication both rely on chemical signals that are similarly released and received by cells, several prominent differences exist. One major difference is where the messages can travel. Hormonal messages can reach far more destinations—they travel via the circulatory system, so can reach any cell that receives blood and cover distances up to meters. Neural messages are much more limited in where they can travel—action potentials can only travel along existing neural pathways connected by synapses, and neurotransmitters travel the short distance across the synapse (~20 nanometers).

In addition to “synaptic transmission” (across the synapse), another type of signaling in the brain is **neuromodulation**. In neuromodulation, chemical substances are released into the extracellular space and affect many neurons, rather than just a single postsynaptic neuron (Marder, 2012). Common neuromodulators include some neurotransmitters (e.g., dopamine, serotonin, and acetylcholine) and neurohormones made in the brain, such as oxytocin and vasopressin. When released from a cell, they can alter the firing properties and synaptic connectivity of tens of thousands of neurons.

The timing and strength of neural and hormonal messages also differ. Action potentials are all-or-none events with a rapid onset and offset, occurring in milliseconds. When neuromodulators are released, their effects are more graded and can linger for hundreds of milliseconds to several minutes. Hormonal messages may unfold over seconds or hours. Therefore, neural messages often mediate rapid changes in the body like movement, whereas hormonal messages are involved in longer-term processes such as growth, development, reproduction, and metabolism. Lastly, there is often more voluntary control of neural signals than hormonal ones. For example, moving limbs on command is easy for most, but it’s virtually impossible to will a change in thyroid-hormone levels.

Table 1-A: Prominent Hormones That Influence Behavior

Steroid Hormones	
Cortisol	Increases carbohydrate metabolism; mediates stress responses
Estradiol	Uterine and other female tissue development; regulates sexual motivation and performance in females and males
Testosterone	Promotes sperm production and male secondary sexual characteristics; promotes sexual motivation and behavior, sometimes by being converted to estradiol

Table 1-B: Prominent Hormones That Influence Behavior

Peptides and Protein Hormones	
Oxytocin	Stimulates milk letdown and uterine contractions during birth; Promotes social bonding
Prolactin	Many actions relating to reproduction, water balance, and behavior associated with parental care
Thyroxine	Increases oxidation rates in tissue and affects neural development
Vasopressin	Increases water reabsorption in the kidney and affects learning, memory, social behavior

Hormones coordinate the physiology and behavior of individuals by regulating, integrating, and controlling bodily functions. Over evolutionary time, hormones have often been co-opted by the nervous system to influence behavior to ensure reproductive success. For example, the same hormones, testosterone and estradiol, that cause gamete (egg or sperm) maturation also promote mating behavior. This dual hormonal function ensures that mating behavior occurs when animals have mature gametes available for fertilization. Another example of endocrine regulation of physiology and behavior is provided by pregnancy. Estrogens and progesterone concentrations are elevated during pregnancy, and these hormones are often involved in mediating **maternal behavior** in the mothers.

Not all cells are influenced by every hormone. Rather, a hormone can directly influence only cells with **receptors** specific for that hormone. Cells with these specific receptors are called **target cells** for the hormone. After a hormone binds to its target cell, a series of cellular events activates enzymatic pathways or turns on or off genes that regulate protein synthesis. The newly synthesized proteins may activate or deactivate other genes, causing another cascade of cellular events. Importantly, sufficient numbers of hormone receptors must be available for a hormone to produce any effects. For example, testosterone is important for male sexual behavior. If men have too little testosterone, then sexual motivation may be low, and it can be restored by testosterone treatment. However, if men have normal or elevated levels of testosterone yet display low sexual drive, then it might be caused by a lack of receptors, so treatment with additional hormones will not be effective.

To illustrate how hormones can affect behavior, let's consider singing in zebra finches (Goodson et al., 2005). Only male zebra finches sing, and they sing to attract mates. If adult male finches have their testes removed (i.e., are castrated), then the birds reduce singing. But castrated finches regain singing behavior if their testes are reimplanted or if they are treated with either testosterone or estradiol. While androgens and estrogens are often considered 'male' and 'female' hormones respectively, testosterone, an androgen, is commonly converted to estradiol, an estrogen (Figure 1). Thus, many male-like behaviors are associated with the actions of estrogens!

Branching chart showing the biochemical Pathway for Steroid Hormone Synthesis. See caption and text for details.

Figure 1: Biochemical Pathway for Steroid Hormone Synthesis: It is important to note that testosterone (an androgen) can be converted to another androgen, DHT, or an estrogen, estradiol. Too much or too little converting enzyme can influence the brain and behavior.

The birdsong example demonstrates how hormones can affect behavior, but the reciprocal relation also occurs—behavior can affect hormone levels. For example, seeing a territorial intruder may elevate a male bird's testosterone concentrations and thereby stimulate singing or fighting behavior. Similarly, male mice or rhesus monkeys that lose a fight decrease circulating testosterone concentrations for days or even weeks afterward. Comparable results occur in humans. Testosterone concentrations in humans are affected after physical combat, and even after simulated battles. For example, testosterone concentrations were elevated in winners and reduced in losers of regional chess tournaments.

Couple holding hands

Figure 2. The expectation of events can influence one's hormonal activity. How do you think hormonal activity is affected if you anticipate going on a date with a romantic interest?

People's hormone concentrations can also be affected by a contest even when they are not directly involved. Researchers measured testosterone levels of male soccer fans. Brazilian and Italian fans provided saliva samples before and after watching the 1994 World Cup final. Brazil won on a last-minute penalty kick. Their fans were elated and Italian fans were dejected. Results showed that, compared to pre-game baseline values, 11 of 12 Brazilian fans had increased testosterone, and 9 of 9 Italian fans had decreased testosterone (Dabbs & Dabbs, 2000).

Hormones can be affected by anticipation of behavior. Testosterone levels are known to influence sexual motivation and behavior in women, and one study compared testosterone levels in women for three activities: sexual intercourse, cuddling, and exercise

(van Anders et al., 2007). Women provided a saliva sample from pre-activity, post-activity, and the next morning. Analyses revealed that the women's testosterone was elevated before intercourse as compared to other times, showing an anticipatory relationship between testosterone and sexual behavior. Testosterone levels were also higher post-intercourse compared to exercise, suggesting that sexual behavior may also influence hormone concentrations in women.

In sum, this section explores the bidirectional relationship between hormones and behavior, highlighting how hormones like testosterone and estradiol can influence behaviors such as singing in birds and sexual motivation in humans. While hormones can affect behavior, behaviors and even the anticipation of events can also impact hormone levels, as seen in studies involving competition and sexual activities. The field of neuroendocrinology, which studies the interface between the endocrine and nervous systems, is likely to yield significant insights into the hormone-behavior relationship.

Focus Topic 2: Bisphenol A (BPA) and Endocrine Disruption

You may have heard about the effects of bisphenol A (BPA), a chemical used in many plastic food-storage containers, drinking cups, aluminum cans, and other products. Research suggests BPA is an endocrine disruptor, meaning that it interferes with the endocrine system. BPA mimics estrogens, and is particularly disruptive during prenatal and postnatal development.

The U.S. Food and Drug Administration (FDA) acknowledges concerns about BPA's potential effects on the brain, behavior, and prostate gland in fetuses, infants, and young children. In response, many US companies have removed BPA from baby products, and both Canada and the European Union have banned its use in these items. You'll now often see reusable water bottles boast "BPA free."

Studies in animals and humans have linked BPA exposure to various health issues, including developmental delays, altered thyroid signaling, sexual dysfunction, changes in brain structure and function, and increased cancer risks. However, some experts caution that more research is needed. In the meantime, the FDA recommends that consumers limit their exposure to BPA. In addition to purchasing foods in BPA-free packaging, consumers should avoid storing foods or liquids in containers with the recycling code 3 or 7. Foods and liquids should not be microwaved in any form of plastic: use paper, glass, or ceramics instead.

In addition to BPA, hundreds of other chemicals are considered endocrine disruptors with possible health risks to humans and other animals (NIEHS, n.d.). Well-studied chemicals that could disrupt your endocrine system (e.g., Atrazine, Dioxins, Phthalates, PFAS, PCBs, and Triclosan) are found in many everyday products, including some cosmetics, toys, packaging, non-stick pans, textile coatings, flame retardants, carpet, and pesticides. These chemicals end up in the environment and contact may occur through air, diet, skin, and water. Even in low levels, endocrine disruptors can interfere with normal hormone function. Exposure is linked to health problems affecting the immune system, puberty (e.g., premature onset in girls and breast development in boys), reproduction (e.g., sexual dysfunction and reduced fertility), nervous system and psychological functioning (e.g., increased neurotoxicity, ADHD risk, memory issues), and cancer risk. Endocrine-disrupting chemicals cannot be completely avoided or removed; however, you can make informed choices to reduce exposure and risk of potential health effects.

Text Attributions

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Betts, J. G., Young, K. A., Wise, J. A., Johnson, E., Poe, B., Kruse, D. H., Korol, O., Jonhson, J. E., Womble, M., & DeSaix, P. (2022). 17.2 Hormones. In Anatomy and Physiology 2e. OpenStax. Access for free at https://openstax.org/books/anatomy-and-physiology-2e/pages/17-2-hormones

National Institute of Environmental Health Sciences (NIEHS) (n.d.). Endocrine Disruptors. https://www.niehs.nih.gov/health/topics/agents/endocrine

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definition

An organic chemical messenger released from endocrine cells that travels through the blood to interact with target cells at some distance to cause a biological response.

×Close definition

A ductless gland from which hormones are released into the blood system in response to specific biological signals.

×Close definition

Chemical substance released by the presynaptic terminal button that acts on the postsynaptic cell.

×Close definition

The primary androgen secreted by the testes of most vertebrate animals, including men.

×Close definition

A primary progestin that is involved in pregnancy and mating behaviors.

×Close definition

A peptide hormone secreted by the pituitary gland to trigger lactation, as well as social bonding.

×Close definition

A protein hormone that is highly conserved throughout the animal kingdom. It has many biological functions associated with reproduction and synergistic actions with steroid hormones.

×Close definition

the process by which neurons use chemical signals (e.g., some neurotransmitters) to bias many neurons, resulting in changes to neuronal properties such as firing activity and synaptic connectivity.

×Close definition

Parental behavior performed by the mother.

×Close definition

A chemical structure on the cell surface or inside of a cell that has an affinity for a specific chemical configuration of a hormone, neurotransmitter, or other compound.

×Close definition

A cell that has receptors for a specific chemical messenger (hormone or neurotransmitter).

×Close definition

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13.2: Sexual Differentiation

Sexual differentiation is the process by which a person develops into either a male or a female. For this chapter, the content will be based on a male/female binary to introduce the basic concepts of reproductive development. However, it is important to recognize that in real life, chromosomal sex, physical sex, and gender exist on a continuum and cannot always be simplified into a two-structure system.

During development, the body and the brain undergo A) feminization and de-masculinization or B) masculinization and de-feminization. In most cases, the differentiated brain will lead to behaviors that correspond appropriately to the differentiated gonads.

Chromosomal Sex

In humans, DNA is organized into 46 chromosomes—23 from the mother and 23 from the father. Twenty-two pairs are autosomal chromosomes, containing the same genes but potentially different alleles from each parent. The last pair are the sex chromosomes, X or Y, which determine biological sex (Figure 3). During fertilization, an egg (always one X chromosome) fuses with a sperm (one X or Y chromosome). An XX combination results in a female fetus, while XY results in a male fetus.

22 pairs of autosomal chromosomes and 1 pair of sex chromosomes. Details in text and caption.

Figure 3. Humans have 23 pairs of chromosomes, making 46 total. 22 pairs are called autosomal and have similar structure from each parent. The final pair are the sex chromosomes that determine if the individual is a male or female. Sex chromosomes are named either X or Y.

Gonadal Differentiation

Six weeks after fertilization, fetuses have primordial gonads that could develop into testes or ovaries, as well as Wolfian ducts and Müllerian ducts that could develop into male or female reproductive organs, respectively. Proteins and hormones released over the following weeks lead to differentiation into male or female anatomy. In males, the sex-determining region (SRY) gene on the Y chromosome is activated, producing testis-determining factor, which results in the gonads becoming testes and testosterone secretion. In females, when the SRY gene and secreted hormones are absent, the gonads differentiate into the ovaries.

Hormones During Development

In addition to differentiating the reproductive organs, the presence or absence of gonadal hormones during development also differentiates the rest of the body, including the brain. Testosterone causes the brain, body, and behavior to be masculinized and defeminized (Figure 4). The inactive ovaries do not release hormones; this causes the brain, body, and behavior to be feminized and demasculinized. Extensive research has established these principles in non-human animals. While hypothesized to extend to human brain and behavior, the evidence in humans is less conclusive.

Hormone effects during development. Details in text and caption.

Figure 4. Testosterone presence during development masculinizes and defeminizes the body's physical traits. Based on animal studies, researchers hypothesize that testosterone may similarly affect brain structure and behavior patterns. Conversely, no hormone exposure during development feminizes and demasculinizes physical traits. Animal research suggests that no hormone exposure also feminizes brain and behavior, though more research is needed to confirm these effects in humans.

Critical Period. Secreted testosterone's effects on the brain must take place during a specific time in development, called a critical period. This early role of testosterone is called an **organizational effect** and results in a permanent change in organizing the nervous system and therefore behavior. Organizational effects of hormones lead to major, generally irreversible, aspects of cell and tissue differentiation. Organizational effects occur during critical periods like prenatal development and puberty (Figure 5). During puberty, higher levels of androgens in males lead to masculinizing organization, while ovarian hormone exposure has organizational effects in females (Schulz et al., 2009). In cases of pre-puberty castration, sexual maturation does not occur unless hormone replacement is provided.

In adulthood, the same hormones activate responses like inducing reproductive behavior or ovulation, but these influences, called **activational effects**, are reversible and short-lived. Removing the activating hormone stops the behavior, but reintroducing the

hormone later restarts the response. This occurs because the brain was previously organized to produce these behaviors in the presence of hormones.

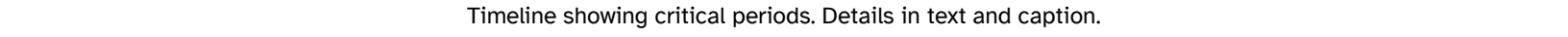


Figure 5. Hormones can have long-lasting, organizational effects when present during critical periods such as during the prenatal period or puberty. This phenomenon is well-established in the differentiation of human reproductive anatomy. For brain development and behavior, most evidence comes from non-human animal studies. During critical periods, hormones will alter the structure of the nervous system, setting up cells and circuits needed to display sex-typical behaviors later in life. Those sex-typical behaviors are then activated in adulthood by gonadal hormones.

The role of activational hormones can be demonstrated by adult castration in male rats. Healthy males with intact testes will show sexual behavior when placed with a female rat. Castration, the removal of the testes, will cause males to stop showing sexual behavior because the activating hormone, testosterone, is no longer present. However, if the castrated males receive testosterone replacement, they will resume showing sexual behavior. The sexual behavior brain circuit was organized during development by exposure to gonadal hormones, and in adulthood that circuit can be activated by testosterone. The adult behavior can only be seen when the activating hormone is present (Figure 6).

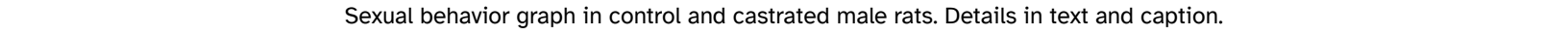


Figure 6. Removing testosterone by castrating an adult male rat will decrease the amount of sexual behavior displayed because the hormone can no longer activate sexual behaviors (solid orange and dotted blue lines). However, if the castrated animal is treated with testosterone, sexual behavior returns (solid orange line).

Key Takeaways

- During development, the body and the brain undergo either A) feminization and de-masculinization or B) masculinization and de-feminization.
- The sex chromosomes, X and Y, make up one pair of the 23 total pairs of chromosomes in humans. Females are genetically XX and males are genetically XY.
- The SRY gene on the Y chromosome is responsible for the development of the male reproductive system.
- In the absence of hormones, the female reproductive system develops.
- Organizational, long-lasting hormone effects take place during critical periods in development.
- Activational, short-lasting hormone effects “activate” the circuits organized by hormones in development.

Text Attributions

Section adapted from:

Henley, C. (2021). Foundations of Neuroscience: Open Edition. https://openbooks.lib.msu.edu/neuroscience/chapter/sexual-differentiation/ CC BY-NC-SA 4.0

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definition

The process by which individuals develop the characteristics associated with being male or female. Differential exposure to gonadal steroids during early development causes sexual differentiation of several structures including the brain.

×Close definition

Early, generally irreversible, effects of steroid hormones that occur during development

×Close definition

Physiological and behavioral responses that are reversible and short-lived, occurring in adulthood

×Close definition

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13.3: Biological Mechanisms of Sexual Determination and Differentiation

Learning Objectives

By the end of this section, you should be able to

- Identify the basic principles and diversity of sex determination mechanisms, including genetic and environmental sex determination
- Describe the extensive variety in sex determination mechanisms across species, and how this diversity challenges the conventional view of a widespread male-female fixed dichotomy
- Define what steroid hormones are and describe the concept of organizational and activational effects driving the differentiation of tissues into male or female-like forms

In the previous section, we explored hypotheses explaining the evolution and conservation of sexual reproduction and sexual dimorphism across eukaryotes, highlighting their impacts on male and female biology beyond reproductive contexts. But how is it decided whether an individual becomes a biological male or female? In this section, we will delve into the fascinating biological mechanisms underlying sex determination. We will explore how these mechanisms vary widely across different species, from the well-studied genetic sex determination in humans to the remarkable environmental influences observed in other organisms. Additionally, we will examine how a special group of hormones produced by the reproductive organs in each sex further drive the differentiation of tissues into male or female-like forms, acting both early in development and later in life.

Developmental perspective: Genetic and Ecological Factors of Sex Determination

One of the most fascinating aspects of sex determination is its remarkable diversity across species (Nagahama et al. 2021). Animals belonging to species that reproduce sexually, and therefore have two sexes, all start development with what we call bipotential gonads. Gonads are the reproductive tissue that will produce gametes (eggs in female mammals or sperm in male mammals, for example). Bipotential gonads are the undifferentiated gonads that are apparently identical at early stages of embryonic development in both sexes. During the early embryonic stage of development, these gonads differentiate into either testes or ovaries. While all species require a cue to trigger the differentiation of the bipotential gonads, this cue varies significantly. In some species, it is based on genetic factors (genetic sex determination); in others, environmental cues such as temperature play a critical role (environmental sex determination); and in some species, sex determination involves a combination of genetic and environmental factors. Remarkably, although rare, some fish species even change sex within an individual's lifetime through a process called sequential hermaphroditism. Let’s delve into each of these mechanisms.

Genetic Sex Determination

To grasp the concept of genetic sex determination, let’s first revisit how genetic information is organized within our cells. Our genetic material, DNA, is packaged into structures called chromosomes. In cells with two sets of chromosomes, known as diploid cells, there is a pair of each chromosome type. Among these pairs, one special pair comprises the sex chromosomes, which play a critical role in determining an individual's sex by carrying genes specific to sexual development and reproductive functions. The other chromosomes are known as autosomes, and they carry genes that are responsible for a wide array of bodily functions and characteristics, such as enzyme production and hair color, but do not directly determine sex.

In most mammals, including humans, the sex chromosomes are designated as X and Y. Females have two X chromosomes (XX), while males possess one X and one Y chromosome (XY). During meiosis—the process that produces reproductive cells, or gametes—these chromosomes are segregated so that each gamete ends up with just one copy of each chromosome, including one sex chromosome. Consequently, all eggs produced by females contain an X chromosome. However, males produce sperm that may carry either an X or a Y chromosome. The sex of the resulting embryo is then determined at fertilization, depending on whether it receives an X or a Y from the sperm, alongside an X from the egg. The combination of these chromosomes (XX for

females and XY for males) establishes the genetic sex of the embryo (Figure 11.9). So how does this work?

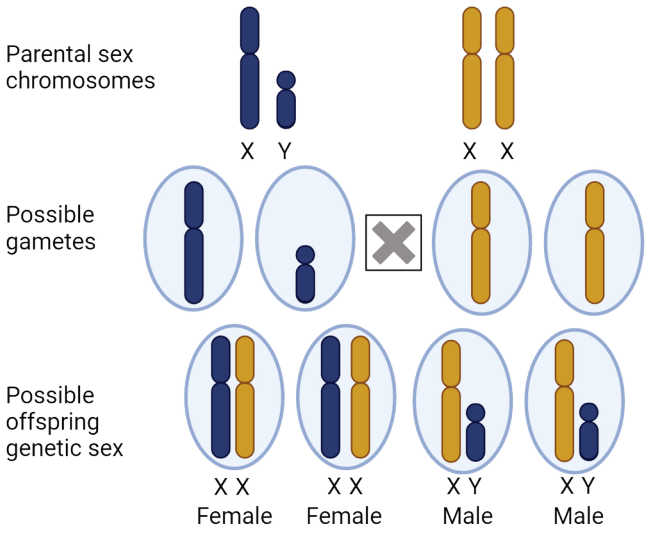


Figure 11.9 Genetic determination of sex in mammals

The Y chromosome carries a crucial gene called the sex-determining region Y (SRY in humans, Sry in mice), sometimes also referred to as “testes determining factor” or “TDF” , which is key to initiating the development of testes (Step 1 in Figure 11.10) (Kashimada and Koopman 2010). SRY expression activates another gene called Sox9, a gene located in a non-sex chromosome, which in turn guides the differentiation of somatic cells in the bipotential gonads into Sertoli cells, which are essential for supporting and nurturing the developing sperm cells, defining the initial stage in the development of the embryonic testis (Step 2 in Figure 11.10). Sertoli cells will orchestrate the further differentiation of the male reproductive organs through two main mechanisms: the induction of Leydig cell development in the testes—which will secrete of testosterone—and the secretion of anti-Müllerian hormone directly from the Sertoli cells (Step 3 in Figure 11.10). During the earlier stages of development, the internal reproductive tract is similar in both sexes and consists of a set of two ducts, the Wolffian and Müllerian ducts, which will eventually become the male or female internal reproductive organs, respectively. Leydig cells will produce androgens (sex hormones more abundant in males) such as testosterone, which will promote the differentiation of the Wolffian duct to develop into male internal genitalia, such as the epididymis, vas deferens, and seminal vesicles (Step 4 in Figure 11.10). At the same time, the anti-Müllerian hormone will result in the degeneration of the Müllerian duct, preventing the development of female internal genitalia such as the uterus and fallopian tubes (also Step 4).

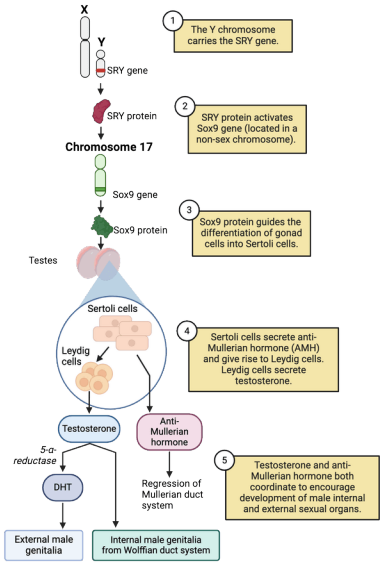


Figure 11.10 X- and Y-driven genetic sex determination of tissue differentiation

The basic anatomy of these changes in the ducts with differentiation into a male phenotype is shown on bottom of Figure 11.11. It is important to mention that although SRY is key in this process, it is not the only mechanism underlying gonadal determination, and instead it is complemented by a complex network of genes whose balanced expression levels either activate the testis pathway and simultaneously repress the ovarian pathway or vice versa(Nagahama et al. 2021).

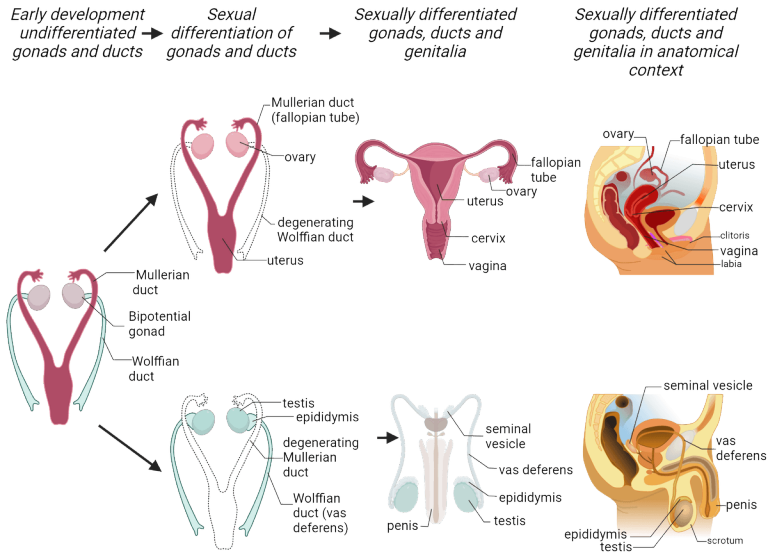


Figure 11.11 Wolffian and Müllerian duct system development Image credit: Anatomical context cartoons on far right by Tsaitgaist (labels added) - This file was derived from: Anatomy of male and female human genitalia - blanc.png, CC BY-SA 3.0, https://commons.wikimedia.org/w/inde...curid=73139956

In contrast, embryos inheriting a copy of the X chromosome from their male parent will develop into XX individuals. Because in XX individuals SRY is not present, no androgens or anti-Müllerian hormones will be secreted, and the bipotential gonads, as well as the internal ducts, will follow a developmental pathway towards female differentiation. Gonadal somatic cells differentiate into granulosa cells instead of Sertoli cells, and theca cells instead of Leydig cells and the Müllerian duct will develop into female internal genitalia such as the uterus, fallopian tubes, and the internal portion of the vagina. The basic anatomy of these changes in the ducts with differentiation into a female phenotype is shown on top of Figure 11.11. While the granulosa and theca cells do not secrete hormones during early development, they will secrete two key hormones starting in adolescence: estrogen and progesterone, respectively.

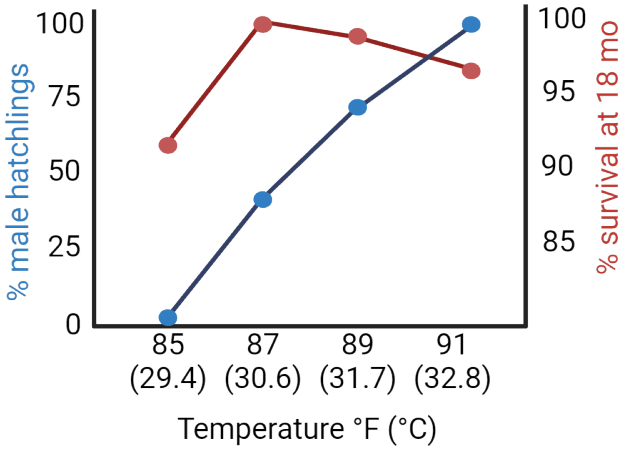
While the XY system is the most common genetic sex determination structure in mammals, most birds and reptiles utilize a different sex chromosome system. In these groups, the heterogametic sex is the female, which carries one Z chromosome and one W chromosome, while males carry two Z chromosomes. Thus, in this system, the female parent determines the sex of the offspring by passing on either a Z or a W chromosome, which will result in the embryo developing into a male or a female, respectively (Ezaz et al. 2006).

However, things can get a bit more complicated: in some animals, such as the African pygmy mice (*Mus minutoides*) (Baudat, de Massy, and Veyrunes 2019) and some cichlid fishes (like M. pyrsonotus) (Ser, Roberts, and Kocher 2010), sex is determined by multiple genetic factors scattered across the genome, a process known as polygenic sex determination (Moore and Roberts 2013). This means that several genetic elements, not just one chromosome, collectively influence the sexual development of these organisms. Take the African pygmy mice as an example. Besides the usual X and Y chromosomes, these mice have a unique feminizing X chromosome variant referred to as X*. This variant can override the Y chromosome, resulting in different types of females. Specifically, in this species, there is only one type of male (XY), but three types of females: XX, XX*, and X*Y. In such a system, one might expect that litters would end up with significantly more female pups than males, right? Intriguingly, this is not the case. Research shows that male mice transmit a Y chromosome 80% of the time when mating with XX females, but only 36% of the time when mating with X*Y females. This suggests that males are selectively 'saving' their Y chromosomes for mates with at least one regular X chromosome, thereby ensuring a higher proportion of XY male offspring (Saunders et al. 2022).

This is just one example of the many diverse mechanisms involved in sex determination across species. As we will see in the next section, some species' sex determination is not influenced by genetic factors at all!

Environmental Sex Determination

In many animals, the switch to develop into a female or male is not solely determined by genes. Instead, sex determination relies on external stimuli to control this process. One of the most widespread mechanisms, found among crocodiles, most turtles, and some lizards, is temperature-dependent sex determination. This process relies on the environmental temperature during egg incubation, which in turn guides gene expression —many of which are the same genes driven by the Sry gene in mammals—driving the development of males or females (Yatsu et al. 2016). For example, in the American alligator (*Alligator mississippiensis*), eggs incubated at a constant temperature of 30°C (86°F) result in 100% female hatchlings, while incubation at higher temperatures, 34°C (93°F) or above, results in 100% male hatchlings (Ferguson and Joanen 1982) (Figure 11.12). Recent artificial incubation experiments have revealed an adaptive benefit to this mechanism. Researchers found that hatchlings incubated at male-promoting temperatures have higher survival rates compared to those incubated at female-promoting temperatures (Bock et al. 2023). Since male alligators reach sexual maturity much later than females, these findings suggest an evolutionary advantage: favoring females in conditions of lower survival ensures that some will reproduce in time, while favoring males in higher survival conditions ensures more males live long enough to reproduce. Fascinating!





In the American Alligator, temperature of the egg determines the sex of the offspring and likelihood of their survival.

Figure 11.12 Temperature-dependent sex example Image credit: Data based on findings ofJoanen, T., McNease, L., Ferguson, M.W.J. (1987): The effects of egg incubation temperature on post-hatching growth in American alligators. In: Wildlife Management: Crocodiles and Alligators, p. 535-538. Gebb, G.J.W., Manolis, S.C., Whitehead, P.J., Eds, Surrey Beatty and Sons, Sydney. Photo of alligators by Ianaré Sévi - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/inde...?curid=6424341

Temperature, however, is not the only environmental factor influencing sex determination. For instance, in the amphipod *Echinogammarus marinus*, the photoperiod (the length of day and night) influences their sex determination, with more males developing over a long-day photoperiod regime (usually spring and early summer) and more females developing over a short-day photoperiod regime (Guler et al. 2012) (late summer and fall). Additionally, social factors can determine sex in many coral-reef-dwelling fish and limpets. For example, in the coral–dwelling fish *Gobiodon erythrospilus*, contact with a potential mating partner determines both the timing of maturation and the sex of a maturing individual, with juveniles maturing into the sex opposite to that of the adult partner (Hobbs, Munday, and Jones 2004).

The remarkable diversity of sex determination mechanisms extends beyond early development into the adult stages of some species, particularly among fish. An extraordinary example of this is sequential hermaphroditism, where adult animals have the ability to switch sexes. This adaptation can take two main forms: protandry, where individuals initially mature as males and later transform into females, and protogyny, where they start as females and later become males. Take, for instance, the clownfish (*Amphiprion percula*), which are protandrous. These fish typically live in social groups consisting of a dominant female, always the largest in size, surrounded by a large male (which will breed with the female) and several smaller, non-breeding males. In this fascinating social structure, if the dominant female is removed or dies, the breeding male changes sex to become female. Concurrently, the next largest male in the hierarchy grows rapidly, taking over as the new breeding male. Now consider the clownfish featured in Disney's 'Finding Nemo'. Had the movie reflected actual clownfish behavior, Nemo's plot would diverge sharply from the familiar storyline: following the death of his mate, Marlin would have transformed into a female, and Nemo, growing up, would likely have taken his place as the new breeding male.

But there are even more extreme examples. The Okinawa rubble gobiid fish (*Trimma okinawae*) has a mating system in which

the social group consists of one dominant male who mates with multiple females, typically referred to as a harem. Removal of the dominant male from the harem results in female-to-male sex change by the largest female within just five days, but, if the dominant male is returned to the harem, the fish that underwent the sex change transforms back into a female (Manabe et al. 2007). Thus, this species is capable of bidirectional sex change within the lifetime of a single individual!

As you can appreciate now, there is immense variety across species in the mechanisms underlying sex determination. Understanding and embracing this variety can greatly enrich our understanding of the biology of sex, demonstrating that the widespread notion of a purely dichotomous male vs. female division in nature is overly simplistic and not reflective of the true biological diversity.

Having explored the diverse genetic and environmental factors that influence sex determination, we can now turn our attention to the next stage of development: sexual differentiation. This phase involves the specific processes through which the predetermined sex develops distinct biological and physiological characteristics. In the next section, we will learn that hormones play a pivotal role in this process through organizational and activational mechanisms, each contributing uniquely to the development and functioning of sexual characteristics.

Role of Hormones in Sexual Differentiation: Organizational vs Activational Mechanisms

We have already examined how the presence of specific sex chromosomes (XX in females and XY in males) or environmental cues leads to the development of an individual as male or female. This process initiates the differentiation of the bipotential gonads into either testes in males or ovaries in females. Following this differentiation, the gonads start to produce hormones in a sex-specific manner, which then triggers a cascade of events affecting not only the gonads themselves but also various other tissues and organs throughout the body. The key hormones involved are androgens and estrogens, which belong to a class of hormones known as steroid hormones. These hormones are derived from cholesterol and are notable for their fat-soluble properties, allowing them to easily penetrate cell membranes.

Before we dive deeper into how hormones from the gonads drive sex differences, it is important to mention that research in the past two decades has shown that many sex differences throughout tissues in the body, including the brain, are a result of the inherent differences between the X and Y chromosomes, independent of hormones. For example, in tammar wallabies, researchers have found that some sexual differences in body tissues appear many days before there is any visible development of the testes, suggesting that these differences are independent of testes-derived testosterone (Renfree and Short 1988). This indicates that certain characteristics in the body can develop differently based simply on whether the cells contain two X chromosomes or one X and one Y chromosome, even before hormonal influences come into play. Similarly, mice that have been gonadectomized (surgically removing their gonads to eliminate the influence of endogenous hormones) and treated equally with exogenous testosterone, show differences in sexual behavior depending on the number of X chromosomes, indicating that chromosomes can influence sexually related behaviors independently of hormones (Bonthuis, Cox, and Rissman 2012).

Lastly, it is also important to know that while androgens and estrogens are typically referred to as male and female sex hormones, respectively, both hormones are important for various functions in both sexes, albeit to varying degrees. Testosterone, the most well-known androgen, is predominantly produced in the testes in males and in smaller quantities in the ovaries in females. Both sexes also produce testosterone in their adrenal glands. Meanwhile, estrogens are mainly produced in the ovaries in females and, to a lesser extent, in the testes and adrenal glands in males. In females, estrogens are essential for the development and maintenance of reproductive tissues such as the breasts and uterus and play a crucial role in the estrous cycle and overall reproductive health. Additionally, both androgens and estrogens contribute significantly to other physiological processes, including bone density, muscle mass, and even mood regulation, underscoring their broad and critical impact on health.

Now we are ready to explore how androgens and estrogens contribute to sexual differentiation! These hormones influence development through two main mechanisms: organizational and activational effects.

Organizational Mechanisms of Sex Hormones

The organizational effects of androgens and estrogens are crucial for sexual differentiation, exerting their influence primarily during sensitive developmental stages such as embryogenesis and puberty. These hormonal effects lead to the permanent organization of neural and anatomical structures essential for sex-specific physiological functions and behaviors.

The initial organizational effects begin with the differential secretion of steroid hormones by the developing gonads during the

prenatal period. In males, the testes begin to produce high levels of androgens during the fetal and early neonatal periods, significantly influencing sexual differentiation. In contrast, female gonads remain relatively quiescent, not producing substantial hormone levels until puberty (Figure 11.13). During these critical early stages, tissues exhibit heightened sensitivity to circulating androgens, which drive the "permanent" masculinization of various structures. For example, testosterone secreted by fetal Leydig cells in males triggers the development of male external genitalia, such as the penis and scrotum. Conversely, in females, the absence of significant testosterone levels allows the external genitalia to develop along a female typical trajectory, resulting in the formation of structures like the clitoris and labia. These developmental changes are considered permanent because they establish stable anatomical features that are maintained throughout life without the need for ongoing hormonal influence.

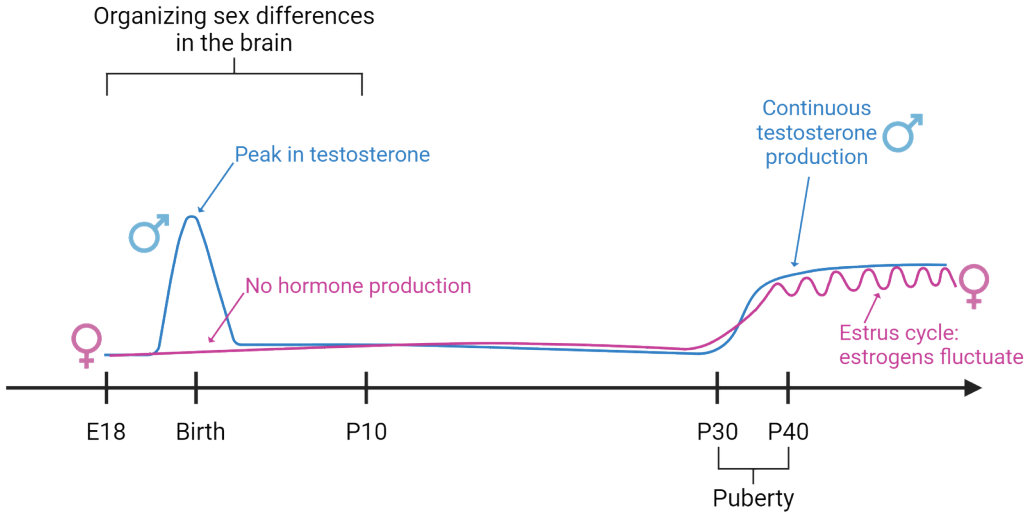


Figure 11.13 Organizational effects of gonadal testosterone in rodents

The organizational effects of hormones during critical developmental periods significantly influence not only the reproductive organs but also extend to the phenotypic differentiation of non-gonadal tissues, including the brain. In the brain, the influence of androgens during these sensitive periods does not typically manifest as major anatomical differences; instead, these hormones "prime" neural tissues to respond to androgens later in life (in other words, the organizational effects establish a framework within which androgens can later act, ensuring that sex-specific behaviors and functions are expressed appropriately). Take the preoptic area of the hypothalamus, a brain region involved in male copulatory behavior, as an example. In adult male rats, a subsection of the preoptic area called the sexually dimorphic nucleus (SDN-POA) is several-fold larger than in adult females. You can see an example of what this looks like in the left two photomicrographs of Figure 11.14.

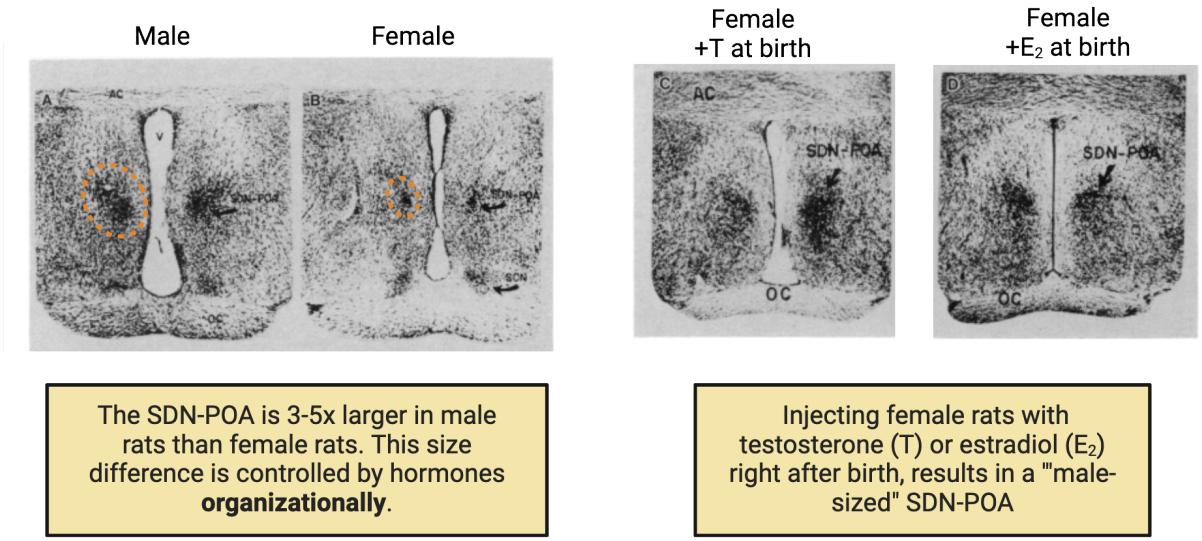
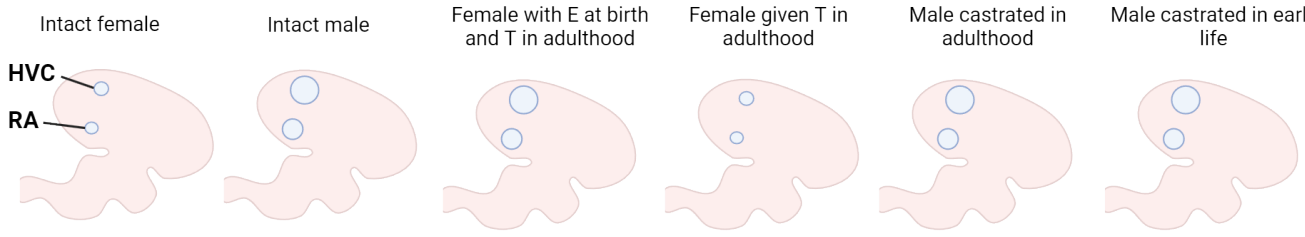


Figure 11.14 Organization hormones dictate SDN POA size Image credit: Image from: Gorski. 1974. "The neuroendocrine regulation of sex behavior." Advances in Psychobiology, 2: 1-58.

The patches of dark pigment on either side of the ventricle mark the cells of the SDN-POA of a male and a female rat. Treating female rats with testosterone just before and just after birth causes this nucleus to become as large as in normal males in adulthood, whereas removing testes (and testosterone) in male rats at birth causes the development of a smaller, feminine SDN-POA in adulthood (Döhler et al. 1984). A photomicrograph on the right side of Figure 11.14 shows an example of the SDN-POA of a genetically female rat treated with testosterone at birth; it looks large like an intact male. In contrast, hormone manipulations in adulthood, after the period of naturally occurring neuronal death, have no effect on the volume of this nucleus (Gorski et al. 1978). Thus, the sexual differentiation of this nucleus resembles that of the genitalia—male hormones early in life permanently masculinize this brain region. One difference is that it is not testosterone itself but a metabolite of testosterone that masculinizes the SDN-POA. The enzyme aromatase, which is abundant in the hypothalamus, converts androgens (such as testosterone) into estrogens (such as estradiol). Estrogen then interacts with estrogen receptors, not androgen receptors, to induce a masculine SDN-POA. In fact, you can masculinize the SDN-POA by injecting females at birth with just estradiol, a potent estrogen hormone. You can see this effect on the far right of Figure 11.14.

Why doesn't estrogen make all female brains masculinized then? Remember that while ovaries are present early on in females, they will not start secreting large amounts of estrogens until puberty (Figure 11.13). This means that estrogens are low in females around birth. The testes of males, in contrast, make plenty of steroid hormones, testosterone specifically, around birth. This peak in testosterone production drives many masculinization processes in the body and brain. In places like the hypothalamus, aromatase converts that testosterone to estrogen and drives masculinization of neural regions.

Similarly, in zebra finches (*Poephila guttata*), a species of songbirds where males sing more than females, the forebrain regions controlling song, including the higher vocal center (HVC) and the nucleus robustus archistriatum (RA), are larger in males. Treatment of newly hatched female zebra finches with estrogen, followed by testosterone treatment in adulthood, masculinizes the females in terms of both singing and the volume of RA and HVC (Gurney 1981). In contrast, castration of adult male finches reduces singing only modestly, and testosterone treatment of adult females cannot induce them to sing nor their brain regions to grow (A. P. Arnold 1975), suggesting that hormone influences during early developmental stages permanently masculinize the zebra finch brain. However, something very interesting was observed in zebra finches that did not fit what was observed in rats: neither early-life castration nor pharmacological blockade of steroid hormone receptors prevents these nuclei from developing a masculine phenotype in genetic males (A. P. Arnold 1996). Remember what we talked about the genotype itself causing sex differences independent of gonadal hormones? It turns out that the male genotype causes the zebra finch brain to locally produce steroid hormones, which then masculinize the birdsong system (Holloway and Clayton 2001). Figure 11.15 summarizes these different treatments and outcomes. This highlights, once again, the complex interplay between genetic and hormonal factors in the development of sex-specific behaviors.



	Intact female	Intact male	Female with E at birth and T in adulthood	Female given T in adulthood	Male castrated in adulthood	Male castrated in early life
HVC/RA size	Small/female typical	Large/male typical	Large/male typical	Small/female typical	Large/male typical	Large/male typical
Sings?	No	Yes	Yes	No	Yes	Yes
Genome	Female	Male	Female	Female	Male	Male
Early T exposure	no T	T	T	no T	T	no T

Figure 11.15 Sexually dimorphic RA/HVC size in zebra finches

Activational Mechanisms

Activational effects of hormones occur after the initial organizational phase and are pivotal during adulthood, continuing to influence the body throughout an individual's life. These effects are triggered by the fluctuation of hormone levels, particularly during puberty, adulthood, and into old age. Unlike organizational effects, which are permanent and shape developmental pathways, activational effects are reversible and depend on the presence of hormones at any given time.

Let's explore what happens during puberty. During this critical phase, the hypothalamic-pituitary-gonadal axis is activated both in males and females, initiating the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This hormone stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), collectively known as gonadotropins. These gonadotropins then promote the production of estrogens and progesterone in the ovaries for females, and testosterone in the testes for males (see Figure 11.16). Each of these hormones exerts activational effects across various tissues.

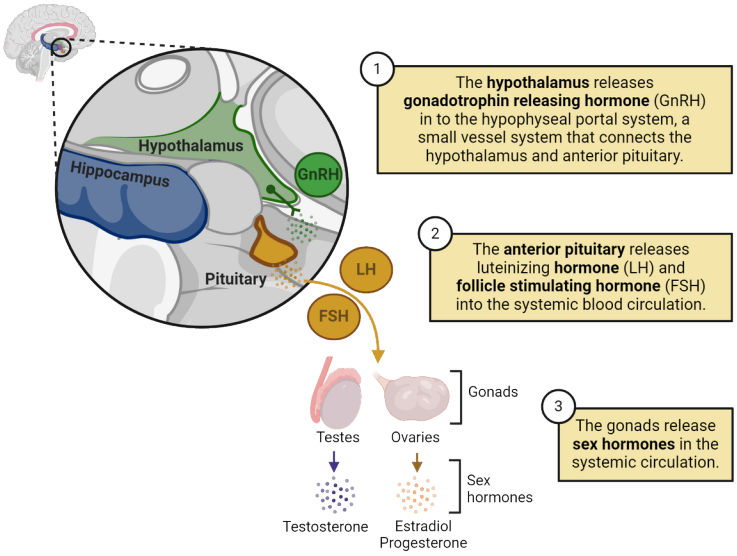


Figure 11.16 HPG axis

For example, in adult female mammals, the cyclic release of estrogen and progesterone by the ovaries during the estrous cycle has activational effects on the reproductive tract. Estrogen causes the uterine lining to thicken, preparing it for the potential

implantation of an embryo. Progesterone, released after ovulation, further prepares the uterus for pregnancy and maintains the uterine lining. If pregnancy does not occur, the levels of these hormones drop, leading to the shedding of the uterine lining in menstruation. If we inject adult males with estrogen and progesterone, however, they will not undergo these changes. This example shows how activational mechanisms can dynamically regulate female physiology as long as the tissue has been previously organized to be female.

Just like organizational effects, activational mechanisms are not limited to the reproductive tract but also extend to other tissues, including the brain. For instance, the posterodorsal medial amygdala (MePD), a brain area that plays a crucial role in male sexual arousal triggered by olfactory cues in rodents, is about 1.5 times larger in males than in females. However, if testes are removed, the size of this nucleus can be completely feminized within 30 days, which is accompanied by a reduction in male arousal to airborne cues from receptive females. Conversely, administering testosterone to adult females for a month increases the MePD to a masculine size (Cooke, Tabibnia, and Breedlove 1999). This shows that androgens play an activational role in affecting the size of MePD.

In sum, both genetic and hormonal factors play key roles in shaping sex-specific physiological processes and behaviors, but it is important to recognize that the social and physical environment also exerts profound effects, especially in humans. From birth, human infants are immersed in a highly gendered social and physical environment. Boys and girls are often expected and encouraged to behave differently and tend to choose different occupations and life paths. These choices lead to variations in physical and emotional stress, diet, and numerous other factors (Arthur P. Arnold 2017). The substantial differences in environmental experiences between the sexes can contribute to functional differences in the brain and other tissues, as well as susceptibility to diseases.

Sex as a biological variable: Why Including Sex as a Biological Variable Matters in Biomedical Research

Incorporating sex as a biological variable in biomedical research is crucial for achieving robust, rigorous, and reproducible science. Before we continue, it is crucial to remember the differences between 'sex'—the biological differences including chromosomes, hormonal profiles, and internal and external organs—and 'gender,' which encompasses the socially constructed roles, behaviors, identities, and norms. Historically, the majority of research has focused disproportionately on male subjects, from laboratory animals to human clinical trial participants, leading to significant gaps in our medical knowledge. This oversight can result in skewed data and potentially harmful clinical outcomes, especially for women (Zucker, Prendergast, and Beery 2022). Sex differences can profoundly influence various biological processes, from cellular responses and gene expression to the manifestation of diseases and how drugs are metabolized. Ignoring these differences has led to a systemic lack of representation not only of females but also of transgender and intersex populations, and individuals with variations in sex characteristics. This oversight has compromised the quality of healthcare, often resulting in delayed or misdiagnosed conditions in these groups. Additionally, the underrepresentation of female participants in clinical trials and the absence of sex-based data analysis have culminated in medications that are less effective and potentially more harmful for female patients. A compelling illustration of the importance of including sex as a biological variable is evident in stroke research. Stroke, a leading cause of death and disability worldwide, has a higher lifetime risk in women than in men. Research has uncovered significant differences in how strokes affect males and females, with variations in incidence, outcomes, and treatment responses. For example, estrogen's neuroprotective effects influence stroke outcomes differently across sexes. Drugs that showed promise in male models often failed to translate the same benefits to females, likely due to these hormonal differences. These findings emphasize the critical need for sex-specific treatment approaches in stroke therapies, showcasing how integrating sex as a biological variable provides essential insights into how diseases and treatments uniquely impact males and females. This approach is vital for developing effective, personalized medical treatments that cater to the specific needs of all patients.

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13.4: Sex Differences in Psychology and the Brain

The process of sexual differentiation is relatively well understood for reproductive body parts and behaviors. They are sexually dimorphic, meaning they come in two distinct types—male or female.[1] Conversely, non-reproductive behaviors and body structures, including the brain, vary much more within and across sexes. Structures may differ between males and females on average, but their distributions greatly overlap, and they do not have a distinct male or female form (i.e., are not sexually dimorphic). Thus, sex differences in the brain and behavior are less clear, less well understood, and subject to greater debate.

The uncertainty and contention on sex differences stem from various factors. First, most early animal studies on brain and behavior included only male animals, making it impossible to study sex differences. This only recently changed and now funding agencies generally require that studies include both males and females and address how biological variables such as sex are factored into the research design (Clayton & Collins, 2014; Pinel & Barnes, 2021). Second, sex differences in human psychology can be politically and emotionally charged—given the historical misuse of biological data to justify sexist ideas, some fear that recognizing sex differences could lead to more sexist or discriminatory policies; conversely ignoring biological sex differences due to concerns about sexism may harm health outcomes by hindering the development of optimized sex-specific treatments.

Finally, human studies on sex differences are methodologically challenging; when differences are observed, effects are often small and their causes (biological and/or experiential) remain unclear. For example, a sex difference in the size of a brain region could stem from biological differences linked to the sex chromosomes, exposure to hormones, experiences of developing in a gendered society, and/or interactions among such factors (e.g., hormones or gendered experience could trigger epigenetic modifications, leading to gene expression or silencing that results in sex differences in the brain; Nugent & McCarthy, 2011). Ethical and practical constraints prevent experimental manipulation of variables in humans, while animal models may not generalize to the complexities of human sex differences.

Sex Differences in Psychology

Despite the scientific challenges, understanding sex differences could provide insights into behaviors, cognitive functions, and psychiatric disorders that manifest differently in males and females. The prevalence of several psychiatric conditions differs between males and females. Conditions more common in males include autism spectrum disorder, ADHD, schizophrenia, specific language impairment, and dyslexia. Conditions more common in females include Alzheimer's disease, anxiety disorders, anorexia nervosa, and depression (Ritchie et al., 2018; Ruigrok et al., 2014).

Sex differences have also been established in cognitive abilities, emotion, personality, and behavior. For example, on average, males perform better on some spatial tasks, such as rotating 3D objects. Males also show higher rates of aggression (Archer, 2004) and risk-taking (Cross et al., 2011). On average, females perform better on some memory tasks such as remembering object identities and faces. Girls outperform boys on some verbal tasks including reading and writing (Miller & Halpern, 2014). Females also score higher on average for tests of empathy, self-reported interest in people versus things, and the personality trait agreeableness (Christov-Moore et al., 2014; Ritchie et al., 2018).

It's crucial to note that these differences represent average tendencies, and there is substantial overlap in performance for males and females on all these measures. In sum, several psychological phenomena differ between males and females and these differences likely arise from many biological and environmental factors. Investigating sex differences in the brain may provide insight into these psychological patterns, enhancing our understanding of cognition and behavior.

Sex Differences in the Brain

Research has identified several differences between male and female brains. Males have larger brains on average than females; with 9-13% greater volume in total brain, white matter, grey matter, and cerebrospinal fluid (Ruigrok et al., 2014). These overall size differences might be unsurprising, as males also have bigger bodies, hearts, lungs, feet, etc. Despite smaller brains, females have greater cortical thickness throughout most of the brain (Ritchie et al., 2018). Differences in volume occur in some brain regions.

An MRI study of over 5000 English adults found males had larger volumes in many subcortical regions, including the amygdala (involved in emotion and threat detection), hippocampus (involved in memory and spatial processing), and the nucleus

accumbens (involved in reward processing). These sex differences persisted when controlling for height, but were less pronounced when controlling for total brain volume (Ritchie et al., 2018).

Recent debates challenge the extent of sex differences in the brain. Eliot et al. (2021) argue that when properly controlling for brain volume, sex-related differences in specific regions become limited and weak, and conclude that the brain is not sexually dimorphic (i.e., it does not come in a distinct male and female form). Most researchers would reject the extreme binary concept of 'sexually dimorphic' brains. However, a meta-analysis that considered the methodological quality of studies found "highly reproducible sex differences in regional brain anatomy" beyond overall brain size. These sex differences are in the mean value of largely overlapping distributions, and they show small-to-moderate effect sizes (DeCasien et al., 2022).

The causal factors (biology versus experience) shaping sex differences in the brain continues to be a crucial area of scientific inquiry. Sex differences in the brain were most apparent in "mature" age participants (ages 18-59) (Ruigrok et al., 2014); and in the large English study, participants averaged 62 years of age (Ritchie et al., 2018). This raises the question of whether observed sex differences primarily result from long-term exposure to gendered societal experiences rather than innate biological factors such as hormones or genes.

However, some sex differences exist at birth, before gendered experience. Newborn males have 6% larger brains and more neocortical neurons than females, even when controlling for birth weight. Region-specific differences are also present: males have a larger medial temporal cortex (involved in sensory processing), while females have greater grey matter volume in the temporal-parietal junction (involved in social cognition) (Gilmore et al., 2018). These differences that developed before birth may relate to brain function later in life.

For an interesting overview, see the debate between Profs. Gina Rippon and Simon Baron-Cohen on sex differences and whether the brain is gendered. Video link. Podcast link.

Size and Distribution of Sex Differences

Although reliable sex differences exist in human brains and psychological phenomena, the effect sizes are typically small to moderate and there is more variation within each sex than between sexes. Figure 7 (adapted from Maney, 2016) illustrates this concept by plotting male and female distributions for three traits.

Figure 7a shows external genitalia size, a sexually dimorphic trait with distinct male and female ranges (data from Wallen & Lloyd, 2008, Maney 2016). In this sample, all measurements from the females fall in one range, and all males fall in a separate range. So based on this trait, females and males could be accurately categorized (with only rare exceptions).

Figure shows distributions of the size of external genitalia in females and males. The distributions are non-overlapping.

Figure 7a. The distributions of the size of the external genitalia—the "genital tubercle derivative" (i.e., the clitoris or penis) in a sample of human females (in pink) and males (in blue).

As shown in Figure 7b, height differs between males and females on average, but the distributions overlap considerably, and many females are taller than many males. If you only know someone's height, you cannot accurately categorize them as male or female.

Figure shows distributions of the height of females and males. The distributions overlap some, indicating that there are many females who are taller than many males.

Figure 7b. The distributions of height in a sample of females and males. Overlap of distributions is shown in purple.

Figure 7c plots connectivity between brain regions, a small but reliable sex difference in the brain (data from Tunç et al., 2016). If you only knew someone's brain connectivity, you would correctly guess their sex about 51% of the time (Maney, 2016). This is only slightly above chance but reflects a reliable sex difference. Small differences can be important, but should be interpreted cautiously.

Figure shows distributions of a measure of brain connectivity of females and males. The distributions overlap nearly completely; the average for males is slightly higher (showing a statistically significant difference).

Figure 7c. The distribution of measurements of brain connectivity in a sample of females and males.

Given the considerable overlap in distributions of brain regions that show sex differences, human brains cannot be categorized into two distinct classes: "male brain" or "female brain." Very few brains feature all male-associated regions or all female-associated regions. Human brains exist along a spectrum of traits associated with sex. Joel and colleagues (2015) thus proposed

the concept of the “mosaic brain”, wherein “most brains are comprised of unique ‘mosaics’ of features, some more common in females compared with males, some more common in males compared with females, and some common in both females and males.”

While humans cannot look at a brain and accurately categorize it as male or female, recent artificial intelligence approaches can. Machine learning algorithms simultaneously using many features of the brain “mosaic”, can successfully identify whether a brain is from a male or female with over 90% accuracy (Ryali et al., 2024).

Brains and Hormones

Many causal factors can shape sex differences in the brain, including genetic encoding on the sex chromosomes, experience, and hormones (DeCasien et al., 2022; Ruigrok et al., 2014). We conclude this section with two examples of hormonal influences on sex differences in brain and behavior.

In rats, a region of the hypothalamus, the sexually dimorphic nucleus of the Preoptic Area (SDN-POA), is (as its name indicates) sexually dimorphic—it is 2.6 times larger in males than females. It is involved in reproduction. Lesioning it completely disrupts a male rat’s ability to engage in sexual behavior. Experiments demonstrate that exposure to gonadal steroid hormones during early development have an “organizing” effect on this brain structure. Exposure to testosterone (which is converted to estradiol) or estradiol causes masculinization of the brain. Figure 8 shows the SDN-POA (dark cell bodies) in a male (left), a female (center), and a female treated with testosterone as a newborn (right). The SDN-POA of the untreated male is substantially larger than the untreated female, but is equal in size to the testosterone-treated female. This illustrates how early gonadal hormone exposure dramatically affects brain structure.

Image of sexually dimorphic nuclei of the preoptic area (SDN-POA) Gonadal steroid hormones have organizing effects upon brain and behavior.

Figure 8. The sexually dimorphic nuclei of the preoptic area (SDN-POA) shown as dark cell bodies in an untreated male rat (left), an untreated female rat (center), and a female rat treated with testosterone as a newborn (right). Note that the SDN-POA of the male are substantially larger than those of the untreated female, but are equal in size to those of the testosterone-treated female. Exposure to testosterone (which is converted to estradiol) or estradiol causes masculinization of the brain. OC = optic chiasm; SCN = suprachiasmatic nucleus; V = third ventricle.

In humans, researchers cannot experimentally manipulate hormone levels that a newborn or fetus is exposed to. However, if the fluid in the amniotic sac around the fetus is measured for medical reasons, researchers can also measure the prenatal testosterone levels. Such data show that male fetuses are exposed to more testosterone on average than female fetuses. Interestingly, longitudinal studies have shown that prenatal hormone levels relate to behavior and brain structure many years later. For example, girls with higher levels of *prenatal* testosterone performed better on a test of mental rotation at age 7 (Grimshaw et al., 1995), and boys with higher levels of *prenatal* testosterone performed worse on a test of empathy at age 6-8 (Chapman et al., 2006).

Fetal testosterone levels also correlated with the volume of brain regions in a group of 8-11 year olds in a way that was congruent with sex differences observed in those regions (Lombardo et al., 2012). For example, some regions that were generally bigger in males, were also associated with higher levels of prenatal testosterone (and vice versa). While only correlational (and not causal like the rat experiment), these results suggest that prenatal hormone exposure could play some role in organizing brain structure and sex differences in brain and behavior.

Text Attributions

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1. As noted throughout the chapter, biological sex cannot always be simplified into a strict two-structure dichotomy; it exists along a continuum, and intersex conditions occur more frequently than many realize. 6.03: Sex Differences in Psychology and the Brain#return-footnote-189-1

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13.5: Neural Mechanisms of Sexual Behavior

Learning Objectives

- Understand basic biological mechanisms regulating sexual behavior and motivation
- Appreciate the importance of Alfred Kinsey's research on human sexuality
- Recognize the contributions that William Masters and Virginia Johnson's research made to our understanding of the sexual response cycle
- Define sexual orientation and gender identity

Like food, sex is an important part of our lives. From an evolutionary perspective, the reason is obvious—perpetuation of the species. Sexual behavior in humans, however, involves much more than reproduction. This section provides an overview of research that has been conducted on human sexual behavior and motivation. This section will close with a discussion of issues related to gender and sexual orientation.

Physiological Mechanisms of Sexual Behavior and Motivation

Much of what we know about the physiological mechanisms that underlie sexual behavior and motivation comes from animal research. As you've learned, the hypothalamus plays an important role in motivated behaviors, and sex is no exception. In fact, lesions to an area of the hypothalamus called the medial preoptic area completely disrupt a male rat's ability to engage in sexual behavior. Surprisingly, medial preoptic lesions do not change how hard a male rat is willing to work to gain access to a sexually receptive female (See figure 10.14). This suggests that the ability to engage in sexual behavior and the motivation to do so may be mediated by neural systems distinct from one another.



Figure 10.14 A male rat that cannot engage in sexual behavior still seeks receptive females, suggesting that the ability to engage in sexual behavior and the motivation to do so are mediated by different systems in the brain. (credit: Jason Snyder)

Animal research suggests that limbic system structures such as the amygdala and nucleus accumbens are especially important for sexual motivation. Damage to these areas results in a decreased motivation to engage in sexual behavior, while leaving the ability to do so intact (See figure 10.15) (Everett, 1990). Similar dissociations of sexual motivation and sexual ability have also been observed in the female rat (Becker, Rudick, & Jenkins, 2001; Jenkins & Becker, 2001).

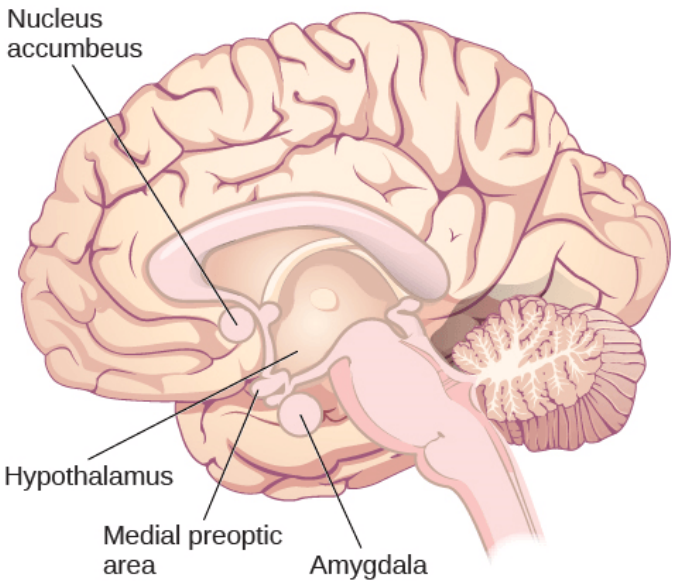


Figure 10.15 The medial preoptic area, an area of the hypothalamus, is involved in the ability to engage in sexual behavior, but it does not affect sexual motivation. In contrast, the amygdala and nucleus accumbens are involved in motivation for sexual behavior, but they do not affect the ability to engage in it.

Although human sexual behavior is much more complex than that seen in rats, some parallels between animals and humans can be drawn from this research. The worldwide popularity of drugs used to treat erectile dysfunction (Conrad, 2005) speaks to the fact that sexual motivation and the ability to engage in sexual behavior can also be dissociated in humans. Moreover, disorders that involve abnormal hypothalamic function are often associated with hypogonadism (reduced function of the gonads) and reduced sexual function (e.g., Prader-Willi syndrome). Given the hypothalamus's role in endocrine function, it is not surprising that hormones secreted by the endocrine system also play important roles in sexual motivation and behavior. For example, many animals show no sign of sexual motivation in the absence of the appropriate combination of sex hormones from their gonads. While this is not the case for humans, there is considerable evidence that sexual motivation for both men and women varies as a function of circulating testosterone levels (Bhasin, Enzlin, Coviello, & Basson, 2007; Carter, 1992; Sherwin, 1988).

Kinsey's Research

Before the late 1940s, access to reliable, empirically-based information on sex was limited. Physicians were considered authorities on all issues related to sex, despite the fact that they had little to no training in these issues, and it is likely that most of what people knew about sex had been learned either through their own experiences or by talking with their peers. Convinced that people would benefit from a more open dialogue on issues related to human sexuality, Dr. Alfred **Kinsey** of Indiana University initiated large-scale survey research on the topic (See figure 10.16). The results of some of these efforts were published in two books—*Sexual Behavior in the Human Male* and *Sexual Behavior in the Human Female*—which were published in 1948 and 1953, respectively (Bullough, 1998).



Figure 10.16 In 1947, Alfred Kinsey established The Kinsey Institute for Research, Sex, Gender and Reproduction at Indiana University, shown here in 2011. The Kinsey Institute has continued as a research site of important psychological studies for decades.

At the time, the Kinsey reports were quite sensational. Never before had the American public seen its private sexual behavior become the focus of scientific scrutiny on such a large scale. The books, which were filled with statistics and scientific lingo, sold remarkably well to the general public, and people began to engage in open conversations about human sexuality. As you might imagine, not everyone was happy that this information was being published. In fact, these books were banned in some countries. Ultimately, the controversy resulted in Kinsey losing funding that he had secured from the Rockefeller Foundation to continue his research efforts (Bancroft, 2004).

Although Kinsey's research has been widely criticized as being riddled with sampling and statistical errors (Jenkins, 2010), there is little doubt that this research was very influential in shaping future research on human sexual behavior and motivation. Kinsey described a remarkably diverse range of sexual behaviors and experiences reported by the volunteers participating in his research. Behaviors that had once been considered exceedingly rare or problematic were demonstrated to be much more common and innocuous than previously imagined (Bancroft, 2004; Bullough, 1998).

Link to Learning

Watch this trailer for the 2004 film *Kinsey* that depicts Alfred Kinsey's life and research to learn more.

Among the results of Kinsey's research were the findings that women are as interested and experienced in sex as their male counterparts, that both males and females masturbate without adverse health consequences, and that homosexual acts are fairly common (Bancroft, 2004). Kinsey also developed a continuum known as the Kinsey scale that is still commonly used today to categorize an individual's sexual orientation (Jenkins, 2010). **Sexual orientation** is an individual's emotional and erotic attractions to same-sexed individuals (**homosexual**), opposite-sexed individuals (**heterosexual**), or both (**bisexual**).

Masters and Johnson's Research

In 1966, William **Masters** and Virginia **Johnson** published a book detailing the results of their observations of nearly 700 people who agreed to participate in their study of physiological responses during sexual behavior. Unlike Kinsey, who used personal interviews and surveys to collect data, Masters and Johnson observed people having intercourse in a variety of positions, and they observed people masturbating, manually or with the aid of a device. While this was occurring, researchers recorded measurements of physiological variables, such as blood pressure and respiration rate, as well as measurements of sexual arousal, such as vaginal lubrication and penile tumescence (swelling associated with an erection). In total, Masters and Johnson observed nearly $10,000$ sexual acts as a part of their research (Hock, 2008).

Based on these observations, Masters and Johnson divided the **sexual response cycle** into four phases that are fairly similar in men and women: excitement, plateau, orgasm, and resolution (See figure 10.17). The **excitement** phase is the arousal phase of the sexual response cycle, and it is marked by erection of the penis or clitoris and lubrication and expansion of the vaginal canal. During **plateau**, women experience further swelling of the vagina and increased blood flow to the labia minora, and men experience full erection and often exhibit pre-ejaculatory fluid. Both men and women experience increases in muscle tone during this time. **Orgasm** is marked in women by rhythmic contractions of the pelvis and uterus along with increased muscle tension.

In men, pelvic contractions are accompanied by a buildup of seminal fluid near the urethra that is ultimately forced out by contractions of genital muscles, (i.e., ejaculation). **Resolution** is the relatively rapid return to an unaroused state accompanied by a decrease in blood pressure and muscular relaxation. While many women can quickly repeat the sexual response cycle, men must pass through a longer refractory period as part of resolution. The **refractory period** is a period of time that follows an orgasm during which an individual is incapable of experiencing another orgasm. In men, the duration of the refractory period can vary dramatically from individual to individual with some refractory periods as short as several minutes and others as long as a day. As men age, their refractory periods tend to span longer periods of time.

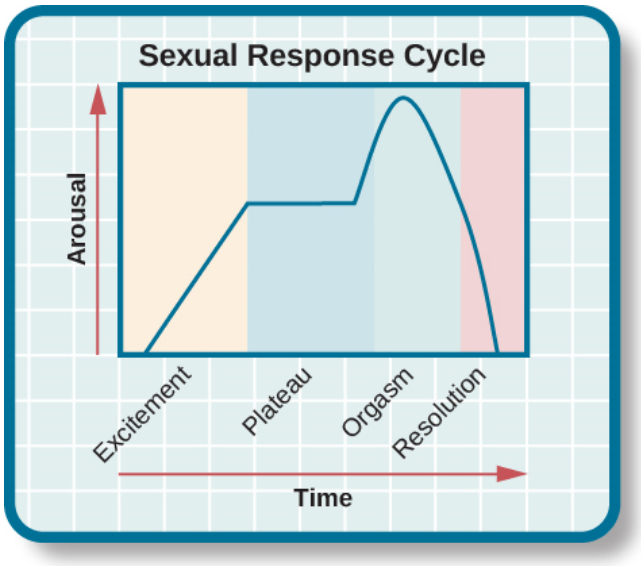


Figure 10.17 This graph illustrates the different phases of the sexual response cycle as described by Masters and Johnson.

In addition to the insights that their research provided with regards to the sexual response cycle and the multi-orgasmic potential of women, Masters and Johnson also collected important information about reproductive anatomy. Their research demonstrated the oft-cited statistic of the average size of a flaccid and an erect penis (3 and 6 inches, respectively) as well as dispelling long-held beliefs about relationships between the size of a man's erect penis and his ability to provide sexual pleasure to his female partner. Furthermore, they determined that the vagina is a very elastic structure that can conform to penises of various sizes (Hock, 2008).

Sexual Orientation

As mentioned earlier, a person's sexual orientation is their emotional and erotic attraction toward another individual (See fig. 10.18). While the majority of people identify as heterosexual, there is a sizable population of people within the United States who identify as either homosexual or bisexual. Research suggests that somewhere between 3% and 10% of the population identifies as homosexual (Kinsey, Pomeroy, & Martin, 1948; LeVay, 1996; Pillard & Bailey, 1995).

Some of these terms have been associated in abbreviations such as LGBTQ (lesbian, gay, bisexual, transgender, and queer or questioning). In some cases, people and organizations may add "I" to represent intersex people (described below), and "A" for asexual or aromantic people (or sometimes for "allies"), as well as one "P" to describe pansexual people and sometimes another "P" to describe polysexual people. Finally, some people and organizations add a plus sign (+) to represent other possible identities or orientations. Sexuality and gender terminology are constantly changing, and may mean different things to different people; they are not universal, and each individual defines them for themselves (UC Davis LGBTQIA Resource Center 2020).



Figure 10.18 Between 3% and 10% of the adult population identifies as homosexual. (credit: Till Krech)

Issues of sexual orientation have long fascinated scientists interested in determining what causes one individual to be heterosexual while another is homosexual. For many years, people believed that these differences arose because of different socialization and familial experiences. However, research has consistently demonstrated that the family backgrounds and experiences are very similar among heterosexuals and homosexuals (Bell, Weinberg, & Hammersmith, 1981; Ross & Arrindell, 1988).

Genetic and biological mechanisms have also been proposed, and the balance of research evidence suggests that sexual orientation has an underlying biological component. For instance, over the past 25 years, research has demonstrated gene-level contributions to sexual orientation (Bailey & Pillard, 1991; Hamer, Hu, Magnuson, Hu, & Pattatucci, 1993; Rodriguez-Larralde & Paradisi, 2009), with some researchers estimating that genes account for at least half of the variability seen in human sexual orientation (Pillard & Bailey, 1998). Other studies report differences in brain structure and function between heterosexuals and homosexuals (Allen & Gorski, 1992; Byne et al., 2001; Hu et al., 2008; LeVay, 1991; Ponseti et al., 2006; Rahman & Wilson, 2003a; Swaab & Hofman, 1990), and even differences in basic body structure and function have been observed (Hall & Kimura, 1994; Lippa, 2003; Loehlin & McFadden, 2003; McFadden & Champlin, 2000; McFadden & Pasanen, 1998; Rahman & Wilson, 2003b). In aggregate, the data suggest that to a significant extent, sexual orientations are something with which we are born.

Misunderstandings about Sexual Orientation

Regardless of how sexual orientation is determined, research has made clear that sexual orientation is not a choice, but rather it is a relatively stable characteristic of a person that cannot be changed. Claims of successful gay conversion therapy have received wide criticism from the research community due to significant concerns with research design, recruitment of experimental participants, and interpretation of data. As such, there is no credible scientific evidence to suggest that individuals can change their sexual orientation (Jenkins, 2010).

Dr. Robert Spitzer, the author of one of the most widely-cited examples of successful conversion therapy, apologized to both the scientific community and the gay community for his mistakes, and he publically recanted his own paper in a public letter addressed to the editor of *Archives of Sexual Behavior* in the spring of 2012 (Carey, 2012). In this letter, Spitzer wrote,

> ***I was considering writing something that would acknowledge that I now judge the major critiques of the study as largely correct. . . . I believe I owe the gay community an apology for my study making unproven claims of the efficacy of reparative therapy. I also apologize to any gay person who wasted time or energy undergoing some form of reparative therapy because they believed that I had proven that reparative therapy works with some "highly motivated" individuals. (Becker, 2012, pars. 2, 5)***

Citing research that suggests not only that gay conversion therapy is ineffective, but also potentially harmful, legislative efforts to make such therapy illegal have either been enacted (e.g., it is now illegal in California) or are underway across the United States, and many professional organizations have issued statements against this practice (Human Rights Campaign, n.d.)

Link to Learning

Read this article about Dr. Spitzer's apology to learn more.

Gender Identity

Many people conflate sexual orientation with gender identity because of stereotypical attitudes that exist about homosexuality. In reality, these are two related, but different, issues. **Gender identity** refers to one's sense of being male or female. Generally, our gender identities correspond to our chromosomal and phenotypic sex, but this is not always the case. When individuals do not feel comfortable identifying with the gender associated with their biological sex, then they experience gender dysphoria. **Gender dysphoria** is a diagnostic category in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) that describes individuals who do not identify as the gender that most people would assume they are. This dysphoria must persist for at least six months and result in significant distress or dysfunction to meet DSM-5 diagnostic criteria. In order for children to be assigned this diagnostic category, they must verbalize their desire to become the other gender.

Many people who are classified as gender dysphoric seek to live their lives in ways that are consistent with their own gender identity. This involves dressing in opposite-sex clothing and assuming an opposite-sex identity. These individuals may also undertake **transgender hormone therapy** in an attempt to make their bodies look more like the opposite sex, and in some cases, they elect to have surgeries to alter the appearance of their external genitalia to resemble that of their gender identity (See figure 13.5.6). While these may sound like drastic changes, gender dysphoric individuals take these steps because their bodies seem to them to be a mistake of nature, and they seek to correct this mistake.

Some transgender individuals may undertake a process of transition, in which they move from living in a way that is more aligned with the sex assigned at birth to living in a way that is aligned with their gender identity. Transitioning may take the form of social, legal, or medical aspects of someone's life, but not everyone undertakes any or all types of transition. Social transition may involve the person's presentation, name, pronouns, and relationships. Legal transition can include changing their gender on government or other official documents, changing their legal name, and so on. Some people may undergo a physical or medical transition, in which they change their outward, physical, or sexual characteristics in order for their physical being to better align with their gender identity (UCSF Transgender Care 2019). Not all transgender individuals choose to alter their bodies: many will maintain their original anatomy but may present themselves to society as another gender. This is typically done by adopting the dress, hairstyle, mannerisms, or other characteristics typically assigned to another gender. It is important to note that people who cross-dress, or wear clothing that is traditionally assigned to a gender different from their biological sex, are not necessarily transgender. Cross-dressing is typically a form of self-expression or personal style, and it does not indicate a person's gender identity or that they are transgender (TSER 2021).

Intersex is a general term used to describe people whose sex traits, reproductive anatomy, hormones, or chromosomes are different from the usual two ways human bodies develop. Some intersex traits are recognized at birth, while others are not recognizable until puberty or later in life (interACT 2021). Intersex and transgender are not interchangeable terms; many transgender people have no intersex traits, and many intersex people do not consider themselves transgender.

Those who identify with the sex they were assigned at birth are often referred to as *cisgender*, utilizing the Latin prefix "cis," which means "on the same side." (The prefix "trans" means "across.") Many cisgender people do not self-identify as such. As with transgender people, the term or usage of cisgender does not indicate a person's sexual orientation, gender, or gender expression (TSER 2021).

Our scientific knowledge and general understanding about gender identity continue to evolve, and young people today have more opportunity to explore and openly express different ideas about what gender means than previous generations. Recent studies indicate that the majority of millennials (those ages 18–34) regard gender as a spectrum instead of a strict male/female binary, and that 12% identify as transgender or gender non-conforming. Additionally, more people know others who use gender-neutral pronouns (such as they/them) (Kennedy, 2017). This change in language may indicate that millennials and Generation Z people understand the experience of gender itself differently. As young people lead this change, other changes are emerging in a range of spheres, from public bathroom policies to retail organizations. For example, some retailers are starting to change traditional gender-based marketing of products, such as removing "pink and blue" clothing and toy aisles. Even with these changes, those who exist outside of traditional gender norms face difficult challenges. Even people who vary slightly from traditional norms are often the target of discrimination and violence.



Figure 10.19 Chaz Bono, a transgender male, is a well-known person who transitioned from female to male. (a) In the 1970s, the world knew Chaz as Chastity Bono, the daughter of the famous entertaining duo Sonny and Cher; here young Chastity is pictured with Sonny. (b) Later in life, Chaz transitioned to align his physical body with his gender identity. (credit b: modification of work by "dvsross"/Flickr)

Link to Learning

Hear firsthand about the transgender experience and overcoming challenges in the face of discrimination and violence. Watch this brief interview with Carmen Carrera and Laverne Cox on Katie Couric's talk show to learn more. This video about transgender immigrants' experiences explains more struggles faced globally by those in the transgender community.

Cultural Factors in Sexual Orientation and Gender Identity

Issues related to sexual orientation and gender identity are very much influenced by sociocultural factors. Even the ways in which we define sexual orientation and gender vary from one culture to the next. While in the United States exclusive heterosexuality is viewed as the norm, there are societies that have different attitudes regarding homosexual behavior. In fact, in some instances, periods of exclusively homosexual behavior are socially prescribed as a part of normal development and maturation. For example, in parts of New Guinea, young boys are expected to engage in sexual behavior with other boys for a given period of time because it is believed that doing so is necessary for these boys to become men (Baldwin & Baldwin, 1989).

There is a two-gendered culture in the United States. We tend to classify an individual as either male or female. However, in some cultures there are additional gender variants resulting in more than two gender categories. For example, in Thailand, you can be male, female, or kathoey. A kathoey is an individual who would be described as intersexed or transgendered in the United States (Tangmunkongvorakul, Banwell, Carmichael, Utomo, & Sleigh, 2010).

DIG DEEPER: The Case of David Reimer

In August of 1965, Janet and Ronald Reimer of Winnipeg, Canada, welcomed the birth of their twin sons, Bruce and Brian. Within a few months, the twins were experiencing urinary problems; doctors recommended the problems could be alleviated by having the boys circumcised. A malfunction of the medical equipment used to perform the circumcision resulted in Bruce's penis being irreparably damaged. Distraught, Janet and Ronald looked to expert advice on what to do with their baby boy. By happenstance, the couple became aware of Dr. John Money at Johns Hopkins University and his theory of psychosexual neutrality (Colapinto, 2000).

Dr. Money had spent a considerable amount of time researching transgendered individuals and individuals born with ambiguous genitalia. As a result of this work, he developed a theory of psychosexual neutrality. His theory asserted that we are essentially neutral at birth with regard to our gender identity and that we don't assume a concrete gender identity until we begin to master language. Furthermore, Dr. Money believed that the way in which we are socialized in early life is ultimately much more important than our biology in determining our gender identity (Money, 1962).

Dr. Money encouraged Janet and Ronald to bring the twins to Johns Hopkins University, and he convinced them that they should raise Bruce as a girl. Left with few other options at the time, Janet and Ronald agreed to have Bruce's testicles removed and to raise him as a girl. When they returned home to Canada, they brought with them Brian and his "sister," Brenda, along with specific instructions to never reveal to Brenda that she had been born a boy (Colapinto, 2000).

Early on, Dr. Money shared with the scientific community the great success of this natural experiment that seemed to fully support his theory of psychosexual neutrality (Money, 1975). Indeed, in early interviews with the children it appeared that Brenda was a typical little girl who liked to play with "girly" toys and do "girly" things.

However, Dr. Money was less than forthcoming with information that seemed to argue against the success of the case. In reality, Brenda's parents were constantly concerned that their little girl wasn't really behaving as most girls did, and by the time Brenda was nearing adolescence, it was painfully obvious to the family that she was really having a hard time identifying as a female. In addition, Brenda was becoming increasingly reluctant to continue her visits with Dr. Money to the point that she threatened suicide if her parents made her go back to see him again.

At that point, Janet and Ronald disclosed the true nature of Brenda's early childhood to their daughter. While initially shocked, Brenda reported that things made sense to her now, and ultimately, by the time she was an adolescent, Brenda had decided to identify as a male. Thus, she became David Reimer.

David was quite comfortable in his masculine role. He made new friends and began to think about his future. Although his castration had left him infertile, he still wanted to be a father. In 1990, David married a single mother and loved his new role as a husband and father. In 1997, David was made aware that Dr. Money was continuing to publicize his case as a success supporting his theory of psychosexual neutrality. This prompted David and his brother to go public with their experiences in attempt to discredit the doctor's publications. While this revelation created a firestorm in the scientific community for Dr. Money, it also triggered a series of unfortunate events that ultimately led to David committing suicide in 2004 (O'Connell, 2004).

This sad story speaks to the complexities involved in gender identity. While the Reimer case had earlier been paraded as a hallmark of how socialization trumped biology in terms of gender identity, the truth of the story made the scientific and medical communities more cautious in dealing with cases that involve intersex children and how to deal with their unique circumstances. In fact, stories like this one have prompted measures to prevent unnecessary harm and suffering to children who might have issues with gender identity. For example, in 2013, a law took effect in Germany allowing parents of intersex children to classify their children as indeterminate so that children can self-assign the appropriate gender once they have fully developed their own gender identities (Paramaguru, 2013).

Link to Learning

Watch this news story about the experiences of David Reimer and his family to learn more.

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13.6: Hormones, Aggression, and Parental Behaviors

Many different hormones can affect a wide range of behaviors. This section gives a brief overview of two illustrative examples: the effects of hormones on aggression and in parental behaviors and bonding.

Aggressive Behaviors

Aggressive behavior can arise whenever individuals' interests are in conflict (Nelson, 2006). Conflicts most often arise over limited resources such as territory, food, or mates. A social interaction decides which animal gains access to the contested resource. Sometimes that interaction involves physical aggression, but in many cases, a submissive posture from one animal or ritualized combat to establish dominance can resolve conflicts without physical harm.

Overwhelming evidence suggests that androgenic steroid hormones, particularly testosterone, mediate male aggressive behavior across many species. First, seasonal variations in blood concentrations of testosterone coincide with variations in aggression. For instance, aggressive behavior peaks for male deer in autumn when they are secreting high levels of testosterone. Second, aggressive behaviors increase during puberty when the testes become active, and blood concentrations of androgens rise. Juvenile deer do not participate in the fighting during the mating season. Third, male mammals are generally more aggressive than females. This is certainly true of deer—female deer rarely display aggressive behavior. Finally, castration typically reduces aggression in males, and subsequent testosterone-replacement therapy restores aggression to pre-castration levels. Some exceptions to these general observations are outside the scope of this chapter.

In humans, males are generally more physically aggressive than females.[1] From early childhood, males consistently initiate more physical aggression than females, and many more men than women are convicted of violent crimes in North America. This sex difference in humans is widely recognized, but the underlying causes remain a subject of intense scientific debate. It is possible that males are more aggressive than females because: a) androgens promote aggressive behavior and males have higher androgen levels; b) brains of males are exposed to androgens prenatally causing brain "wiring" to organize in a way that increases aggression; and/or c) males are encouraged, and females are discouraged by family, peers, or others from acting aggressively. These hypotheses are not mutually exclusive, and are difficult to separate to account for sex differences in human aggression.

Figure 9. Researchers have electrically stimulated particular regions in people's brains, and these individuals have burst into aggressive, violent behavior, helping demonstrate that such responses are hardwired into us.

In humans, disentangling environmental and physiological influences on behavior is challenging. For instance, males and females differ in their rough-and-tumble play at a very young age, which might suggest an early physiological influence. However, parents usually play more roughly with male infants, which might suggest that sex differences in aggression are learned. Experimentally manipulating variables (e.g., by injecting testosterone) and tightly controlling the environment is not possible in human studies, so hormonal effects on sex-differentiated behavior is studied in non-human animal models.

Studies on mice reveal that sex differences in aggression result from both perinatal and adult androgen exposure. Male mice castrated early show low aggression even with adult testosterone treatment, while females given testosterone perinatally and in adulthood show male-like aggression. Thus, in mice and many other species, androgens both "organize" the brain perinatally for aggression and "activate" aggressive behavior in adulthood. Finally, while we focus on testosterone here, other hormones including cortisol, corticosterone, and vasopressin are involved in aggression, and there is no one-to-one relationship between a hormone and behavior.

Parental Behaviors and Bonding

Parental behavior in mammals is crucial for offspring survival. In rats, who give birth to underdeveloped (altricial) young, mothers exhibit stereotyped behaviors like nest-building, nursing, and pup retrieval. Typically, adult rats avoid pups due to aversion to their smell and neophobia (the fear of new things), but daily exposure can sensitize them to behave maternally. However, for new mothers, immediate maternal behavior is necessary for survival, and is hormonally mediated. Around the time a mother gives birth, a rapid decline in progesterone, coupled with high estradiol, prolactin, and oxytocin levels overrides the fear response, enabling maternal behavior in the presence of newborns.

Rat maternal behavior involves brain activity of the hypothalamus' medial preoptic area. This region can be inhibited by the amygdala and fear responses. Lesions in the amygdala or its input smell pathways can disinhibit (i.e., increase) maternal behavior. Hormones likely reduce amygdala activation, thus permitting maternal behavior. Studies show that giving female rats oxytocin increases maternal behavior and attachment to their pups (Kendrick, 2000).

One of the best studied examples of the biological basis of social bonding and attachment comes from prairie voles. Prairie voles are a North American rodent that display highly social behavior, have monogamous relationships after mating, and share parental duties such as resource collection and care for their young (Figure 10). Their close relative, the montane vole, on the other hand, is a non-social species that does not form pair bonds and only the female cares for the young. Comparing these species has allowed researchers to identify several neurochemical signals implicated in bonding.

Prairie vole parents with pups.

Figure 10. Prairie voles are monogamous rodents known for social behavior and shared parental care.

Oxytocin and vasopressin, similar neuropeptides, are crucial for pair bonding. In the social prairie voles, oxytocin and vasopressin are released by the hypothalamus in response to mating and act on limbic and reward systems. Female prairie voles have more oxytocin receptors in reward circuitry than asocial montane voles. After mating, oxytocin binds to these receptors to increase pair bonding and reinforce the rewarding association with a partner. Experiments show that giving oxytocin to female prairie voles increases bonding, while blocking oxytocin receptors decreases bonding. In male prairie voles, similar effects occur with vasopressin. Male prairie voles release vasopressin after mating; they have more vasopressin receptors in reward circuitry compared to montane voles; and giving vasopressin increases bonding, while blocking it decreases bonding. Notably, when males of a promiscuous species are genetically modified to have more vasopressin receptors, those males display increased pair bonding and parental behavior (Rigney et al., 2022). This underscores the causal role of hormones in social bonding.

Human bonding and parental behaviors (most often studied in mothers) are also shaped by hormones. Oxytocin, vasopressin, and the reward system play crucial roles in human bonding. **fMRI** studies show increased activation in reward-related brain regions when subjects view pictures of their children or partners, compared to friends. These regions express oxytocin and vasopressin receptors, and the hormones are released during bond-forming activities like breastfeeding and intercourse. In addition to oxytocin and vasopressin, cortisol levels positively correlate with mothers' affectionate and vocal behaviors towards infants, especially in mothers with positive prenatal attitudes. Cortisol likely enhances maternal care indirectly by increasing the mother's arousal and responsiveness to infant cues. High-cortisol mothers are more attracted to and better at identifying their infants' odors and cues (Fleming et al., 1997).

In sum, hormones play a crucial role in shaping parental behaviors and bonding in both mothers and fathers across various species, influencing brain activity and behavioral responses that are essential for offspring care and survival.

A mother cuddles with her daughter.

Figure 11. Although cortisol may not directly increase maternal behaviors, the next time your mom gives you a hug, you know one hormone to thank.

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1. However, females exhibit more relational aggression (i.e., the purposeful harm to another through a social relationship; Bowie,

2007). 6.04: Aggression and Parental Behaviors#return-footnote-192-1

definition

A form of social interaction that includes threat, attack, and fighting.

×Close definition

Functional magnetic resonance imaging (fMRI): A neuroimaging technique that infers brain activation by measuring changes in oxygen levels in the blood.

×Close definition

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13.7: Sex, Gender, and Sexual Orientation

Sex, Gender, and Sexual Orientation: Three Different Aspects of You

Applying for a credit card or filling out a job application requires your name, address, and birth date. Applications also usually ask for your sex or gender. The terms “sex” and “gender” are commonly used interchangeably, but they have distinct meanings.

Sex refers to a set of biological attributes including reproductive/sexual anatomy, genetics, and hormones. Sex is usually categorized as male or female, although variations occur in the biological attributes that comprise sex. By contrast, the term **gender** describes psychological (**gender identity**) and sociological (**gender role**) representations of biological sex. Ideas about gender vary over time and across cultures. At an early age, we begin learning cultural norms for what is considered masculine and feminine. For example, children may associate long hair or dresses with femininity. As adults, we often conform to these norms by behaving in gender-specific ways (Marshall, 1989; Money et al., 1955; Weinraub et al., 1984).

Sex and gender are important aspects of a person’s identity. However, they do not inform us about a person’s sexual orientation (Rule & Ambady, 2008). **Sexual orientation** refers to a person’s sexual attraction to others.

The international scientific and medical communities (e.g., World Health Organization, World Medical Association, World Psychiatric Association, Association for Psychological Science) view variations of sex, gender, and sexual orientation as normal. Furthermore, variations of sex, gender, and sexual orientation occur naturally throughout the animal kingdom. More than 500 animal species display homosexual or bisexual behavior (Sommer & Vasey, 2006; Figure 12). Hermaphroditism—having both functional testes and ovaries and being able to produce both female and male gametes (i.e., viable eggs and sperm)—is a normal mode of reproduction in a wide range of animals (but is virtually nonexistent in humans). **Intersex** is characterized as having sexual characteristics that do not fall neatly into male and female categories (e.g., absence or combination of male and female reproductive organs, sex hormones, or sex chromosomes). Intersex occurs in both animals and humans (Hrabovszky & Hutson, 2002). In humans, estimates of the prevalence of intersex individuals vary widely: from 0.018% to 1.7% of the population depending on how it is defined (Blackless et al., 2000; Sax, 2002). Many conditions have been considered intersex, such as Androgen Insensitivity Syndrome and Turner’s Syndrome (Lee et al., 2006). The term “syndrome” can be misleading, as they otherwise lead relatively normal intellectual, personal, and social lives. In any case, intersex individuals demonstrate the diverse variations of biological sex.

Figure 12. A male Mallard duck couple—one of hundreds of species displaying homosexual or bisexual behavior.

Variations in Gender

Just as biological sex varies more widely than is commonly thought, so too does gender. Cisgender individuals’ gender identities correspond with their birth sexes, whereas transgender individuals’ gender identities do not correspond with their birth sexes. Because gender is so deeply ingrained culturally, rates of transgender individuals vary widely around the world (see Table 2). Some cultures formally recognize the presence of people who do not conform to an expectation that gender identity match biological sex (Figure 13).

Table 2: Nations vary in the number of transgender people in their populations (De Gascun et al., 2006; Dulko & Imielinskia, 2004; Landen et al., 1996; Okabe et al., 2008; Conron et al., 2012; Winter, 2009). Note that these sources are a few decades old, but they illustrate major variation across cultures.

Figure 13: First photo: Hjira dancer in Nepal; Second photo: Kathoey performers at a cabaret in Pattaya, Thailand.

Transgender rates and subtypes differ significantly between cultures and over time. **Transgender women** (TGW; whose birth sex was male and are sometimes called male-to-female or MTF individuals) were more common than **transgender men** (TGM; whose birth sex was female and are sometimes called female-to-male or FTM individuals) in 16 of 18 countries surveyed, and the TGW

to TGM ratio was 3 to 1 (Meier & Labuski, 2013). However, this ratio is changing; in the U.S., the number of individuals seeking hormone therapy for TGW and TGM transitions is becoming more similar (Leinung & Joseph, 2020). This change could reflect greater acceptance, destigmatization, and decreasing barriers to care for TGM individuals.

Sex Hormones in Transgender Treatment. Feminizing or masculinizing hormone therapy is the administration of exogenous endocrine agents to induce changes in physical appearance. Transgender women are prescribed estrogen and anti-androgen medication. Transgender men are prescribed testosterone. Hormone therapy is inexpensive relative to surgery, and highly effective in the development of some secondary sex characteristics, such as facial and body hair in transgender men (i.e., female-to-male individuals) or breast development in transgender women (i.e., male-to-female individuals). Thus, hormone therapy is often the first (and sometimes only) medical gender-affirmation intervention accessed by transgender individuals looking to develop masculine or feminine characteristics consistent with their gender identity. In some cases, hormone therapy may be required before surgical interventions can be conducted. Emerging scientific research on gender-affirming hormone therapy has shown that sex hormone applications influence mood, behavior, and cognition, as well as brain structure and function in the adult human brain (Kranz et al., 2020; Nguyen et al., 2018; Nguyen et al., 2019). For example, gender-affirming hormone therapy tends to reduce symptoms of anxiety and depression and lower social distress (Nguyen et al., 2018). Transgender men undergoing testosterone therapy showed brain changes, including increased total brain and hypothalamic volumes and altered white-matter microstructure, aligning more closely with cisgender male patterns (Nguyen et al., 2019).

Societal Understanding of Gender Variations. Our understanding of gender identity continues to evolve, and young people today have more opportunity to explore and openly express gender than previous generations. The transgender community has gained visibility in American society—an estimated 0.6% of adults in the USA identified as transgender in 2016 (Meerwijk & Sevelius, 2017), and that population growth is driven by younger generations. A 2017 survey revealed that 1.8% of high school students identified as transgender and another 1.6% were questioning their gender (Johns et al., 2019; Scheim et al., 2022). Recent studies indicate that most Millennials (birth years 1981-1996) regard gender as a continuum instead of a strict male/female binary. As young people lead the changing views on gender, other changes are emerging in a range of spheres, from public bathroom policies to retail organizations. For example, some retailers are changing traditional gender-based marketing of products, such as removing “pink and blue” clothing and toy aisles. Despite these changes, those outside of traditional gender norms face difficult challenges. Even people who vary slightly from traditional norms can be the target of discrimination and even violence.

Sexual Orientation

A person’s **sexual orientation** is their sexual and emotional attraction to a particular sex or gender, including a continuing pattern of romantic or sexual attraction to persons of a given sex or gender. According to the American Psychological Association (APA) (2016), sexual orientation also refers to a person’s sense of identity based on those attractions, related behaviors, and membership in a community of others who share those attractions. Although a person’s intimate behavior may have sexual fluidity—changing due to circumstances (Diamond, 2008)—sexual orientations are relatively stable over one’s lifespan, and are influenced by genetics and other biological factors (Frankowski, 2004).

Lesbian couple

Figure 14: First photo: “Victory!” — This lesbian couple has been waiting 31 years to be able to marry (Sacramento, CA). Second photo: Two men holding hands, Gay Pride Project (Baltimore, MD).

A Continuum of Sexual Orientation. Sexual orientation is as diverse as gender identity. Instead of thinking of sexual orientation as being two categories—homosexual and heterosexual—sexuality researcher Alfred Kinsey argued that it’s a continuum (Kinsey, Pomeroy, & Martin, 1948). He measured sexual orientation on a continuum, using a 7-point Likert scale called the Heterosexual-Homosexual Rating Scale, in which 0 is exclusively **heterosexual**, 3 is **bisexual** with equal attractions to the same and opposite sexes, and 6 is exclusively **homosexual** (Figure 14). Later researchers using this method have found 18% to 39% of Europeans and Americans identify as somewhere between heterosexual and homosexual (Lucas et al., 2017; YouGov.com, 2015). These percentages drop dramatically (0.5% to 1.9%) when researchers force individuals to respond using only two categories (Copen, Chandra, & Febo-Vazquez, 2016; Gates, 2011).

Figure 15: The Kinsey scale, a tool that enables an individual to select a response on a scale between heterosexual and homosexual. 0= exclusively heterosexual, 1= predominantly heterosexual, only incidentally homosexual, 2= predominantly heterosexual, more than incidentally homosexual, 3= equally heterosexual and homosexual, 4= predominantly homosexual, more than incidentally heterosexual, 5= predominantly homosexual, only incidentally heterosexual, and 6= exclusively homosexual. More blue on the horizontal axis corresponds to a higher score on the Kinsey scale.

Development and Origins of Sexual Orientation

Individuals are usually, but not always, aware of their sexual orientation between middle childhood and early adolescence, and sexual activity is not necessary for this recognition. There is no scientific consensus regarding the root cause(s) of sexual orientation, but it is not a conscious "choice" for either heterosexual or non-heterosexual individuals. Research has examined many possible biological, developmental, social, and cultural influences on sexual orientation. Social factors (such as having homosexual parents, recruitment by homosexual adults, and experiencing disordered parenting) are generally not scientifically supported (Bailey et al., 2016). Nonsocial causes (such as genetics, prenatal hormone exposure, fraternal-birth order) have much more supporting evidence.

Genetics. One method of measuring the genetic roots of sexual orientation is concordance rates, which is the probability that a pair of individuals has the same sexual orientation. If both twins have the same sexual orientation, they are "concordant" for this trait. Concordance rates are compared between people who share the same genetics (**monozygotic twins**), some of the same genetics (**dizygotic twins** and siblings, 50%), and non-related people (randomly selected from the population). Concordance for sexual orientation is highest for monozygotic twins; and concordance rates for dizygotic twins, siblings, and randomly selected pairs are not significantly different (Bailey et al. 2016; Kendler et al., 2000). Since concordance rates (i.e. having the same sexual orientation) are higher for monozygotic twins, this indicates that "nature" (genetics) influences sexual orientation. However, monozygotic twins do not always have the same sexual orientation, so "nurture" (the environment and individual experiences) also plays a role in determining sexual orientation. Nonetheless, because sexual orientation is a debated issue, an appreciation of the genetic aspects of attraction is an important piece of this dialogue.

Prenatal Hormone Exposure. Adult hormone levels do not relate to sexual orientation. On average, gay and heterosexual men have similar levels of hormones, and lesbian and heterosexual women have similar levels of hormones. Sexual orientation is not affected by adult treatment with androgens or estrogens or adult gonadectomy (surgical removal of testes or ovaries resulting in loss of gonadal production of sex steroids) (Balthazart, 2011). However, hormone levels during early sensitive periods of brain development do impact sexual development and sexual orientation. In animal studies, experimentally manipulating prenatal exposure to sex hormones, including testosterone, impacts sexual physiology and behavior, such as mounting and same-sex partner preference (Balthazart, 2011). In humans, excess or deficient exposure to hormones during prenatal development has been linked to non-heterosexual orientation. Females exposed to abnormally high amounts of prenatal androgens due to congenital adrenal hyperplasia (CAH) are much more likely to identify as bisexual or lesbian (Cohen-Bendahan, van de Beek, & Berenbaum, 2005).

Fraternal-Birth-Order Effect. The "fraternal-birth-order effect" refers to the consistent cross-cultural finding that homosexual males tend to have more older brothers than heterosexual males (Bailey et al., 2016). "The effect is almost certainly causal, with each additional older brother causing an increase in the chance of a man being homosexual. … Assuming that a man without any older brothers has a 2% chance of being homosexual, a man with one older brother has a 2.6% chance; with two, three, and four older brothers, the chances are 3.5%, 4.6%, and 6.0%, respectively" (Bailey et al., 2016, page 79). This effect only occurs for biological brothers (Figure 15), meaning that the number of sons gestated by the mother is the important factor, whether or not the man was raised with those brothers. One proposed mechanism for this is that the mother creates antibodies against proteins on her developing son's Y chromosome (a possibility which increases with each pregnancy of a son) and that those antibodies may alter the functioning of subsequent sons' Y chromosomes (Bailey et al., 2016; O'Hanlan et al., 2018).

Figure 16: The Marx Brothers in "I'll Say She Is!"—caricatures by John Decker (1924). Every biological older brother increases the likelihood of a man being homosexual. Groucho (the brother with the mustache) was the fourth brother and called himself "straight but curved around the edges" (http://everydayheterosexism.blogspot...-brothers.html).

In Closing: Gender and Sexual Orientation

Sex, gender, and sexual orientation are distinct aspects of human identity. Sex refers to the biological characteristics of anatomy,

genetics, and hormones, while gender describes psychological (gender identity) and sociological (gender role) representations of biological sex. Sexual orientation describes the pattern of emotional, romantic, and sexual attraction. All three of these concepts exist along continuums rather than binary categories. There is natural variation across individuals and cultures in how sex, gender, and sexual orientation manifest. Current scientific evidence indicates these traits have strong biological underpinnings, with factors like genetics, prenatal hormone exposure, and fraternal birth order influencing their development, often before birth (O'Hanlan et al., 2018). Though historically stigmatized, modern perspectives increasingly recognize gender and sexual diversity as normal variations. Moving forward, reducing discrimination and achieving greater equality and acceptance for people across the full spectrums of sex, gender, and sexual orientation remain important goals.

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definition

A biological descriptor based on reproductive, hormonal, anatomical, and genetic characteristics. Typical sex categories include male, female, and intersex.

×Close definition

The psychological and sociological representations of one's biological sex.

×Close definition

Personal depictions of masculinity and femininity.

×Close definition

Societal expectations of masculinity and femininity.

×Close definition

A person's sexual attraction to other people.

×Close definition

Born with either an absence or some combination of male and female reproductive organs, sex hormones, or sex chromosomes.

×Close definition

A transgender person whose birth sex was male.

×Close definition

A transgender person whose birth sex was female.

×Close definition

Personal sexual attributes changing due to psychosocial circumstances.

×Close definition

Opposite-sex attraction.

×Close definition

Attraction to two sexes.

×Close definition

Same-sex attraction.

×Close definition

Twins conceived from a single ovum and a single sperm, therefore genetically identical.

×Close definition

Twins conceived from two ova and two sperm.

×Close definition

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14: SLEEP AND CIRCADIAN RHYTHMS

14.1: What Are Circadian Rhythms?
14.2: Where Are Rhythms in the Brain?
14.3: Regulation of Sleep
14.4: Dreams
14.5: Disorders of Sleep and Circadian Rhythms
14.6: Parasomnias
14.7: Circadian Rhythms and Society

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14.1: What Are Circadian Rhythms?

Learning Objectives

By the end of this section, you should be able to

- Name and define different biological rhythms.
- Draw and label the components of a circadian rhythm.
- Draw and label the components of a phase response curve.

Neuroscience Across Species: Why Are Rhythms Important?

The earth orbits the sun with a period of about 365 days and rotates on its axis every 24 hours. These rotations create a cyclical and predictable environment including rhythmic changes in light and dark, ambient temperature, and resource availability. Animals, plants, fungus and bacteria evolved during these predictable environments and have adapted their biological systems as a result. Thus, one significant benefit of biological rhythms is to synchronize the biology of an organism to environmental cycles in anticipation of recurring events. For example, organisms can increase their survival by avoiding predation, preparing for hibernation, gathering food, or finding mates when they can anticipate changes in the environment. Mammals increase their metabolism prior to the start of their active period when they eat their first meal of the day, mobilizing energy reserves in anticipation of increased demands on the body. Another example is that the mechanisms responsible for clearing out metabolic by-products from the brain go into high gear when we are sleeping, potentially helping create a neural environment conducive to new learning. Arctic mammals can prepare for a cold winter by reducing their metabolic rate and body temperature and hibernating for a portion of the year, and adult fruit flies emerge from their pupa in a timed manner, about 1-2 hours before dawn, which is the onset of their active period.

Examples of Rhythms

There are many different types of rhythms, with periods ranging in length from seconds to hours to days (Figure 15.2). Neuron electrical action potentials within the brain can occur at the level of milliseconds, neuronal firing rates can show spontaneous 24 hour rhythms, hormone surges such as the morning rise in cortisol can occur every 24 hours, and the reproductive or ovulatory cycle in laboratory rodents occurs every 4-5 days whereas it can occur around every 28 days in humans.

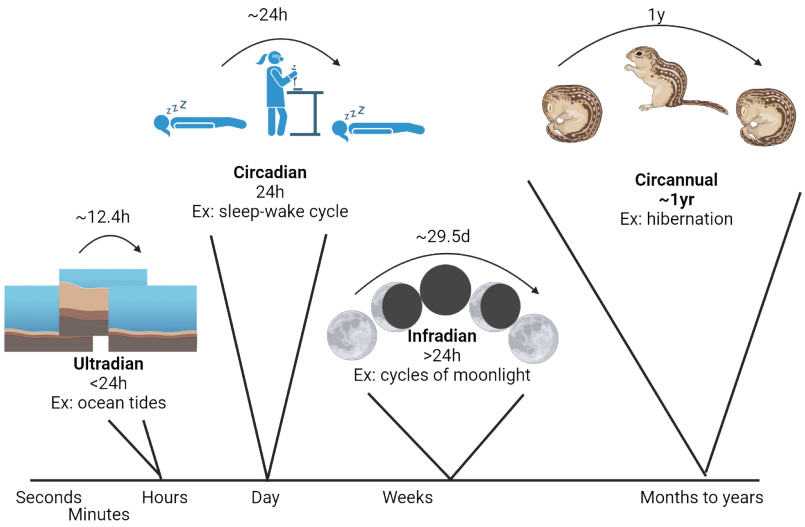


Figure 15.2 Types of rhythms

Circadian rhythms (circa = about, dia = day) describe rhythms with a period of about 24 hours and the best known of these is the daily rhythm of sleeping and wakefulness that many animals experience.

Ultradian rhythms have periods significantly shorter than 24 hours. An example of this would be heart rate, or the occurrence of multiple sleep cycles during the night (see below). Another type of ultradian rhythm are those that follow the cycles of tides; these are called circatidal and occur around every 12.4 hours. Marine organisms such as crabs time their locomotor activity to the occurrence of tides.

Infradian rhythms have periods significantly longer than 24 hours. For example, the reproductive rhythm (menstrual cycle) of women is a type of infradian rhythm. Circalunar rhythms are a type of infradian rhythm that follow the amount of moonlight that is available and last about 29.5 days. Examples of circalunar rhythms are seen in the reproductive cycles of marine animals. Circannual rhythms are another type of infradian rhythms—these are cycles that recur with a period of about 1 year. The onset of hibernation each year in Arctic ground squirrels would be a circannual rhythm.

Qualities of a Rhythm

A rhythm is a repeating event that occurs with a regular pattern (Figure 15.3). We can characterize the features of a rhythm by describing its period or the duration of time it takes one cycle of the rhythm to occur. The phase of a rhythm describes a marker or point in a daily rhythm. A phase could be measured at the peak of a daily rhythm, such as the peak of melatonin secretion, or a trough in a rhythm such as the time when your body temperature is the lowest. A phase relationship or phase difference is the timing of the phase of a rhythm in relation to another daily timing event. For example, we can talk about the phase difference between when you wake up each day (the phase) and the time when your alarm goes off. The mesor of a rhythm is the average level of the rhythm across a full cycle, and the amplitude of a rhythm is the difference between the peak and trough of that rhythm. Frequency describes how often the rhythm occurs within a period of time. For example, pulses of luteinizing hormone secretion might occur at a frequency of 4 per hour.

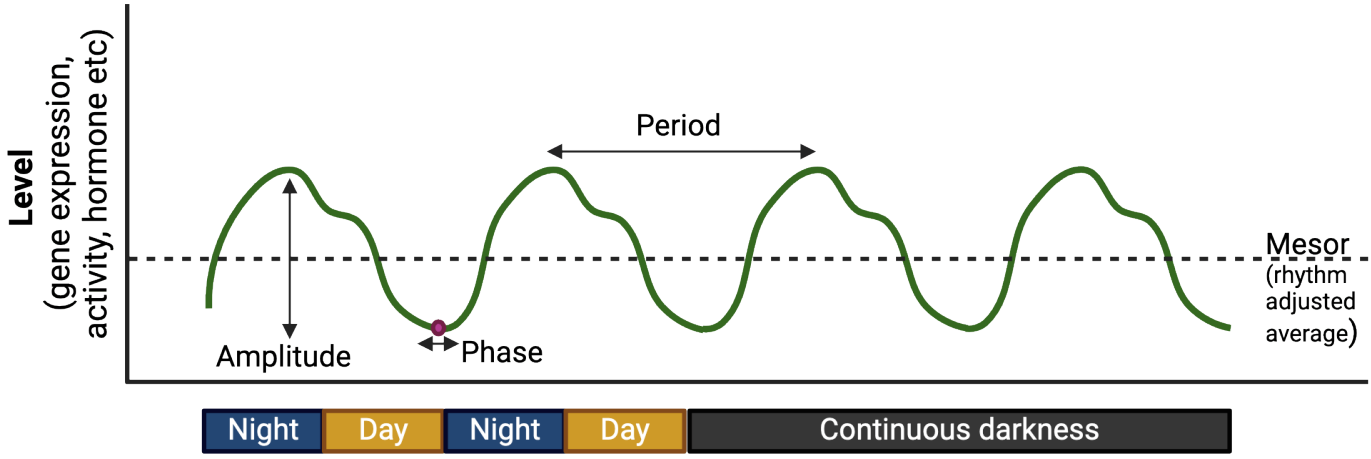


Figure 15.3 Circadian rhythm A biological rhythm has many independent components that can be analyzed.

One fascinating concept about biological rhythms is that they are endogenous, meaning that they are driven by internal physiology rather than being entirely generated by external or exogenous cues. This means that rhythms will continue to be expressed even if the organism is isolated from the environment. For example, a variety of circadian rhythms continue to be expressed, even when the organism is maintained in an environment with constant lighting conditions, which lack any cues as to the time of day. This experiment has been done with numerous species including placing humans in underground apartments, or housing laboratory rodents or fruit flies in constant darkness. These experiments demonstrate that biological rhythms continue to oscillate in a consistent manner, though this rhythm may not perfectly match the solar day or other rhythmic environmental cues such as temperature fluctuations. For example, if you were to live in dim light in a sleep lab for seven days and we measured the time when you woke up each day, we would learn that the period of your daily sleep-wake cycle may run slightly faster or slightly slower than 24 hours. Under these constant conditions the rhythm is described as free-running. Humans can have a free-running period that normally ranges from 23.5 to 24.7 hours. In nocturnal lab rodents, a typical free-running period can range from 23-25 hours long, and in fruit flies population rhythms in emergence from the pupa and individual activity rhythm is about 24.5 hours. Of course, most organisms do not live in environments absent of cues, thus when an organism's internally generated rhythm is synchronized to the rhythms of the external environment we refer to this as entrainment.

Chronotypes

Are you someone who tends to stay up late into the night? A "night owl"? Or perhaps you go to bed early and wake up early? A “lark”? The tendencies of your body towards sleeping at some hours of the day and being more alert at other times of day is called a chronotype. Chronotypes exist on a spectrum and can be influenced by age, gender, and genetics. Chronotype has been linked to health outcomes, mood such as anxiety and depression, and the time of day you are most productive. For example, evening types ("owls") are more likely to have depression, anxiety, obesity, and lower grades compared to morning types ("larks") (van der Merwe, Munch, and Kruger, 2022; Walsh, Repa, and Garland, 2022; Yeo et al., 2023). Individuals with severe morningness or eveningness chronotypes may be diagnosed with conditions such as advanced sleep-wake phase disorder or delayed sleep-wake phase disorder.

Your chronotype typically changes across your lifespan. Young children tend towards a morning preference and wake up and go to bed relatively early, whereas after adolescence, teenagers and young adults have difficulties falling asleep before 11 pm and may struggle to wake up for an early morning class or job. The peak in an evening chronotype occurs around age 19 after which the chronotype begins to shift to an earlier time. Thus, older individuals tend to be morning types, and this tendency to be a morning type continues to increase from age 35-80 (Roenneberg et al., 2007). Interestingly, there is also a sex difference in chronotypes, with women typically being earlier (larks) compared to men (Fischer et al., 2017). Some researchers hypothesized that these sex differences could be attributed to circulating hormones. This is supported by the fact that as women age and go through menopause and hormone depletion around the age of 40-50, the sex difference in chronotype goes away.

Although you can adapt your circadian rhythms to new environmental light cycles, such as would occur if you traveled to another time zone, it is difficult to intentionally change a chronotype. However, light therapy, melatonin treatment, and adherence to a sleep schedule (sleep hygiene) can help shift the timing of rhythms. People with an evening chronotype report that shifting their rhythms towards a morning chronotype can reduce depression and stress, improve mood, and improve cognitive performance (Facer-Child et al., 2019).

Neuroscience in the Lab

Photic Phase Response Curve

How does your internal clock adjust your sleep-wake pattern when you fly to a new time zone? How does your body stay entrained to your rhythmic environment without drifting? There are many types of environmental cues that can entrain a biological rhythm including cycling changes in temperature, humidity, food availability, and social cues. However, the strongest entraining cue for most animals is the light:dark cycle driven by the earth’s rotation. In mammals, the biological clock in our brains responds to light cues and helps synchronize it to the external rhythm. If the endogenous clock isn’t in alignment with the 24 hr day/night cycle, the clock needs to be adjusted to bring it back in synchrony with the environment. Both the magnitude of the response and the direction of that response depend upon when the light cue is perceived by the clock. To phrase this another way, your body can respond to light cues and "reset" the clock. However, the degree to which your clock is adjusted depends upon the time when you were exposed to a light cue.

Consider an experiment where we house a laboratory rodent in constant darkness and measure the onset of their daily bout of activity in a running wheel. This wheel running occurs during the animal’s active time of day, thus in this nocturnal animal wheel running would reflect its subjective night. When the rodent is sleeping, it would reflect the subjective day. We use the term “subjective” because it reflects the brain’s internal interpretation of time, not the actual environmental condition experienced. Figure 15.4 shows how we often represent the data from an experiment like this, where a single bar represents a 24h period and light and dark shading within that bar represent periods of low and high activity, which we learn by recording turns of the running wheel.

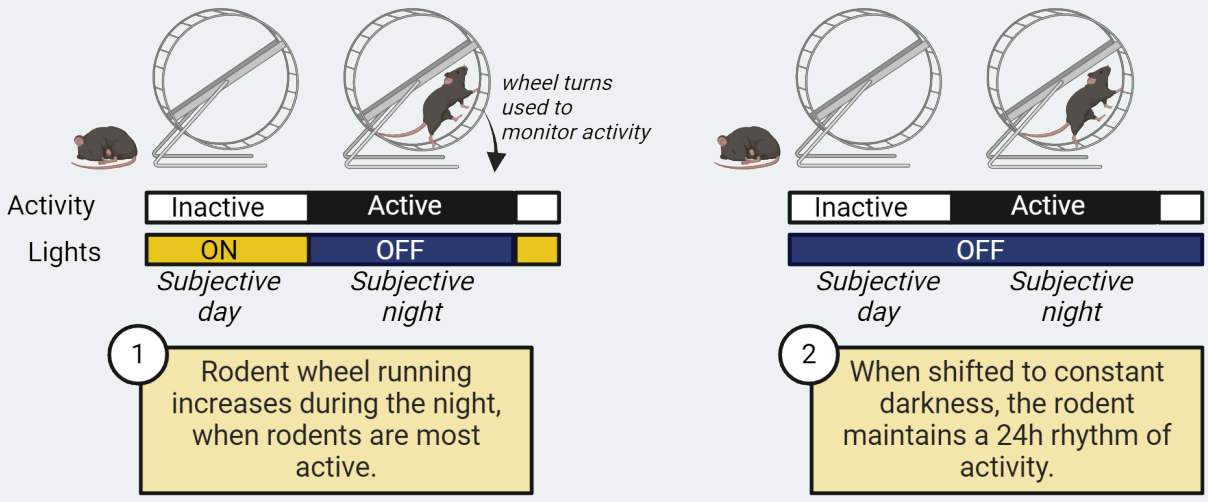


Figure 15.4 Measuring rhythms in rodents

In the lab, we can use rodent activity to study how biological clocks entrain to external cues depending on when they are given. For example, we can expose animals living in constant darkness to a 10-min pulse of light at various times across their subjective day and subjective night. We then measure the effect of that light cue on the timing of the wheel running onset. The observed change from the original activity onset to the new, adjusted onset is called a phase shift. We can plot phase shifts using a phase response curve (Figure 15.5).

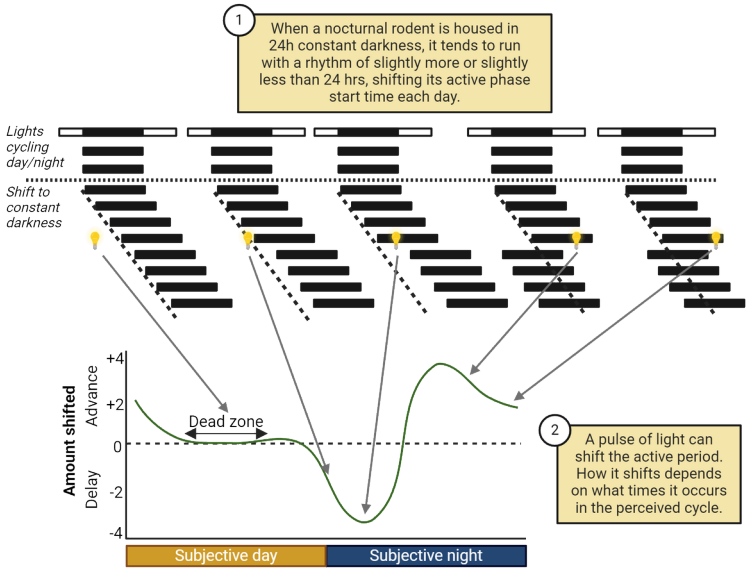


Figure 15.5 Circadian shift

Conventionally, we plot advances (waking up earlier) in the timing of activity as positive numbers and delays (waking up later) as negative numbers, against the time of day when the animals were exposed to the light pulse. By plotting the response to light pulses, we can see there is a pattern in sensitivity to the light cue. Generally speaking, if the animal was given a pulse of light during its subjective day there is little to no change in the onset of the wheel running the next day. This is to be expected because this is the time of day when light would normally be present. This part of the curve is referred to as a dead zone. However, when exposed to light in the early portion of the night, animals have a dramatic shift in the timing of wheel running or activity, such that it is delayed compared to when it was predicted to occur. Conceptually, think of this as the animal's brain interpreting the light as meaning that it is still daytime, the animal got up too early, and therefore tomorrow it should become active at a later time. Conversely, light pulses given in the second half of the evening result in advances in the timing of the wheel running onset (the animal stayed up too late—it should shift its activity to an earlier time). This light sensitivity that varies as a function of the time

of day is a critical function for how biological clocks synchronize to the environment. This same methodology has been used to determine the phase response curve in a variety of other species including fruit flies (Vinayak et al., 2013), sparrows (Binkley and Mosher, 1987), and flying squirrels (DeCoursey, 1960).

Interestingly, the shape of the phase response curve looks remarkably similar in diurnal and nocturnal organisms suggesting that there are similar clock processes underlying this response to light, despite behavioral rhythms having different patterns. Diurnal animals are those who are most active during the daytime hours whereas nocturnal animals are those who are active during the dark period of the day. Humans, and many species of primates, squirrels, and birds are diurnal. Similarly, there are birds such as owls, and primates such as lemurs that are nocturnal. Much of the basic research done on biological rhythms uses laboratory rodents which are either nocturnal or diurnal, or fruit flies, which are diurnal, but the principles of biological clock function are remarkably conserved across species and ecological niches.

People Behind the Science: Dr. Pat DeCoursey

The very first phase response curve has been credited to Dr. Pat DeCoursey. Dr. DeCoursey was always interested in science and while in high school conducted a census of songbirds in a tract in Long Island, NY. She entered her project into a science talent contest where she won scholarship money that helped her attend Cornell University. This was followed by graduate school at University of Wisconsin, Madison where she studied the emerging field of chronobiology. She was working with flying squirrels which have a precise free running period of nearly 24 hours and she was interested in asking questions about entrainment. She gave the animals light pulses and plotted their dramatic shifts in activity onset to create the first photic phase response curve. In her long career in biological rhythms, she worked with numerous species including Eastern chipmunks, antelope squirrels, hamsters, and golden mantled ground squirrels and she helped write and edit a textbook entitled *Chronobiology*. Later in her career, she performed exceptionally challenging experiments designed to examine the importance of a functional circadian clock to the survival of animals in the wild.

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14.2: Where Are Rhythms in the Brain?

Learning Objectives

By the end of this section, you should be able to

- Draw the pathway from light to the master clock in the brain and from the master clock to its targets.
- Explain how the negative feedback loop of clock gene transcription and translation functions.
- Explain the experiments and evidence that demonstrated that the master clock is contained in the SCN.
- Explain the role of the SCN, retina, and the pineal gland in circadian rhythmicity.

Where in the body is the biological clock that regulates circadian rhythmicity? As we have described in the previous section, nearly all organisms possess circadian rhythms, including birds, mammals, plants, and single celled organisms. Across these various organisms you can find functional clock mechanisms within many different tissues. For example, the retina secretes melatonin in a rhythmic daily pattern in birds. Here we will focus on the clock in mammals, which is located in an area of the brain known as the suprachiasmatic nucleus (SCN) (Figure 15.6), but we will also note organismal variation. The SCN is often described as the master clock in mammals, as it drives rhythms in physiology and behavior that, in turn, synchronize the timing of clocks in other tissues. The SCN receives light input from cells in the retina, and in turn this brain structure regulates rhythms throughout the body.

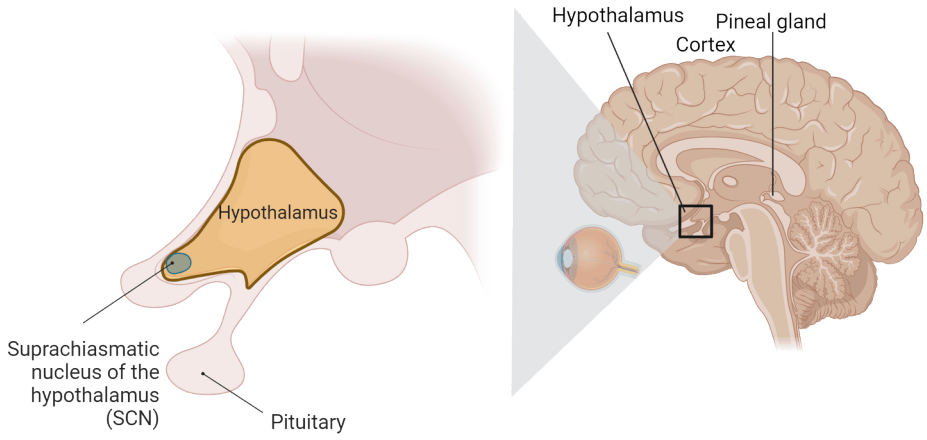


Figure 15.6 Suprachiasmatic nucleus of the hypothalamus

The Retina

In mammals, the retinas transmit photic information from the environment to the brain in order to synchronize internal rhythms with the external world. The retina possesses a multilayered structure designed to detect and process light and transmit that information to the brain, for both image forming and non-image forming purposes. Rods and cones are the primary photoreceptors for detecting light for image formation, but there is also a subset of retinal ganglion cells that contain photopigments and can detect light. These intrinsically photosensitive retinal ganglion cells (ipRGCs) send their long axons directly to the SCN in the hypothalamus. The SCN contains the master circadian clock which we will discuss next. The ipRGCs communicate to the SCN via the retinohypothalamic tract, providing a rod and cone-independent photoreceptive mechanism (Figure 15.7). The presence of these cells is a reason why some individuals with blindness caused by the degeneration of rods and cones can still show entrainment to light/dark cycles.

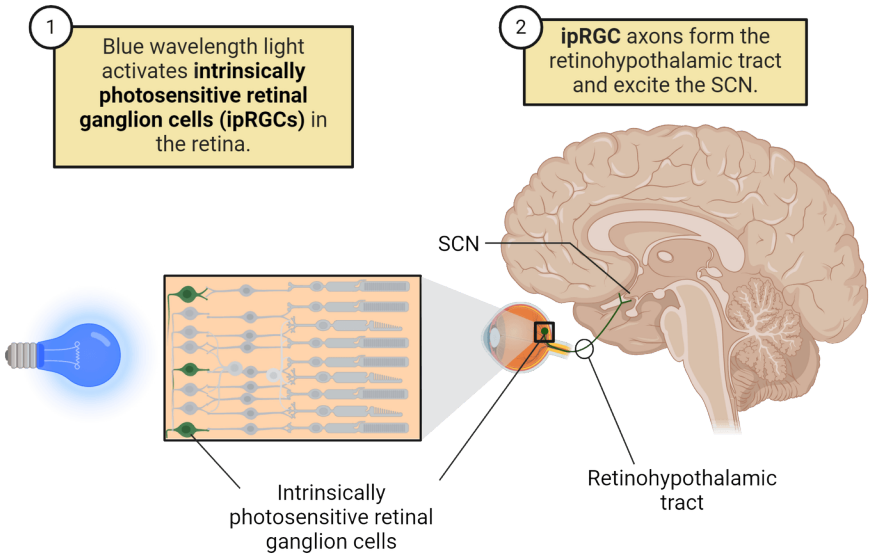


Figure 15.7 Non-image-forming retinal ganglion cells

ipRGCs use a novel photopigment called melanopsin for transducing energy from photons into chemical signals. Melanopsin is specifically found only in ipRGCs and, in its absence, ipRGCs lose their photoreceptive responses. Melanopsin is maximally sensitive to light at a wavelength of about 480 nm, which is in the blue part of the spectrum. Blue light is emitted by many common devices that you probably use everyday, including smart phones, computer screens, tablets, video game systems, and LED lights. Humans are sensitive to blue light and this sensitivity to blue light exposure is linked to the negative effects of artificial light at night on sleep and circadian rhythms. Specifically, blue light suppresses melatonin secretion (see below section on melatonin), which can disrupt rhythms and lead to reduced sleep, disrupted sleep quality and delays the timing of sleep (Silvani, Werder, Perret; 2022). The use of blue light (“night mode”) filters for cellular phones and screens, or wearing blue light filtered glasses at night when you are working on screens are two ways of mitigating the negative impacts of too much blue light exposure at night.

The Suprachiasmatic Nucleus of the Hypothalamus

The SCN are bilateral structures that are located in the ventral portion of the brain within the hypothalamus. They are medially located and are positioned next to the 3rd ventricle, a space where cerebrospinal fluid flows. They are also located above (supra) the optic chiasm, the location of the crossing of the optic nerves. They contain roughly 20,000 cells (in a rodent) that produce a variety of neurotransmitters including vasopressin, vasoactive intestinal polypeptide, gastrin-releasing peptide, somatostatin, and GABA.

There are numerous pieces of evidence that have established that the master circadian clock is located within these paired nuclei. First, when this area is removed by electrical lesioning, the animal loses any rhythmic patterns in physiology or behavior. For example, a hamster with a lesioned SCN will continue to exhibit wheel running, but this locomotor activity will no longer occur in a predictable schedule and the animal may have bouts of running throughout the day and night (Ralph et al., 1990). Second, when SCN tissue is removed from an animal and maintained in thin slices in a culture dish, the SCN continues to exhibit spontaneous free-running rhythms in electrical activity and in glucose metabolism for several days, similar to what would be seen if the SCN had remained in the animal (Newman and Hospod, 1986).

Lastly, the most conclusive evidence that the SCN contains the master clock was generated in experiments where the SCN was first removed and then replaced (Ralph et al., 1990). Hamsters had their SCN electrically lesioned, and as expected they had arrhythmic patterns of activity (Figure 15.8, steps 1 and 2). SCN tissue from the brains of fetal hamsters was then transplanted into the 3rd ventricle of the SCN lesioned animals. The ventricle is a space within the brain where cerebrospinal fluid flows, and the tissue was deposited near to the original SCN location. The lesioned animals began to express rhythms in locomotor activity again, that is, they began to have organized bouts of wheel running (Figure 15.8, step 3).

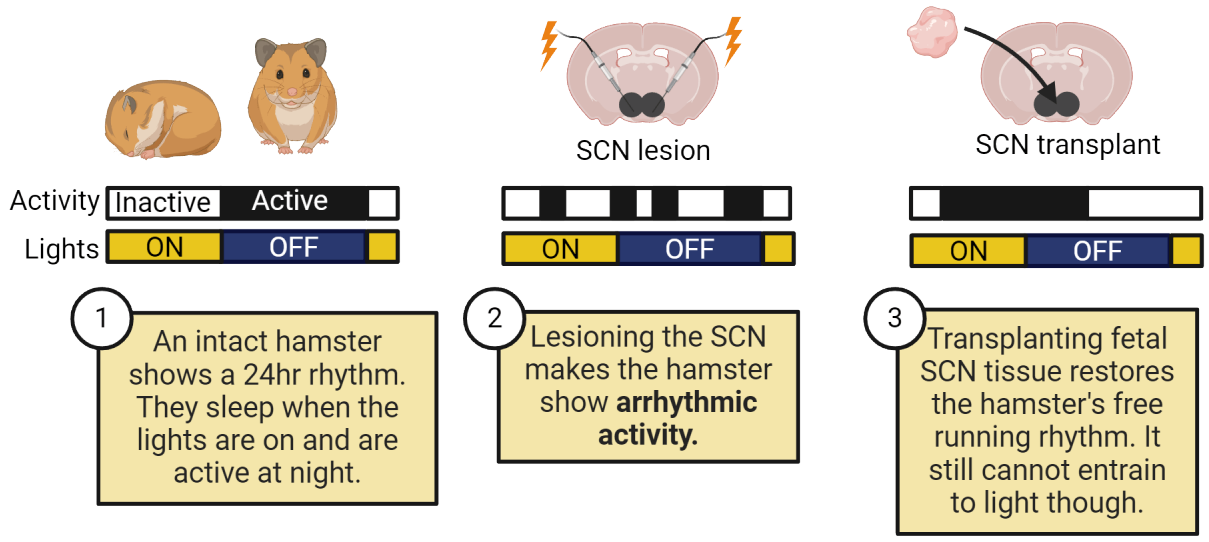


Figure 15.8 SCN lesion and transplant experiment

This study was extended by using hamsters that had a genetic mutation associated specifically with circadian clock function, such that animals that were homozygous for this mutation had a free-running period of 20 hours whereas wildtype hamsters without the mutation had a free-running period of 24 hours. The lesion-replacement experiment was repeated, but in this case the wildtype SCN lesioned animals received fetal SCN tissue collected from the mutant strain of hamsters. They also lesioned the SCN of animals with the mutant gene, and replaced their SCN with tissue from wildtype animals. The lesioned animals regained patterns of locomotor activity. However, the period of that activity matched that of the donor animals and not the host animal. That is, a wildtype animal exhibited wheel running patterns that had a period of 20 hours! Furthermore, through additional experiments investigators established that the implanted SCN tissue could generate rhythms in the host animal through the secretion of a neural factor, rather than by forming synapses with the recipient animal. However, implanted SCN tissue did not result in the recipients being able to entrain to light/dark cycles, indicating that neural connections were necessary for that function. These elegant experiments provided the strongest evidence that the SCN was the neural tissue generating daily rhythms that regulate physiology throughout the body (Silver et al., 1996; Ralph et al., 1990).

The SCN is also found to play a role in circadian rhythmicity in other organisms. In lizards, SCN lesion studies in two different species abolished circadian patterns of locomotor activity (Tosini, Bertolucci, and Foa; 2001). Further, studies in quail and sparrows revealed that there are two paired structures, the ventral SCN and medial SCN which also appear to play similar roles to the mammalian SCN (Cassone, 2014).

Rhythm Circuitry

Central circadian organization in vertebrates is composed of three major structures: the retina, the pineal gland, and the SCN. However, these tissues vary significantly in importance in different organisms. For example, the retina and the pineal gland secrete melatonin in vertebrates, an important hormone for sleep regulation. Additionally, if you take the retina from a non-mammalian vertebrate such as a bird, and incubate it in a dish (*in vitro*), melatonin continues to be released in a circadian manner. Thus, this structure can act as a daily pacemaker (Falcón et al., 2009). Furthermore, the pineal gland in fish and frogs contains photosensitive cells but these are absent in mammals. In this section, we will focus on the circadian clock circuitry in mammals.

As we have discussed, information about environmental light is transmitted to the SCN from the retina via the retinohypothalamic tract, a pathway of retinal ganglion cells that is not part of the image-forming visual system (Figure 15.9).

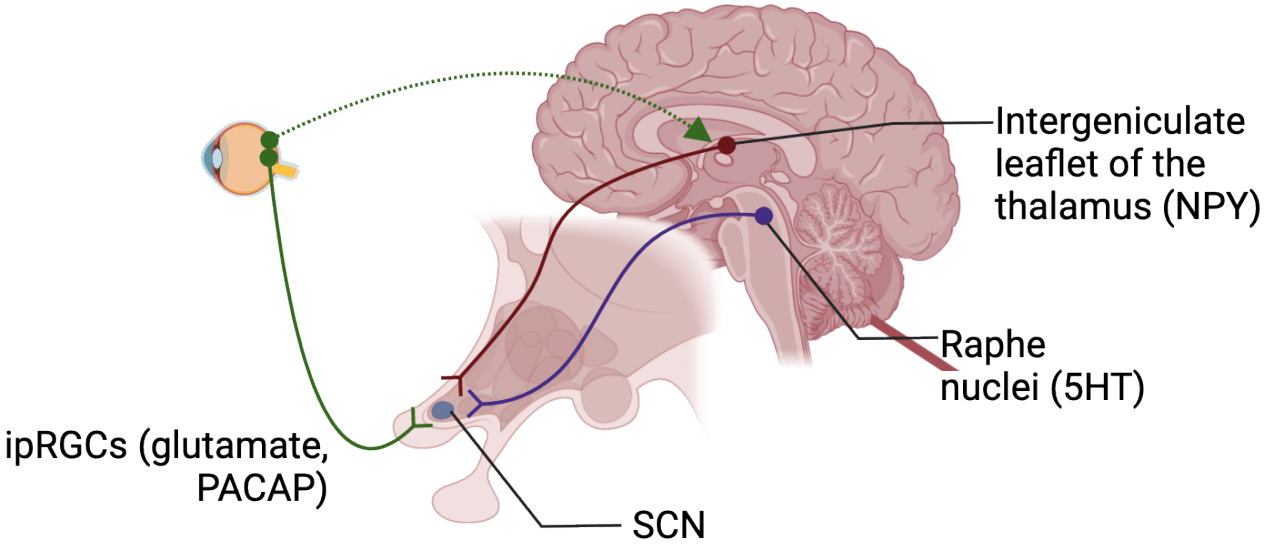


Figure 15.9 Inputs to the SCN The SCN receives several modulating inputs which contribute to entraining its activity to cues.

When light shines on the eyes, this pathway releases glutamate and pituitary adenylate cyclase-activated peptide (PACAP) into the SCN, producing an excitatory response. The influence of this input is modulated by a variety of neuropeptides and other signaling molecules, and its effects on circadian clock function vary with the time of day. The destruction of this pathway renders the circadian clock unable to entrain to light/dark cycles. However, the clock still runs as long as the SCN remains intact, with a period that reflects its own internal rhythm.

A second major input to the SCN is a pathway from the midbrain raphe nuclei which contains the neuropeptide serotonin (5HT). Neural activity in the raphe is highly reflective of the arousal state of an animal, with higher activity levels in the raphe associated with increased locomotor activity. Elevated locomotor activity increases serotonin release in the SCN. Increased locomotor activity and serotonin mimics (agonists) have inhibitory effects on the ability of light to shift the timing of the clock in the SCN. Light signals to the SCN can therefore be adjusted according to the behavioral context in which they are perceived. Thus, an animal exposed to light at night while resting may experience a phase shift, adjusting their clock timing for subsequent days, while one receiving similar light exposure while engaging in an intense activity bout may experience no shift or a lesser shift in timing.

A third pathway, called the geniculo-hypothalamic tract, is a multisynaptic connection from the retina to the intergeniculate leaflet of the thalamus, which in turn sends a Neuropeptide Y (NPY)-containing projection to the SCN. This pathway is thought to integrate both photic (light) and nonphotic information and is capable of regulating the entrainment of the SCN to both light/dark cycles and nonphotic signals. Nonphotic stimuli could be regular presentations of a running wheel, melatonin injections, or meals.

The SCN itself has its own structure of connectivity. This structure is characterized by overlapping subregions that are identified on the basis of synaptic connections or neuropeptide expression. While these divisions are often oversimplifications of the intricate structure of the SCN, they are helpful in understanding the general flow of information within the circadian clock mechanism. One of the most common constructs divides the SCN into a retinorecipient core region and a rhythmic shell. The core is generally located in the ventral part of the mammalian SCN, is heavily innervated by retinal afferents from the optic chiasm, and contains a dense plexus of neurons expressing vasoactive intestinal polypeptide. The shell is characterized by high amplitude rhythmicity in gene expression and is enriched in cells expressing the neuropeptide vasopressin. Regardless of their location within the nucleus and their neuropeptide expression, SCN neurons appear to uniformly express GABA as the primary classical neurotransmitter.

Neurons of the SCN project to a variety of other brain regions, mostly in the hypothalamus and thalamus. These projections are linked to rhythmic control of physiology and behavior, including variables such as body temperature, locomotor activity, the sleep/wake cycle, and various hormonal rhythms.

The Pineal Gland and Melatonin

Melatonin is a hormone produced primarily in mammals by the pineal gland, which is located in the roof of the diencephalon in humans. Melatonin secretion is directly tied to the circadian clock, with high levels during the night and very low levels during the day (Figure 15.10).

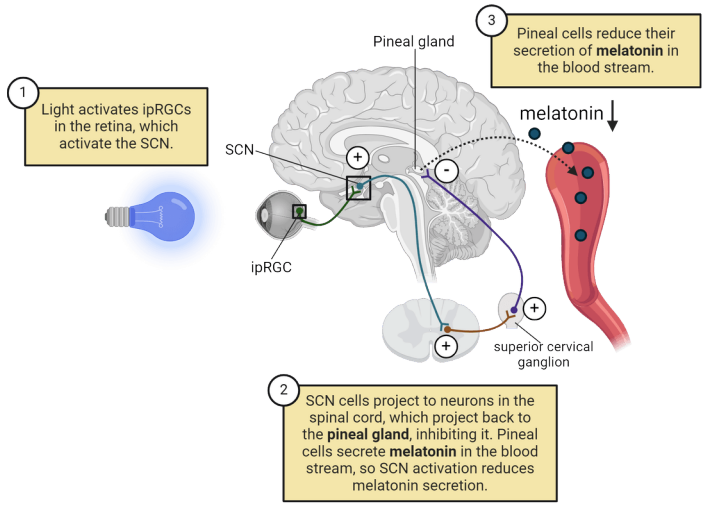


Figure 15.10 How light gets in the brain

Melatonin levels are directly suppressed by the presence of ambient light; thus, exposure to bright light during the night results in a very rapid decline in circulating melatonin. The melatonin rhythm is one of the casualties of screen use in the bedroom—exposing one's eyes to bright light from a phone or tablet screen in the middle of the night suppresses melatonin release and can have negative consequences for sleep quality. Melatonin is currently utilized as a therapeutic for a wide variety of conditions such as insomnia, jet lag, circadian rhythm and shift work sleep disorders, and to help support sleep in the elderly, who may suffer from reduced melatonin production.

Although melatonin's primary role with regard to human health is the treatment of rhythm disorders, it has a major role in the regulation of reproduction in seasonally breeding species such as sheep, deer, and golden hamsters. In these species, the duration of the nocturnal rise in melatonin serves as a measure of daylength, with long nights, and thus long period of melatonin secretion, indicating winter photoperiods and the suppression of reproductive physiology and behavior. Although humans are not considered to be seasonal breeders, there are melatonin receptors present in reproductive tissues in humans and there is some evidence that melatonin may play a role in a variety of reproductive processes (Olcese, 2020).

The pineal gland, through melatonin secretion, may have a more dominant role in circadian clock function in many non-mammalian species. In zebrafish, for example, the pineal gland functions as a central circadian pacemaker and directly regulates the sleep/wake cycle (Aranda-Martínez et al., 2022). Similarly, in pigeons, circadian rhythms in pineal melatonin directly regulate sleep and wakefulness (Phillips and Berger, 1992).

Rhythms in Clock Genes

Circadian rhythms at the level of the organism are ultimately driven by rhythms at the level of individual cells. Within each cellular clock, rhythms are generated and expressed at the level of gene and protein expression. Some genes and proteins may build up throughout the day and decrease during the night, while others may show the opposite pattern. An essential set of genes, known as the core clock genes, interact with one another to produce self-sustaining rhythms with periods close to 24 hours, and which can respond to external stimuli to adjust clock timing when necessary.

The molecular clock is generated by interlocking transcription/translation feedback loops, which function to produce robust rhythms of gene expression with a period of about 24 hours. These negative feedback loops are composed of a set of highly conserved core clock proteins that both participate in the central machinery of the clock and drive rhythmic expression of other

genes (Figure 15.11). Four core clock gene families sit at the center of the molecular clock: *Clock* and *Bmal1*, which code for activators, and *Per* and *Cry*, which are repressors. The proteins CLOCK and BMAL1 are subunits of a transcription factor that activate transcription of *Clock* and *Bmal1* and *Per* and *Cry* genes as well as other clock-controlled output genes (Step 1 in Figure 15.11). Essentially, these proteins turn on the production of the mRNA for *Clock* and *Bmal1*, which code for activators, and *Per* and *Cry*. These genetic mRNAs for *Clock* and *Bmal1*, which code for activators, and *Per* and *Cry* then leave the nucleus and travel to the cytoplasm where they are transcribed into their respective proteins (Step 2 in Figure 15.11). The PER and CRY proteins bind to each other (heterodimerize) in the cytoplasm and move (translocate) to the cell nucleus where they inhibit the transcriptional activation by the CLOCK/BMAL1 complex (Step 3 in Figure 15.11). In other words, the PER/CRY protein complex turns off the activity of the CLOCK/BMAL1 complex. Activity of these proteins are regulated by a variety of kinases, phosphatases, and other modulators. Mutations in many of these regulatory proteins can modulate the free-running period of the clock by changing the degradation rate of one or more of the clock proteins.

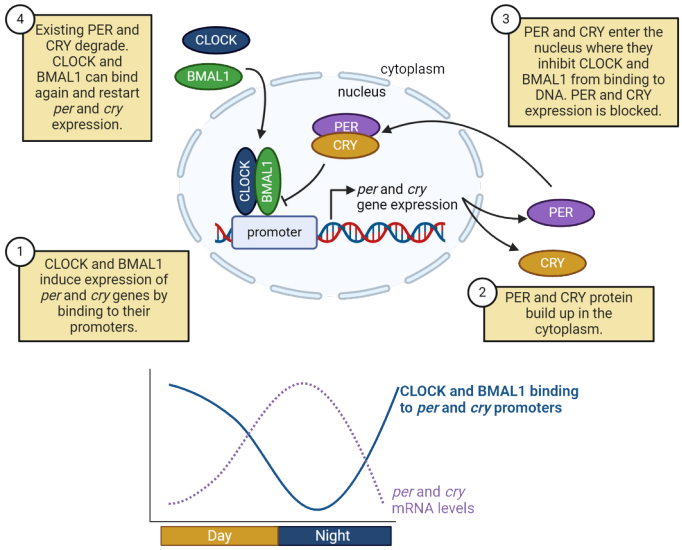


Figure 15.11 Rhythms in clock genes

The presence of interlocking feedback loops strengthens and maintains accurate circadian timing in the presence of noise and environmental disruptions. They also help to generate phase differences in circadian transcriptional output that optimally time gene expression which can differ depending upon the specific tissues or cell types.

The molecular clock mechanism also has a number of functional redundancies that maintain function in the event of genetic mutations. For example, in mice there are three homologues of the period gene called Per1, Per2, and Per3. A knockout of any one of these genes is not sufficient to eliminate circadian rhythmicity, but a mouse with a Per1/Per2 double knockout does lose rhythmicity. The only single gene knockout known to eliminate clock function in the SCN is the Bmal1 knockout. Such mice lack molecular and behavioral circadian rhythms, and have additional abnormal phenotypes such as decreased activity, decreased body weight, and shortened lifespan. Although the SCN is a network of thousands of neurons that together function as a circadian clock, many, if not most, individual cells have the cellular machinery necessary to function as a clock. That is, cells throughout the body have the same circadian clock gene components.

Neuroscience across Species: Discovery of Molecular Clocks

The molecular underpinning of the circadian clock owes much to the foundation that was done with work in fruit flies. In 1968, Ronald Konopka began to screen strains of fruit flies to determine if there was one that had problems with the timing of eclosion (emergence) of the mature fruit fly from the pupa. Eclosion has a circadian rhythm and flies hatch 1-2 hours before dawn. Three strains were identified, one that had a shorter period of 19 hours, one with a long period of 28 hours, and one that had individuals emerging across the day with no period. This led to a groundbreaking paper that identified the gene responsible for the three mutant strains, which they called *period* (Konopka and Benzer, 1971). This foundational work led to the discovery of additional genes that form a feedback loop within fruit flies, and also led to work in lab rodents, described above.

In fruit flies, the feedback loop is comprised of the CYCLE (CYC) and CLOCK (CLK) proteins which form a dimer. They enter the nucleus of the clock cells and turn on the transcription of the genes *timeless (tim)* and *period (per)*. These genes lead to the production of PER and TIM proteins which are formed in the cytoplasm. TIM is light sensitive and thus builds up at night. PER alone is unstable; it becomes phosphorylated by the protein DBT (encoded by the gene *doubletime*) which leads to its being degraded in the cytoplasm. However, when TIM and PER heterodimerize in the cytoplasm they become stable and increase in the cytoplasm, enter the nucleus, and block their own transcription. This is done by PER inhibiting CLK which prevents the PER/CLK dimer from binding to the DNA. Thus, PER negatively inhibits its own production (Rosato, Tauber, and Kyriacou; 2006, Bhadra et al., (2017).

A second feedback loop occurs where CLK protein has a peak in the daytime, opposite to that of TIM. CLK/CYC dimers initiate the transcription and translation of two proteins VRI (encoded by the gene *Vrille*) and PDP1e (encoded by the gene *Pdp1e*). VRI is a negative inhibitor of the transcription of *Clk* and PDP1e is a positive regulation of this gene, thus they act in opposite ways on the transcription of Clk (Rosato, Tauber, and Kyriacou; 2006). The initial characterization of these clock gene loops in fruit flies led to a Nobel Prize to be awarded to three circadian biologists in 2017, Drs. Hall, Rosbash, and Young.

Neuroscience across Species: Evolution of Clocks

Circadian rhythms do not require a brain. Well-regulated circadian clocks are found in plants, fungi, and even some types of bacteria. Further, they are found in animals that do not have an SCN such as fruit flies, honey bees, and roundworms. Circadian rhythms are found across vertebrates from fish to sloths, from rodents to humans. There has been much speculation as to how clocks evolved in such a diverse array of species and for what purpose. One foundational assumption is that possession of a daily clock confers an advantage to the organism. This has led to the idea that some fundamental advantage of having biological rhythms is so important that clocks may have evolved multiple times across varied species. Interestingly, another hypothesis speculates that biological clocks may have originated as a fundamental process for detoxifying cells from oxidative stress. Peroxiredoxin protein, which plays a role in eliminating reactive oxygen species, has a daily rhythm in mice, bacteria, flies, and fungus (Loudon, 2012). Thus, there is much to be determined as to when biological rhythms emerged.

In animals, overall control of rhythmicity is generally coordinated by a set of clock generating cells in the central nervous system. For example, in fruit flies, there are about 150 clock neurons in the brain. These neurons are subdivided into groups that regulate a variety of aspects of circadian rhythmicity, and the neuroanatomical organization of these cells is well known. In vertebrates, the primary circadian clocks are best represented by some combination of clocks located in the retinas, pineal gland, and the hypothalamus (Menaker, Moreira, and Tosini, 1997). This group of clocks has been best studied in birds, where all three of these areas contain circadian clocks, with the relative importance of each varying from species to species. For example, the pineal gland has circadian oscillations in some but not all bird species. In mammals, the SCN acts as a master circadian clock, driving rhythms of physiology and behavior. The pineal gland and retinas still have rhythmic activity, but the contribution of these clocks to overall circadian rhythms has diminished. The SCN has a structure that is remarkably conserved across mammalian species, and is characterized by direct retinal input and a separation of neurons into distinct groupings on the basis of neuropeptide content. The interaction of these clocks was appropriately described as a neuroendocrine loop, which maintains synchrony amongst independent circadian clocks in each tissue through hormonal and neuronal signals. Ultimately, additional research needs to be conducted across species to determine commonalities and differences.

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14.3: Regulation of Sleep

Learning Objectives

By the end of this section, you should be able to

- Describe several theories to explain why we sleep.
- Differentiate between the different stages of sleep.
- Differentiate between circadian and homeostatic regulation of sleep.
- List several ways in which disruption of sleep (shift work, light at night) impacts human health.

Why Does Sleep Exist?

At first glance, the entire process of sleep seems maladaptive. While sleeping, organisms are not searching for food or mates and have reduced sensitivity to environmental stimuli, making them more vulnerable to predators or hazardous events. Despite this, almost all animals appear to sleep, even when they lack a central nervous system as is the case with Hydra (Kanaya et al., 2020). It therefore seems likely that sleep evolved in very primitive animals and gradually took on additional functions throughout the evolution of the animal kingdom.

In humans, sleep regulation can be modeled using the two-process model of sleep regulation. Process C refers to the circadian rhythms in the timing of sleep and wakefulness. There are endogenous rhythms to when you feel sleepy and when you feel most awake. For example, most of us feel fatigued and sleepy during the later hours of the evening, and we feel most alert in the morning hours. There is also a period of reduced alertness which occurs in the midafternoon. You may have experienced this as sleepiness after lunch. These cyclical rhythms in sleepiness and wakefulness are regulated by the circadian timekeeping system and the master clock found in the SCN. Process S refers to the homeostatic pressure to get restorative sleep. The more time it has been since you slept, the greater the pressure to fall asleep. After you have been awake for a while, a certain amount of sleep debt has accumulated, and you need a period of sleep to eliminate the debt. The interaction between these two processes determines the amount of sleep pressure at any given time and the likelihood of falling asleep.

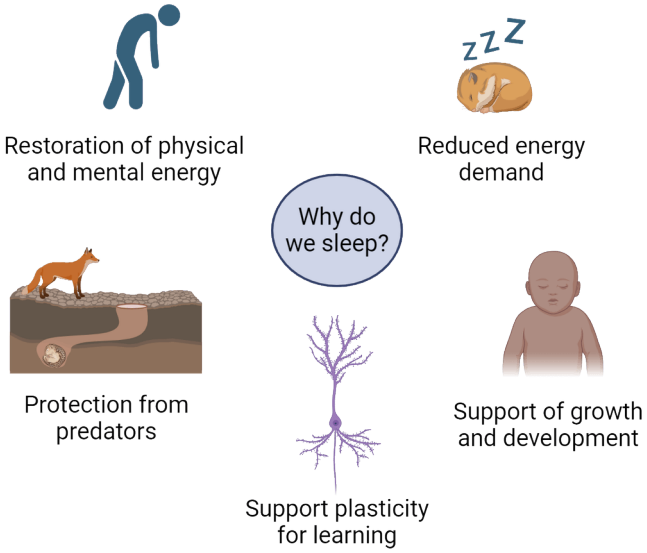


Figure 15.12 Why we sleep

One major theory of the function of sleep is that sleep performs a restorative function, without which an animal's performance is impaired in some fashion (Figure 15.12). In humans, when we don't sleep, we feel tired and our ability to function is decreased on both physical and mental tasks. After sleeping, we feel better. There is significant evidence in support of this function at the behavioral, physiological, and molecular levels. Sleep deprivation impairs, among other things, cognitive function, tissue repair,

attention to tasks, and even increases cancer risk.

One possible mechanism of the restorative function of sleep focuses on the neurotransmitter adenosine. Adenosine is released by neurons in response to excessive firing and metabolic exhaustion (Lovatt et al., 2012). During wakefulness, adenosine builds up in the brain, promoting sleepiness. It is then reduced during sleep. The impact of adenosine is counteracted by caffeine, giving coffee and other caffeinated beverages their ability to defer sleep onset. Caffeine has this effect by blocking action at the A2A adenosine receptor. This effect is temporary—once the caffeine wears off, a person is just as sleepy as if they had never had the caffeine.

Another possible mechanism for the restorative function of sleep is waste clearance. Metabolic waste products are removed from the brain at a higher rate during sleep than during wakefulness (Albrecht and Ripperger, 2018). One mechanism that clears this neural waste is known as the glymphatic system and this has been the subject of new and exciting research in neuroscience. In this system, cerebral spinal fluid (CSF) enters the brain then has an exchange with the brain tissue via the interstitial fluid. The byproducts of metabolism are collected and removed from the brain. The glymphatic system is active when animals are sleeping and it is largely quiet when animals are awake. Research has demonstrated that this rhythm in clearance is circadian in nature (Hablitz et al., 2020). Thus, sleep may serve as an active period when the brain is removing toxic waste (Jessen et al., 2015).

A second popular theory of sleep function is that it serves an energy conservation function. Energy usage is reduced during sleep, with the amount of savings varying from animal to animal. Animals spend a considerable amount of their energy budgets looking for food, and the reduction in energy usage during sleep could make a difference in evolutionary success. In fact, when we sleep our metabolism decreases by 10% (Sharma and Kavuru, 2010). Some species gain significant energy savings during sleep by reducing body temperature, but the reduction in muscle usage provides for significant savings. Many species also adopt sleeping postures that conserve heat, reducing the energy usage for body temperature homeostasis. At times when food is scarce, the reduction in metabolic rate during sleep could allow an animal to survive for a longer period of time than would otherwise be possible. While this theory is appealing, there are examples that do not support it. For example, some animals sleep a lot whereas others sleep very little. Lions and zebras both use relatively little energy; male lions do not hunt and grazing expends a small amount of energy. Yet lions sleep 15-18 hours a day and zebras sleep as little as 3-4 hours a day (Siegel 2005).

A third theory is that sleep enforces inactivity during periods of time when an animal's survival would be negatively impacted by active behaviors. Thus, animals with specialized adaptations for nocturnality sleep during the day, when they would be more vulnerable to predation, and diurnal animals dependent on vision are safer being inactive during the night. However, it is not clear whether sleep is really necessary to enforce this kind of behavior pattern, with the added cost of loss of responsiveness to sensory stimuli.

Finally, there is the idea that in animals with complex nervous systems sleep serves an important role in the growth, development, and plasticity of the brain, particularly as it relates to functions around learning and memory. As an example, sleep deprivation studies have confirmed that learning and memory are negatively impacted by insufficient sleep through effects on signaling in hippocampal neurons.

These theories are not mutually exclusive. It seems likely that sleep evolved in response to bioenergetic pressures that resulted from circadian rhythms of energy availability and took on additional functions as nervous systems developed and became more complex.

Neuroscience in the Lab

How We Measure Sleep

The gold standard for measuring sleep is by the use of a polysomnogram (PSG). Figure 15.13 shows a photo of someone undergoing polysomnography, along with some of the typical measures collected during the session. This is typically done within a lab setting or sleep clinic. Electrodes are attached to standardized locations on the scalp to measure brain electrical activity through electroencephalography (EEG) (see Methods: Sleep Studies and EEG Technology). Fluctuations in voltage are measured and compared between each of the sensors. Electrical signals from the brain vary between waking and sleeping, and between the different stages of sleep. Electrodes are also used to measure movement of the eye muscles through electrooculography (EOG). This detects ocular movement during wakefulness and the different sleep stages and is used to identify Rapid Eye Movement Sleep (REM or REM sleep). Sensors are also used to measure muscle movement through

electromyography (EMG). There are changes in muscle tone that occur as you move from wakefulness with continuous movement to REM sleep with muscle paralysis. Finally, oxygen saturation in your blood, respiratory rate, and heart rate may also be measured.

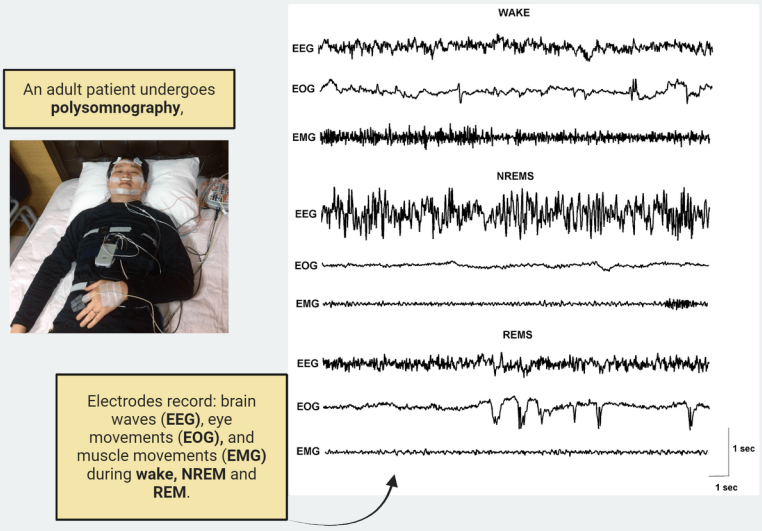


Figure 15.13 EEG measurement of sleep Image credit: Photo of person from: by Kuyohong/Wikimedia Commons, CC BY-SA 4.0. Electrode traces from Kumar, Ramaswamy & Mallick. 2013. "Local Properties of Vigilance States: EMD Analysis of EEG Signals during Sleep-Waking States of Freely Moving Rats." https://doi.org/10.1371/journal.pone.0078174. CC BY 4.0

PSG measures sleep in an objective manner. However, you can also give people surveys or diaries and ask them to describe their sleep. This is referred to as subjective measures. There are many sleep surveys and tools that are used to measure healthy sleep and to assess potential sleep disorders such as insomnia or sleep apnea. These surveys can probe how much an individual sleeps, their level of daytime sleepiness, the quality of their sleep, and their preference for activities at certain times of day. A doctor may also ask for a sleep diary or log where a patient records the time they go to bed, the time they fall asleep, the number of minutes they are awake after they fall asleep and the time they wake up.

In healthy patients, the subjective and objective measures of sleep have a high correlation, but in patients with conditions such as insomnia or depression, the correlation is not as strong. For example, patients with insomnia may report that it takes longer for them to fall asleep than the PSG records would indicate (Rezai et al., 2022). However, both objective and subjective measures of sleep are important for a medical professional to use as data for treating a patient. Recently, new tools using fitness trackers and smart watches have become available that purport to measure sleep time and even to identify the timing of deep and REM sleep. These devices can be very good at identifying periods of sleep but may somewhat overestimate sleep time because they aren't necessarily as good at identifying waking periods. In addition, accuracy in the measurement of sleep stages is not yet up to clinical standards.

Stages of Sleep

There is a clear distinction between your activity levels during sleep when compared to being awake. However, getting a good night of sleep is not a uniform process where you lay immobile in bed and your brain becomes quiet. In reality, your brain and your body cycle through 4 different stages and the whole cycle can take about 90 minutes (Figure 15.14). You may experience 3-5 cycles per evening.

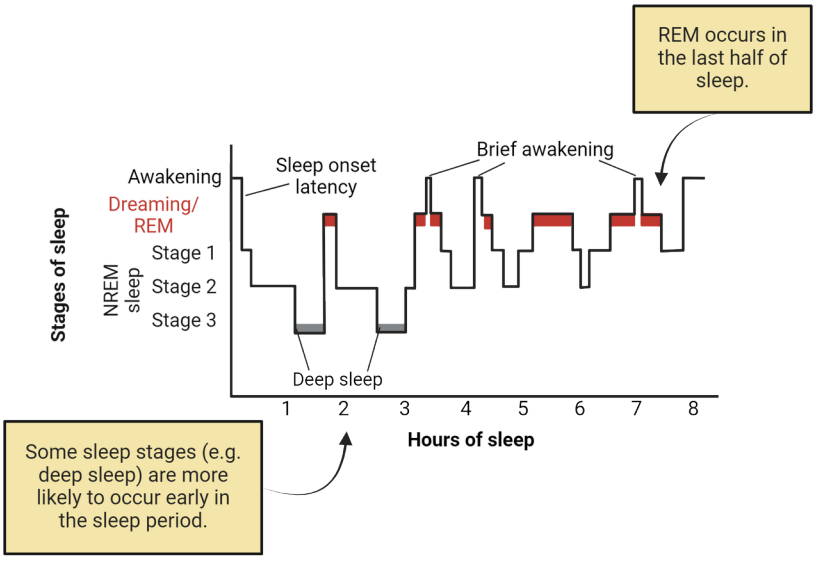


Figure 15.14 Hypnogram

The stages comprising a cycle can be divided into non-REM (3 stages) and REM sleep. Non-REM sleep (also referred to as NREM sleep) is characterized by large amplitude, slow oscillations on the EEG, representing synchrony of electrical activity in the cortex (Figure 15.13). Muscle tone is reduced and movement is limited (but not eliminated).

- Stage 1 non-REM sleep is a transitional stage that occurs as one moves from wakefulness into sleep. This period lasts less than 10 minutes and is considered the lightest stage of sleep because you are easily woken up during this stage.
- Stage 2 non-REM sleep is where the majority of your sleeping time is spent. Your body temperature drops, your breathing rate slows, and your brain electrical patterns exhibit sleep spindles (Figure 15.15). Spindles appear on the EEG as rapid and rhythmic bursts of activity. Spindles are associated with learning capacity. This period lasts about 25 minutes.
- Stage 3 non-REM sleep, or delta sleep, or slow wave sleep is a deeper sleep where it may be hard to wake up even if there are loud noises or stimuli in the environment. The body's breathing rate is slowed and muscles are relaxed. In the EEG, delta waves appear which are slow frequency and high amplitude waves of electrical activity (Figure 15.15). This is the deepest stage of sleep and is the critical stage for restorative sleep as it is a time when the body clears out waste, builds bone and muscle and the immune system is strengthened. Decreases in the amount of slow wave sleep is associated with more fatigue during the day. Importantly, this stage of sleep is critical for memory consolidation.

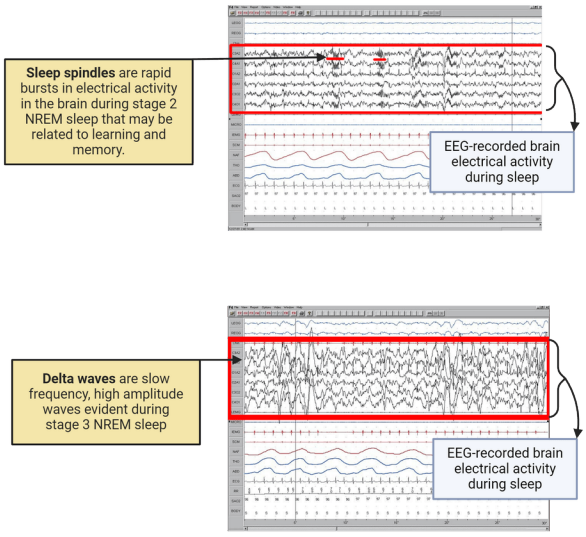


Figure 15.15 Sleep spindles and delta waves Image credit: Sleep spindles from EEG by MrSandman at English Wikipedia. Transferred from w to Commons by en., Public Domain, https://commons.wikimedia.org/w/inde...p?curid=453178. Delta waves from EEG Public Domain, https://commons.wikimedia.org/w/inde...p?curid=453193

Finally, about 90 minutes after you fall asleep you enter the REM sleep phase. Here your brain EEG has electrical activity that resembles wakefulness; as such, this stage is referred to as "paradoxical sleep". Despite brain activity that resembles the waking state, your muscles are immobilized, breathing is fast and irregular, and your eyes exhibit rapid movements. This stage can last 10 minutes in the first sleep cycle of the evening, but as the night progresses, you spend an increased amount of time in the REM portion of the sleep cycle, perhaps as long as 60 minutes by the end of the night. In a typical night of sleep, you do not progress through the sleep stages in order. Initially you may enter stage 1 through 4 in sequence before reaching REM sleep, but at the end of the night you may cycle between REM and stage 2 and stage 3 non-REM sleep.

Cramming for Exams

Have you ever pulled an all-nighter to complete a last-minute project or to study for an exam? This learning strategy is not ideal as research teaches us sleep is critical for optimal learning. We may not yet know the full reasons for why we sleep, but studies show that sleeping helps with our memory formation and retention. Getting enough sleep both before and after you learn material can help strengthen memories. In lab studies, people were allowed to have a full night's sleep, or even a 90-minute nap *prior* to having a memory task of learning face-name pairs. Those that slept had a significantly better learning capacity compared to those with no nap or less sleep. The polysomnogram (PSG) data from the participants were analyzed and it was found that the number of sleep spindles that occurred in the stage 2 non-REM sleep prior to learning was associated with an increase in learning ability. Sleep also helps you strengthen and retain memories after they have been formed. In studies where participants learned word pairs, then took a nap, or slept overnight, it was found that they recalled more words than those that did not sleep. An additional important finding was that the amount of deep non-REM sleep was strongly associated with the amount of information that was retained. We get more deep non-REM in the early part of our sleep cycle, thus, getting a full night's sleep is critical for learning (Walker, 2017).

Regulating Sleep

When we are awake there are multiple brain areas that are actively responsible for keeping us in an awake state. However, you may not realize that when we are asleep our brains are not in an "off" state; instead, our brains remain engaged in active processes. While we sleep there are specific brain areas that are turned "on" to help regulate our sleep. During our waking period there are multiple brain areas, working together as part of the ascending arousal system, that secrete neurotransmitters which then maintain wakefulness (Figure 15.16). The neurotransmitters that are secreted go to a sleep-promoting brain area to turn off its activity. This brain area, known as the ventrolateral preoptic area (VLPO, a region of the hypothalamus), communicates back to the wake-promoting system, and inhibits these structures in order to maintain a quiescent state. Thus, there is a brain area that promotes sleep, a second set of structures that promotes wakefulness, and these two systems inhibit one another. This is referred to as the flip flop switch.

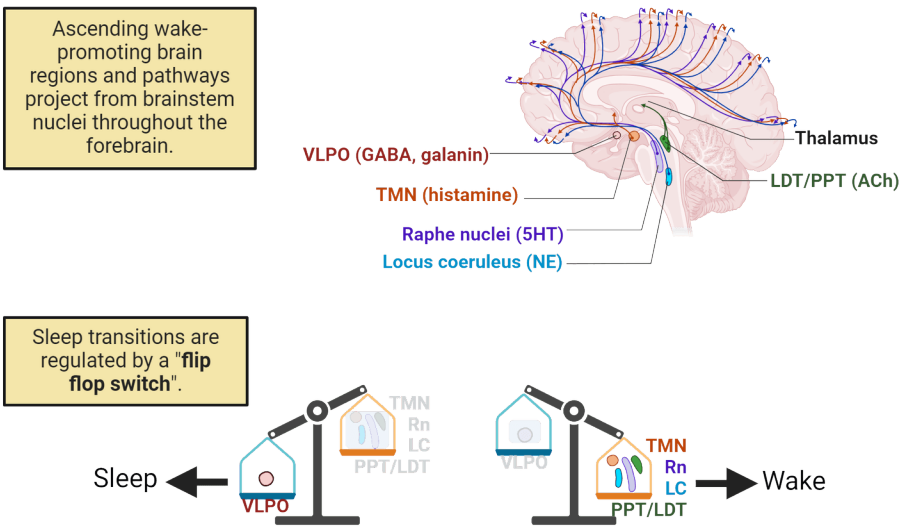


Figure 15.16 Sleep circuitry

To be more specific, during wakefulness, in the brainstem, the locus coeruleus (LC) secretes norepinephrine and the raphe nuclei secretes serotonin. In the hypothalamus, the tuberomammillary nuclei (TMN) secrete histamine. Additionally, in the brainstem, near the pons are two groups of cells that secrete acetylcholine. These cells are located in the lateral dorsal tegmentum (LDT) and the pontine peduncular tegmentum (PPT). Together, these wake-promoting areas send projections through the rest of the brain to help maintain wakefulness. In contrast, there is a group of cells in the VLPO of the hypothalamus which promotes sleep. As mentioned above, there is a mutual inhibition between the sleep-promoting regions of the VLPO and the wake-promoting regions of the brainstem and hypothalamus. Specifically, the VLPO is inhibited by norepinephrine and serotonin via connections from LC and raphe nuclei; this occurs during wakefulness. The cells of the VLPO send neuronal projections containing the inhibitory amino acid GABA and the inhibitory neurotransmitter galanin to the aforementioned sleep-promoting brain areas. The VLPO thus inhibits these areas and as a result maintains sleep. These connections are diagrammed in Figure 15.17.

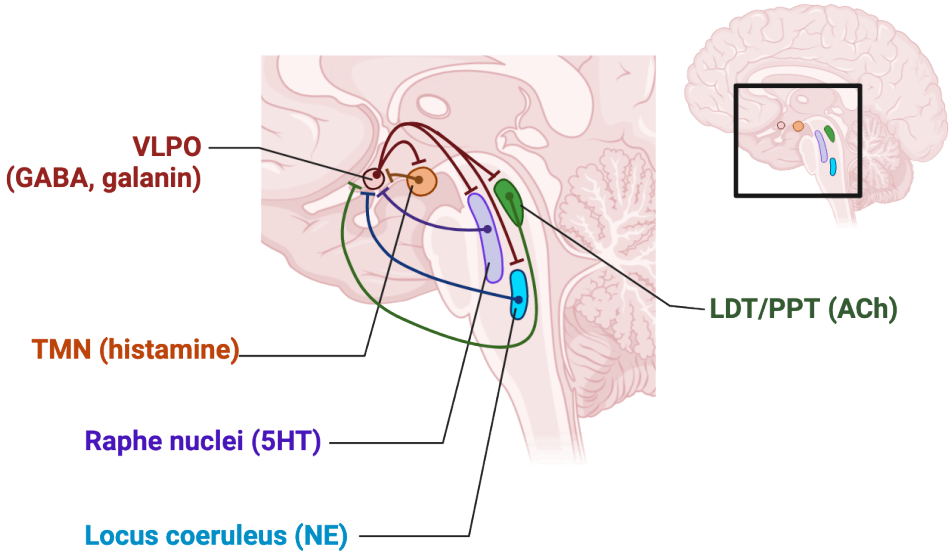


Figure 15.17 Reciprocal inhibitory connections of sleep areas Wake and sleep promoting regions inhibit each other.

Neuroscience across Species: Comparative Sleep

Adaptation to a variety of ecological niches has resulted in a wide range of sleep strategies and some unusual variations in sleep physiology. Just across mammals, sleep duration can vary from 4-20 hours per day, and length of time spent sleeping represents just one way in which sleep differs between species. Sleep may confer an advantage to remain quiet when predators are present, or to conserve energy for when food (prey) is abundant. For example, in sloths in the wild, predation appears to determine when they are sleeping and when they are awake (Voirin et al., 2014). The little brown bat sleeps for up to 20 hours a day, which might be due to the fact that its food source of moths and mosquitos is only present in a small window of time at dusk (Siegel, 2022).

Some mammals (whales, dolphins, fur seals, and sea lions) exhibit an unusual pattern of sleep called unihemispheric sleep. When in this state, one half of the brain is in a state of slow wave sleep at a time. Given the requirements of living in an aquatic environment, this makes sense: aquatic mammals must retain voluntary muscle control because they need to swim and surface to breathe, and maintain contact with conspecifics and be alert for threats. Behaviorally, the animals generally keep one eye open and one closed, with the open eye connected to the cerebral hemisphere that is awake. The open eye is usually the one directed towards other members of the group, rather than looking outward for threats, suggesting that these animals are utilizing unihemispheric sleep, in part, to maintain group cohesion. Unihemispheric sleep is also thought to occur in some birds and eared seals.

Sleep-like states can also be measured in other organisms that do not have an SCN, such as fruit flies. In this versatile lab model, circadian rhythms are controlled by about 150 cells which are clustered into groups (reviewed by Dubowy and Sehgal, 2017). Together these groups function like the mammalian SCN. Further, these clusters also have differences in neurotransmitter expression, much like the different subregions of the SCN. Fruit flies have states of rest (quiescence) which resemble sleep. These periods of resting are circadian regulated and therefore occur rhythmically. Further, there is a homeostatic drive and flies can be deprived of this rest period after which they show sleep recovery periods. These recovery periods have longer and deeper sleep, indicating a potentially restorative function. Lastly, during the sleep period the fly requires a stronger stimulus to arouse it, much like you would require a stronger stimulus to get your attention when you were sleeping compared to when you were awake

(Dubowy and Sehgal, 2017). This laboratory model has proven to be extremely useful in dissecting the genetic underpinnings of sleep, since the genes and behaviors underlying sleep are conserved.

Sleep qualities have been examined in humans from industrialized areas and compared to hunter-gatherer tribes that have little outside contact and no electricity (Siegel, 2022). Interestingly, in both types of cultures, humans do remain awake after the sun has set. In the tribal communities, humans remain awake for about 3 hours after dark, and further, they acquire about 7 hours of sleep a night. An additional interesting result is that there are relatively low reports of insomnia in individuals from hunter gatherer societies (2% compared to 10-30% in industrialized societies).

Ultimately, sleep can vary within or between species due to mating opportunities, season, food availability and predation. A comparative approach investigating sleep between various species, may lead to a common factor or factors which may determine why sleep is important.

Sex as a Biological Variable: Sex Differences in Sleep Variables

Polysomnography studies both at home and in the sleep lab indicate that women have better objective sleep quality when compared to men. Women fall asleep faster, stay asleep longer, have less wakefulness during their sleep period, and have a greater percentage of slow wave sleep than men. Women also tend to have an earlier bedtime and earlier wake time than men. Men have lighter sleep and spend more time in non-REM stages 1 and 2 and are more easily woken compared to women. Men have less slow wave sleep than do women. Some of these sex differences in sleep variables may be caused by changes in circulating gonadal hormones in males and females. For example, sleep changes and sleep complaints occur in women as they experience fluctuations in hormones such as occurs at the onset of puberty, across menstrual cycles, during pregnancy, and during menopause.

There are studies in men that examine the relationship of testosterone with sleep. Generally, we can suggest that low levels of testosterone are associated with reduced sleep; although not all reports support this conclusion. In healthy males, testosterone peaks around the time that REM sleep stage begins. If a male individual has fragmented sleep or sleep deprivation, then testosterone is reduced. Men with androgen deprivation therapy, which is a treatment for prostate cancer, report an increase in insomnia (Gonzalez et al., 2018). In a study of men 65 years old and older, there was a relationship between low levels of testosterone, increased waking during the night, and less time spent in the restorative slow wave sleep stage (Barrett-Conner et al., 2008). In contrast, high levels of testosterone replacement in older men or young men taking androgenic steroids have a decrease in the amount of total sleep (Liu et al., 2003).

There is still a relative lack of research into how and why sleep is regulated differently in women compared to men. Some of this lack of information may exist because of differences in how sleep is measured, how hormone profiles are determined, and males and females report sleep problems (Mallampalli and Carter, 2014). However, we can describe some consistent changes that are associated with ovarian hormones in sleep in healthy women. During the follicular phase of the menstrual cycle, estradiol is rising. When it reaches a threshold, it triggers a surge of luteinizing hormone and this is followed by ovulation. The period after ovulation is called the luteal phase and this is when progesterone begins to rise. One conclusion that can be made from the literature is that during the luteal phase women experience more awakenings during the night and there is a reduction in slow wave sleep (Baker and Driver, 2007). Furthermore, sleep spindles increase during the luteal phase. Some, but not all, studies have found that the amount of REM may be reduced, REM may start earlier, and there is increased slow wave sleep during the luteal phase. However, when the follicular phase is compared to the luteal phase, PSG studies have found no difference in the time it takes to fall asleep, the time spent awake after falling asleep, or sleep efficiency (time spent asleep/time spent in bed).

Interestingly, changes in hormones such as occurs during menopause are associated with an increase in sleep complaints. As women transition through menopause, they have difficulty falling asleep and they have increased events of waking up during the night. This may be related to the decrease in estradiol and rise in follicular stimulating hormones which occurs at this time. However, some studies also found the speed at which these hormones changed also played a role (Baker et al., 2018). Additionally, women that take birth control report that this affects their sleep patterns. For example, they report more daytime sleepiness and insomnia (Bezarra et al., 2020). Relatively few studies have examined objective sleep measures in women on oral contraceptives. However, in one study, healthy women on oral contraceptives had disrupted sleep; they experienced less slow wave sleep and had a shorter latency to enter REM sleep (Burdick, Hoffmann, and Armitage, 2002).

There are also sex differences in sleep disorders. Insomnia can be defined as difficulty falling asleep and staying asleep, waking up too early, and having poor sleep quality. Insomnia is common in the general population with an estimate that approximately 30% of the population reports at least one insomnia symptom (Sateia et al., 2000). There is a striking difference in men and women with respect to the occurrence of insomnia: women are nearly twice as likely to report insomnia compared to men,

and the risk of reporting insomnia increases with age. In fact women have a 40% greater risk for insomnia in their lifetime compared to men (Mong and Cusmano, 2016). This predisposition for women to have insomnia has been found consistently across studies. Interestingly, the sex difference in the number of complaints about poor sleep and insomnia in women begins at puberty, suggesting that ovarian hormones may be playing a role in this perception.

There are self-reported sleep disruptions that occur during the menstrual cycle, pregnancy, postpartum period, and when women are experiencing the transition to menopause. Sleep disturbances can have a significant impact on quality of life, mood, and health thus identifying how they may occur could lead to therapies. We have already discussed the findings that sleep is more disrupted in the luteal phase of the menstrual cycle. In pregnant women, subjective data indicates total sleep time increases in the first trimester but is dramatically reduced in the third trimester. Women in the last trimester also have more nighttime awakenings (Salari et al., 2021). This disrupted sleep is related, in part, to discomfort due to an increase in pain or decrease in bladder volume. However, treating insomnia in the third trimester can help alleviate postpartum depression (Khazaie et al., 2013). Objective measures of sleep using polysomnography confirmed that sleep variables are changed in pregnant women. Pregnant women had less total sleep, a longer latency to fall asleep, more awakenings, and less slow wave sleep. In the initial postpartum period sleep was significantly disrupted with total sleep time at night being reduced but there was an increase in daytime napping. As the postpartum period progresses, however, sleep quality does improve somewhat. Clearly, there are many factors influencing sleep during pregnancy including the dramatic shift in hormones, the physical discomfort experienced, and the needs of a newborn.

In menopausal women, the decline in sleep quality is one of the most common and problematic symptoms that women report. In this population, declining concentrations of estradiol and rising levels of follicular stimulating hormone are associated with more frequent awakenings and reduced sleep quality. While endocrine changes are likely playing a role in the sex differences seen in insomnia prevalence in all stages of life, we cannot rule out the influence of other factors including aging, quality of health, anxiety, depression, and hot flashes.

In conclusion, there is evidence that sleep in healthy individuals is regulated in part by circulating gonadal hormones and changes in hormones across the lifespan may contribute to sex differences observed in insomnia.

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14.4: Dreams

Learning Objectives

After you read this chapter, you will be able to

- discuss theories about several different dream functions, including emotional healing, memory consolidation, problem-solving, and emotional intelligence development
- explain the role of dreaming in posttraumatic stress disorder recovery
- describe how dreams are created
- compare and contrast several theories about dream interpretation
- discuss dream significance from the perspective of different cultures
- teach someone how to lucid dream
- provide instruction for conducting a dream group

Introduction

In the early moments of trying to fall asleep, we may experience a stunning hallucination that startles us back to reality, leaving us to wonder, “What was that?!” It is disorienting because we feel we were not yet sleeping. These hypnagogic hallucinations occur around sleep onset (Figure 5.1). They are a type of dream—if you define dreaming as something going through your mind while you are asleep—but some people refer to hypnagogic hallucinations as “sleep thinking.” We dream in all stages of sleep, NREM and REM, but during REM sleep, our dreams become more intense in their content and often bizarre in nature. Conversely, if awakened from NREM dreams, many report that it feels as though they were simply thinking about something rather boring. We know dreams occur throughout the night, but in this chapter, dreaming refers, unless stated otherwise, to the dreaming state associated with REM sleep. Let’s begin with a discussion of the importance of dreams to our mental well-being, because in the words of Nobel laureate Elias Canetti, “All things one has forgotten scream for help in dreams.”1

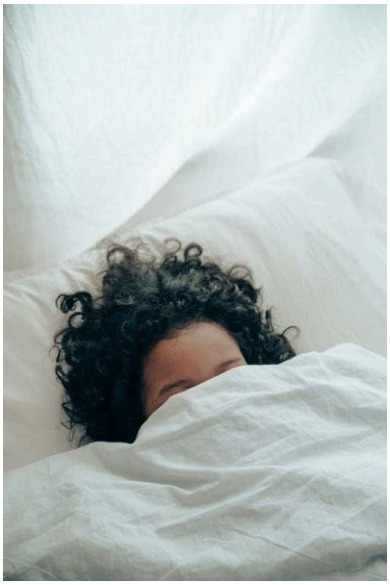


Figure 5.1 Under the covers

Emotional Healing

Dreams help us cope with, and better understand, our emotions. During the day, emotional events happen, but we rarely pause for reflection because we are pressed to continue with the business of the moment. When we are dreaming, it is an opportunity to take the emotions of the day and relate them to memories—even those from long ago—to see if we can make sense of the

situation and be better prepared for the next time something similar occurs.

Imagine an emotional event during the day, such as a group activity in class in which you felt socially uneasy, like you did not fit in (Figure 5.2). Maybe you said something that was poorly received or were given a disapproving look by one of your classmates, but you had to continue with the work at hand. You may or may not have forgotten about it by the time you went to bed. Either way, that night, your dream might have an emotional theme of social rejection, but in a scene involving people you haven't seen in years rather than your current classmates. Through dreams, your brain can create a mash-up of current and previous experiences to optimize your future behavior—the perfect harm-free dress rehearsal.



Figure 5.2 We've all been there

While our dreams are synthesizing such relationships between recent emotions and distant memories, the brain experiences its lowest levels of stress hormones over the course of twenty-four hours. One of these hormones, norepinephrine (also called noradrenaline), is present in the brain at various levels throughout the day and night—except during REM sleep. During our vivid emotional dreams, we can replay events without the stress response triggered by norepinephrine. Matthew Walker, a sleep scientist at the University of California, Berkeley, has led brain imaging research in this area to show how the brain takes advantage of this zero-norepinephrine condition to relate clear recollections of crucial events to previous memories without engaging the flight-or-fight brain circuits that would distract us from calm introspection. The result is that we are able to shed the emotionally painful layer of the memory and still retain details of the situation to help us be better prepared to face another day . . . or that judgy classmate!

Dreaming about emotional events brings us to a place where we are more comfortable with the situation. Psychologist Rosalind Cartwright, also a world-renowned sleep specialist and expert on dreaming, has published extensive research showing the benefit of dreaming for emotional recovery. Dreams mentally evolve us to a point where our daily activities, as well as our sleep, are less disturbed by feelings associated with challenging life events. She says a part of the purpose of dreaming is so that "negative mood [can be] down-regulated overnight."2 Although, she is quick to clarify that recovery from difficult life events will take many nights, maybe months, of dreaming about them. Cartwright has done brilliant research and clinical work with patients experiencing despair at the time of an upsetting life event, such as a breakup with a partner (Figure 5.3). She found people who dreamt of the event, especially around the time of its occurrence, experience a significant amelioration of depression compared to those who did not dream of the event (even if they did still dream of other things).



Figure 5.3 Staying together

This progression to recovery has a more complicated path for individuals faced with trauma and nightmares. If someone experiences a frightening or dangerous event, and feelings of being scared or stressed remain strong long after the danger has passed, they may have posttraumatic stress disorder (PTSD; Figure 5.4). People with PTSD have increased levels of norepinephrine in their brains during REM sleep. This is the opposite of the norepinephrine-free condition responsible for emotional healing during REM dreams, which is experienced by those without PTSD. For folks suffering from PTSD, the presence of norepinephrine during REM sleep disrupts the ability for dreams to reduce the emotional intensity associated with disturbing events. But because the mind still wants to work out the problem while dreaming, it will repeatedly attempt to do so with a dream, sometimes every night, resulting in recurring nightmares—one of the most common symptoms of PTSD.



Figure 5.4 Soldier

Imagery rehearsal therapy (IRT) has been used successfully to help people with PTSD work with a therapist to transform nightmares into less disturbing dreams. The concept is to create a more comfortable version of the nightmare and retain enough nightmare details so the mind will slip into this new version. For example, if a person has a nightmare of being attacked by a shark, the new version will still have water splashing, a fin in the water, and the feeling of a strong bump against the body of an animal. However, in this new version, the splashing is from a dolphin playing nearby, not a shark thrashing; the fin is a dolphin fin, not a shark fin; and the bump to the body is gentle, from the friendly dolphin (Figure 5.5). People write out the new version of the dream, create an art piece depicting it, and tell the new dream as a story to another person. They meditate on the new dream before sleep to train the mind to shift over to this new set of details. Harvard psychologist Deirdre Barrett has written

extensively about the benefit of working with dreams as a part of the recovery process for PTSD. She explains that dreams provide a “barometer” of a person’s mental state, delivering insight into a patient’s progress.3



Figure 5.5 Transforming the nightmare

Memory and Learning

Through dreams, our brains create connections between recent experiences and long-term memories. This equips us with new perspectives, allowing us to better respond to similar situations in the future. Our sense of self or identity also changes through dreams as we see our role in a recent situation through the lens of a memory from our distant past. Procedural memories—those for things like playing a song on the guitar or making your favorite cookies—are also processed and stored through dreaming. When we are learning a new procedure, let’s say a dance routine, we will notice the first time we try it after a night of dreaming, we will do much better than on the previous day. NREM and REM dreams both play a role in memory formation, but there is a difference. NREM dreams serve more to strengthen memories, and REM dreams restructure them, marrying fresh experiences to earlier ones.

Taking a deep look at how dream content has an impact on learning and memory, sleep science experts Erin Wamsley and Robert Stickgold studied navigation in a virtual maze (Figures 5.6a and 5.6b). Human participants trained on the virtual maze and then were allowed to sleep overnight. In prior animal studies on the subject, researchers had already shown that the animals’ brain firing patterns during sleep closely matched the patterns seen when they were learning a maze, but how could we know what the animals were dreaming about? Previous studies on animals and humans also provided evidence of improved performance being associated with sleeping after attempting a task. The novelty of Wamsley and Stickgold’s research was in asking participants about their dreams’ content during the night and establishing the clear relationship between maze-themed content in dreams and success in navigating the maze the next morning. They also found that the participants who did not perform well during practice sessions with the maze were more likely to see the maze in their dreams that night.4 If something is challenging for us, our brain knows we will be more likely to overcome the challenge if we dream about it. This fits well with Antti Revonsuo’s “threat simulation theory,” which posits that dreams help us develop better skills to behave successfully in the midst of difficult situations. He states that through dreams, we are able to rehearse threatening scenarios, with the result being improved outcomes in our next waking encounter with similar challenges.5



Figure 5.6a Virtual reality goggles



Figure 5.6b Maze

Problem Solving and Creativity

Stories of creative inspiration arriving through dreams are pervasive: Dmitri Mendeleev's periodic table of elements, Mary Shelley's idea for *Frankenstein*, Elias Howe's design of the needle for the sewing machine, Friedrich Kekulé's vision of benzene ring structure, Keith Richards' guitar riff in *Satisfaction*, and more all are said to have come from dreams (Figure 5.7). Rather than take space here to provide the details of these worn-out stories, you may Google the topics—and when you do, you will find Google itself was born in a dream!

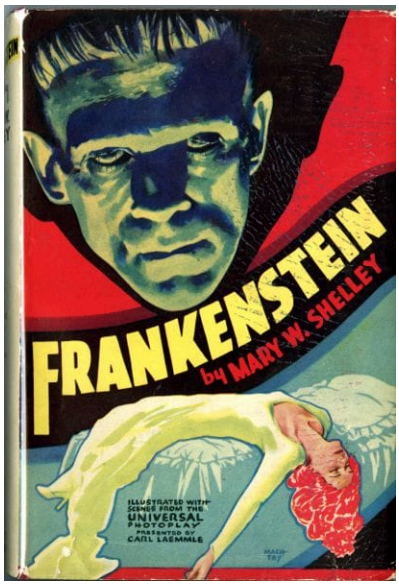


Figure 5.7 Frankenstein

There is one story worth telling here. It is about an inspiring role model, Sarah Breedlove Walker (a.k.a. Madam C. J. Walker), who was a civil rights activist and philanthropist up through the early 1900s (Figure 5.8). The wealth she built to provide the financial resources to support herself and her philanthropy came in small part from a hair-loss remedy recipe that came to her in a dream. I say "small part" because most of her success is likely due to her fortitude. She started life as the daughter of freed slaves, living in financial poverty in Louisiana, and spent years working as a single mother, since her parents and husband died by the time she was twenty. Then after a hard day of work as a washerwoman, she had a dream where a recipe came to her, including ingredients she ultimately had shipped from Africa, for a product to help her restore her hair, which had fallen out. She ultimately became a successful businessperson and multimillionaire, dedicating herself to helping others. W. E. B. Du Bois said of Walker, "It is given to few persons to transform a people in a generation. Yet this was done by the late Madam C. J. Walker."8



Figure 5.8 Madam C.J. Walker

With scores of stories about dreams providing creative solutions, it is no surprise there is a bounty of research that shows sleeping and dreaming on a problem makes us more likely to gain insight into a solution. Psychologist Ullrich Wagner and his colleagues scheduled cognitive testing sessions so that one group of participants would sleep in between their first and second testing sessions, while the other would not. The test consisted of tiresome math problems. Rules were provided for generating the solutions, but it was still a tedious and prolonged experience. But there was a secret shortcut that could be used if the participant had an epiphany about an abstract rule. Such epiphanies, in which the solution to a seemingly unsolvable problem suddenly becomes clear, happen more often if we dream about our problems. Wagner's team found that the people who slept between

their first and second attempts had significantly more revelations that led them to the secret shortcut than those without the opportunity to sleep.9

But what if the participants' epiphanies about the secret shortcut were due simply to the fact that they'd slept and had nothing to do with the brain restructuring memories of the test problems during their dreams? To factor this in, they needed to do additional data collection on participants who took the test only once. They divided participants who had not yet seen the test into two groups, those who slept before the test and those who did not. There was no difference between the two groups in terms of discovery of the hidden rule: the sleepers and nonsleepers had the same rate of epiphanies upon taking the test for the first time. In other words, a participant had to have seen the test problems before sleep (as in the protocol with people taking the test twice) in order for the rate of epiphanies to increase (as they did when those participants saw the problems again). Notice how the researchers included this essential part of the scientific method: seek to disprove your hypothesis and look for alternate explanations, even if it seems you have proven the hypothesis you were seeking to prove.



Ready to Move On?

Before moving on, consider this statement: "If you try only to prove your hypothesis, you will." Take a moment to think about something clearly and obviously true. Now propose a hypothesis that is ridiculous and untrue about the item you are thinking about. Can you see that if you look *only* for reasons your ridiculous hypothesis is true, it is very likely you could find at least one reason and decide to conclude that your hypothesis is true? What is missing? If you want to uncover the truth, you must also seek to disprove your hypothesis.

Emotional Intelligence

One of the pillars of healthy interpersonal relationships is emotional intelligence, which includes the capacity to understand and control one's own emotions and to recognize and interpret the emotions of others (Figure 5.9). One aspect of this is being able to distinguish different facial expressions, such as for fear, anger, or joy. Without the benefit of time in our dream state, this ability drastically deteriorates to the point where not only do we lose the ability to tell the difference between a friendly or angry expression on someone's face but also our tendency is to assume the more threatening option. This was discovered in Matthew Walker's University of California, Berkeley, lab. Regarding how misinterpreting neutral facial expressions as threatening could cause harm, Andrea Goldstein, lead author on the study, urges, "Consider the implications for students pulling all-nighters, emergency-room medical staff, military fighters in war zones and police officers on graveyard shifts." One of the fascinating aspects of the study was that they studied the participants in an MRI scanner, so in addition to having the evidence reported by the subjects themselves, the scientists could also see how well (or poorly in the case of less REM sleep) their brain structures were doing in terms of distinguishing between the different expressions.



Figure 5.9 Facial expressions

How and Where Dreams Are Created

In the 1970s, Harvard medical doctors J. Allan Hobson and Robert McCarley postulated a neurobiological model of dreams. They described REM-associated bursts of electrical activity in cats as originating in the pons (a part of the brainstem), traveling through the thalamus, and arriving at the cerebral cortex (Figure 5.10). Along with this neuronal activity came twitches in whiskers and muscles, as well as jerky eye movements not typical of a cat tracking something visually, which therefore seemed random. The brainstem's electrical activity patterns were not similar to those seen in animals processing real sensory information either; however, the cortex, influenced by this chaotic activation, was still trying to make sense of the activity and synthesizing the brainstem activity into a dream. This is the premise of Hobson and McCarley's activation-synthesis model of dream creation. For some people, the activation-synthesis model makes a case for dreams being meaningless, since they are based on seemingly random activity. However, if we consider that the dreamer interprets dream content based on its relationship with their waking experiences, interpretations of dreams generated according to this model still provide an opportunity for personal insight.

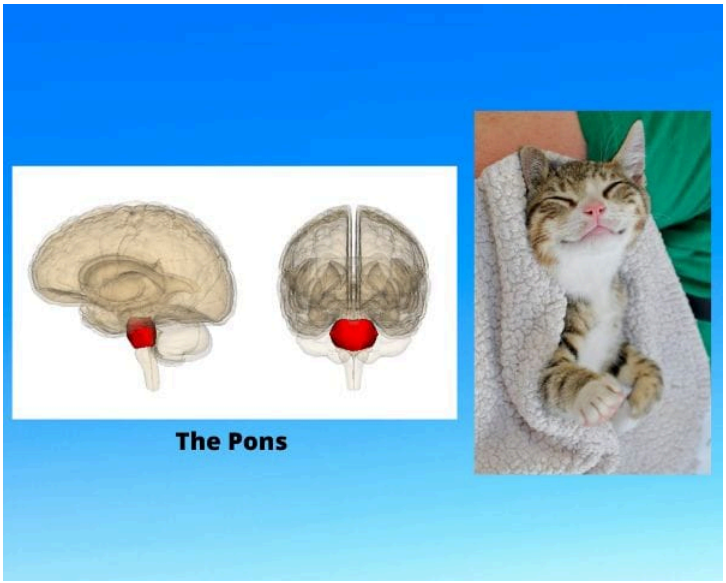


Figure 5.10 The pons is highlighted in red

Debate about the activation-synthesis model continues, but there is no debate about how the advent of magnetic resonance imaging (MRI) has increased awareness of many additional brain regions that are active during dreaming. Contemporary research has utilized MRIs to provide a window into dream-related brain activity, showing high levels of activation in brain regions

associated with feeling emotions, creating movements, and comprehending visual scenery (Figure 5.11). Surprisingly, some of the brain structures, such as the amygdala, anterior cingulate gyrus, and hippocampus—parts of the “emotional brain” or limbic system—are even more active during dreaming than when we are processing information in our waking state.



Figure 5.11 In the MRI



Retrieval Practice

Start at the beginning of the chapter and skim the content through to the end of this section, noting all the reasons we dream. Then set aside the content and your notes and do not let yourself look at that material. Relying only on your memory, make a list of all reasons for dreaming. After you are done honoring that you were able to retrieve some of the content on your own, open the book and your notes and make additions and corrections to your retrieval practice list. Now if someone asks you, “Why do we dream?” do you feel like you are ready with a concise and interesting answer? Retrieval practices are one way to memorize fascinating content so you can gift it to others during your next conversation.

In sharp contrast to the activation-synthesis model, neuropsychologist Mark Solms proposes that dreams are created in the cerebral cortex, specifically the ventromedial prefrontal cortex (Figure 5.12). This part of the brain is involved in a range of functions such as goal-seeking, regulating challenging emotions, recognizing facial expressions, and processing risk. It also provides connections between the limbic system and the frontal cortex. In the early half of the twentieth century, this was one of the brain regions destroyed in attempts to treat mental illness. Solms found that patients with damage to this area, whether from surgeries or other injuries, did not dream.

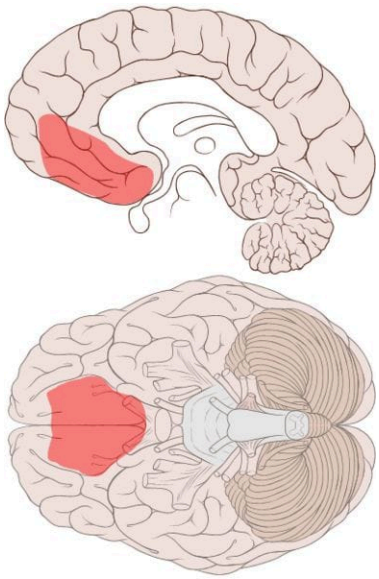


Figure 5.12 Ventromedial prefrontal cortex

In this chapter, we are focused primarily on REM dreams, but let's briefly consider the activity of the limbic system during NREM dreams, which we know are bland and lacking in emotion. So it follows that the limbic system is quite mellow during NREM dreams.

On the other hand, it turns out, if we look further, that there are brain areas that become inactive during REM dreams as well. When we consider the bizarre and sometimes embarrassing things we do in REM dreams, the deactivation of one of these brain regions in particular makes perfect sense: the prefrontal cortex, which guides you to use good judgment and be sensible and socially appropriate, has exceptionally low activity during dreaming (Figure 5.13). Another area that seems to almost drop out of the game during REM dreaming is the primary visual cortex. This region of your brain is involved in consciously detecting visual stimuli from your eyes, so it is logical that, since your eyes are closed while dreaming, the primary visual cortex has almost no activity at that time. The brain is still able to generate visual content for dreams, as it still relies on the visual association cortex—the part of the brain that processes more complex visual information.

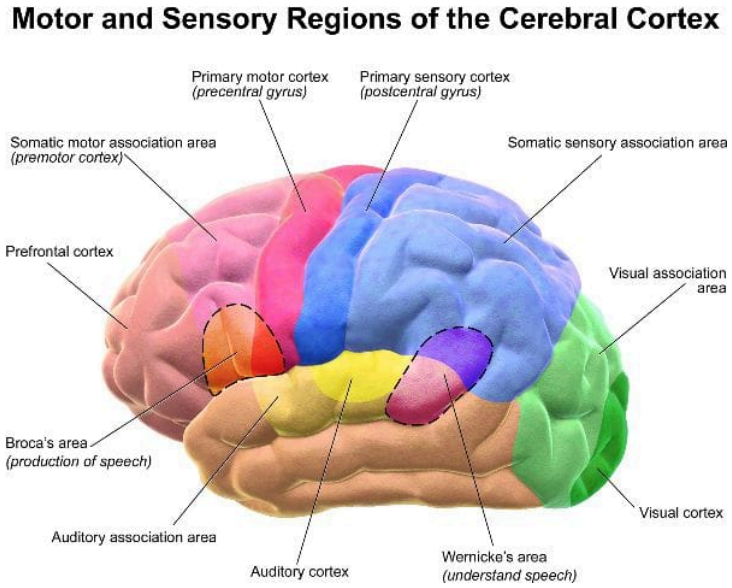


Figure 5.13 Motor and sensory regions of the cerebral cortex

Rather than looking at particular brain structures for the source of dreams, Harvard Medical School sleep researcher Robert Stickgold asked participants to look at the events and emotions of their days for the source of dream content. Participants kept diaries of their daytime activities and their dreams. The dreams were not a replay of daytime events. However, the worries and emotional themes of the day were often incorporated into the dreams. If we leave the activation-synthesis model behind in favor

of theories such as Stickgold's, suggesting dreams contain meaningful information, then it's time to move to the next section for a discussion of how to interpret dreams.10

Interpretation of Dreams

Over five thousand years ago in Mesopotamia, people were having their dreams interpreted and looking to them for divine guidance (Figure 5.14). Throughout the years and around the world, dream interpreters and sometimes priests have been trusted to translate dream content into something meaningful for the dreamer. With the emergence of the discipline of psychology in the nineteenth century, the practice began to include psychologists as interpreters as well.

Sigmund Freud, an Austrian neurologist, believed dreams contained symbolic information requiring interpretation by an expert. He thought dream content would be too disturbing for the dreamer. For example, the dreamer may feel too ashamed to admit to a fantasy they are having, so the content has to come to the dreamer in symbols. (It was convenient for Freud that he, as a self-proclaimed expert, could charge people money for these interpretations.) According to his approach, dreams contain two categories of content: manifest and latent. Manifest content is the obvious material from the dream—the way the dreamer would describe the dream. Latent content is the hidden material that indicates the dreamer's secret desires and fears. These repressed feelings, once revealed in a dream analysis session, could be used to identify and treat a person's problems. There is great value in exploring and analyzing dream content, but Freud's particular method of dream interpretation has been put to the test by scientific studies that have shown that different experts using his technique will come up with vastly different conclusions about the meaning of the same dream. These studies suggest a lack of reliability in his approach to dream analysis.

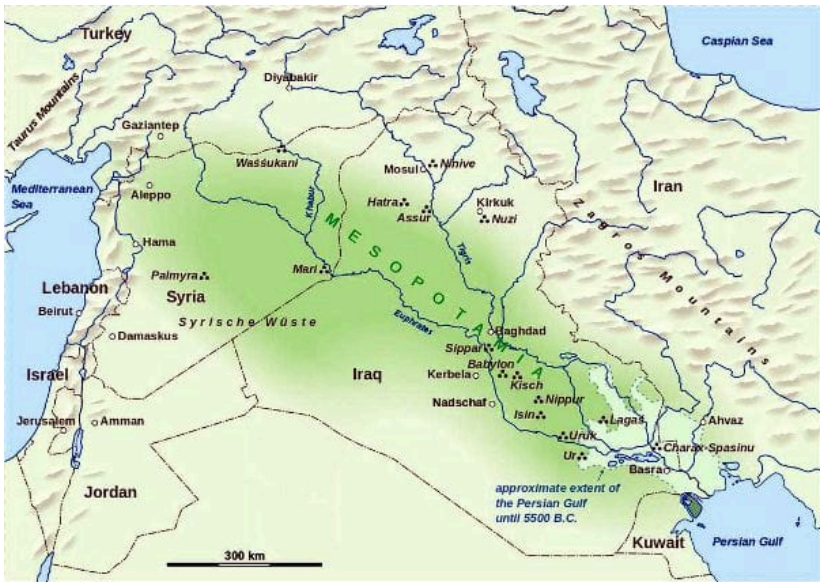


Figure 5.14 Mesopotamia

A psychiatrist colleague of Freud's, Carl Jung, disagreed with Freud on the need for dreams to be deciphered. Jung was convinced that the same symbol means something different to each person, so there was no use in trying to create a book of dream symbols that could be applied as a part of dream analysis. Instead, Jung thought our instincts convey wisdom to our rational mind via dreams. He said we were disconnected from nature and our instincts because of modern society, so we should use our dreams to reconnect and be transformed.

At around the same time that Freud and Jung were placing emphasis on the deep psychological meaning of dreams, Mary Whiton Calkins, a pioneer in psychology, was developing an opposing theory. As a part of her project at Clark University in Massachusetts, she examined over two hundred dream reports and concluded that dream content is closely related to recent experiences, almost like a related replay of the day's events and sensations, and that dreams do not contain hidden meaning. She said, "In fact, my study as a whole must be rather contemptuously set down by any good Freudian as superficially concerned with the mere 'manifest content' of the dream." Calkins must have been courageous not only for challenging conventional wisdom about dreams but because she was attending psychology seminars at Harvard with special permission, since women were not often allowed at the then all-male college. She even fulfilled all the requirements for a doctorate in psychology at Harvard, receiving high recommendations from professors, including William James, but the institution still refused to grant her the degree since she was a woman. However, she went on to Wellesley College, where she created a psychology lab—one of the first in the

nation—and became the first woman to serve as president of the American Psychological Association, soaring beyond Harvard's discriminatory policy.



ʻŌlelo Hawaiʻi (Language of Hawaiʻi)

ʻAumākua is Hawaiian for "ancestral guardian spirits" (Figure 5.15).



Figure 5.15 Green sea turtle

Dreams in Different Cultures

Looking around the world to consider diverse attitudes about dreams, a common theme is that many view dreaming as an opportunity to connect with the divine. In the Quran, one type of dream is called ru'ya. Rather than being created by the dreamer's mind, a ru'ya comes from God or the angels, and therefore a ru'ya is believed to have a purpose and meaning. There is a parallel in Hawaiian culture in that dreams from spirits are thought to have significance, in contrast to dreams the dreamer created, which are thought to be meaningless and pupule (crazy). In Hawaiian tradition, dreams are part of the bond between the spirits of those who are living and those who have passed. While a living person is dreaming, the spirit leaves the body through the luaʻuhane ("pit for the spirit," which is our tear duct) and travels to receive guidance from ʻaumākua (ancestral guardian spirits) and akua (gods).

Ancient Egyptians also used dreams to travel in their dream body and connect with gods and the spirits of the departed. People would visit the temple of a god or goddess, such as the goddess Isis (who has nothing to do with the Islamic State terrorist group) for dream interpretation or incubation (Figure 5.16). The dreamer might spend days preparing for dream incubation—a time to encourage dreams rich in guidance—by purifying themselves through ritualistic bathing, fasting, and praying before sleeping in a temple. After awakening from the dream, an oracle would be available to interpret the dream, which was especially valuable, since one of the strategies was to interpret dream content as the exact opposite of its literal meaning. The temples were also available for visitors who had slept and dreamt at home to consult with priests on dream interpretation.



Figure 5.16 Temple of Isis

Lucid Dreaming

Bringing awareness that we are dreaming into the middle of a dream, opens another world for learning, creativity, resolving trauma, and more. Lucid dreaming refers to the conscious realization that we are dreaming while still remaining asleep and deep in the dream. Taking things one step further, a person who is lucid dreaming can learn to control the content and progression of the dream. This control is particularly beneficial when working with persistent nightmares because dream scenery and outcomes can be resolved and transformed into something pleasant.

Here are some steps to take if you would like to learn to lucid dream:

1. Develop skill at remembering dreams and keep a dream journal. If remembering dreams is difficult for you, one strategy is to set an alarm for two hours before you are supposed to wake up in the morning. After the alarm goes off, remain in bed, eyes closed, and still. Try to recall the last feeling or thought in your mind. After you have that setting established, then go slowly backward in your mind, trying to recall any other impressions. In general, to help improve your dream recall, sleep at least eight hours, because then you will be more likely to awaken after a long REM period with the vivid dreams that are associated with that stage of sleep.
2. Take stock numerous times during the day to notice you are not dreaming. Increase your awareness of the nondreamlike qualities of your waking state: Every time you look at your phone or your watch, the color and shape remain the same. If you are talking to someone, they do not spontaneously turn into someone else. Doing this several times during the day trains your brain to notice the details that indicate the waking state. This task is in contrast to the next step.
3. Notice things about your dreams you do *not* experience in your waking state. The idea is to become intimately familiar with your dreams. During dreams, people *do* turn into other people spontaneously, and your phone or your watch *may* change shape or color if you look away and then look immediately back at them. You might also experience repeating elements, such as the appearance of a friend you have not seen in years or how you are able to fly if you run fast enough. For example, I am a surfer, and in my dreams, water is colossal and defies the laws of physics (Figure 5.17).
4. Combine the previous two steps to increase awareness of whether you are dreaming. Tell yourself ahead of time that if you see your friend from kindergarten or if you notice you can fly when you flap your arms, you will know you are dreaming.
5. Set an alarm to awaken in the middle of the night. After it goes off, keep your eyes closed and hold still, recalling the recent dream. Meditate on the dream and tell yourself you are going to fall back asleep into the same dream and you will be aware you are dreaming. Hopefully, you will drift into a pleasant lucid dream.



Figure 5.17 The wave

Conducting a Dream Group

This is best done in a group of four to six people seated in a circle but is still satisfying and productive in groups of different sizes (Figure 5.18). It is reassuring to state at the beginning that nothing shared in the group will be discussed outside of the group. Everyone is responsible for keeping the group on track with the steps, but it is helpful to designate a leader to take that responsibility. A different person takes over the role of leader when the group finishes all the steps and finishes the analysis of one dream before moving on to the next person's dream. Revelations about each dream's meaning will arise throughout the process, usually in pieces, and the interpretation discussion can continue without structure after the final step. The group should work on one dream at a time, going through all the steps and including the final open discussion about interpretation before moving on to the next person and their dream.



Figure 5.18 Stretching together before the discussion

Dreamer Tells the Group the Entire Dream

Everyone writes down the dream as brief notes in preparation to later read it back to the group.

Group Members Ask Questions

Go around the circle and ask the dreamer about their recent experiences (or those close to the time they had the dream, if it is not a recent dream). This is to establish emotional context. Sample questions might include the following:

> Anything on your mind, like a book or something else you read, a TV show or movie, a phone call? Anything going on at work/school? What's happened lately with friends/family?

Avoid asking "Why do you think you had _____ in your dream?" This is too direct. Rather, ask "Do you have any recent experiences with _____?"

Group Members Read the Dream Out Loud

Go around the circle, with each person reading a small part of the dream, in order, from the notes they created when the dreamer shared their dream in the first step. In this way, the dream is retold by group members with the dreamer listening. This often prompts the dreamer to recall more details from the dream.

During the retelling, the dreamer is encouraged to add in details and share thoughts or theories as they arise.

At any time, group members may ask additional open-ended questions, similar to those in the second step.

Group Member Projections

Go around the circle, with each group member projecting their ideas as if the dream were their own. For example,

> "If I dreamt about _____, it might mean _____."

Each group member is not meant to guess what it means to the dreamer; rather they are projecting what it would mean to themselves.

The dreamer shares any epiphanies as they come up during the projections. Even if the dreamer finds a projection completely unrelatable to their own experience, that is also helpful, as it rules out possibilities on the way to gaining insights.

Open and Unstructured Conversation

Freely discuss and continue to analyze the dream until the group is ready to move on to the next person and their dream. At the end, everyone thanks the dreamer for sharing.

1 Deirdre Barrett, ed., *Trauma and Dreams* (Cambridge, MA: Harvard University Press, 2001), 282.

2 R. D. Cartwright et al., "REM Latency and the Recovery from Depression: Getting Over Divorce," *American Journal of Psychiatry* 148, no. 11 (November 1991): 1530–35, https://doi.org/10.1176/ajp.148.11.1530.

3 Barrett, *Trauma and Dreams*, 282.

4 "National Suicide Prevention Lifeline," accessed on December 3, 2021, https://suicidepreventionlifeline.org/.

5 Erin J. Wamsley and Robert Stickgold, "Memory, Sleep, and Dreaming: Experiencing Consolidation," *Sleep Medicine Clinics* 6, no. 1 (March 2011): 97–108, https://doi.org/10.1016/j.jsmc.2010.12.008.

6 Antti Revonsuo and Katja Valli, "Dreaming and Consciousness: Testing the Threat Simulation Theory of the Function of Dreaming," *Psyche* 6 (October 2000), www.researchgate.net/publication/232499090_Dreaming_and_consciousness_Testing_the_threat_simulation_theory_of_the_function_of_dreaming.

7 "Faculty: Gina Poe," UCLA: Integrative Biology & Physiology, accessed June 6, 2021, https://www.ibp.ucla.edu/faculty/gina-poe/.

8 W. E. Burghardt Du Bois, "A Great Woman," *Crisis* 18, no. 3 (July 1919): 131, https://modjourn.org/issue/bdr512386/.

9 Ullrich Wagner et al., "Sleep Inspires Insight," *Nature* 427, no. 6972 (January 2004): 352–55, https://doi.org/10.1038/nature02223.

10 Magdalena J. Fosse et al., "Dreaming and Episodic Memory: A Functional Dissociation?," *Journal of Cognitive Neuroscience*

15, no. 1 (January 2003): 1–9, www.researchgate.net/publication/10896475_Dreaming_and_Episodic_Memory_A_Functional_Dissociation.

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14.5: Disorders of Sleep and Circadian Rhythms

Learning Objectives

By the end of this section, you should be able to

- Describe how damage to the retinal input pathway to the SCN can lead to problems with entrainment.
- Describe the difference between narcolepsy, non-24 sleep/wake disorder, and delayed sleep-wake phase disorder.
- Describe how an understanding of the timekeeping system helps one develop therapies for sleep or circadian disorders.

Inadequate or disrupted sleep is increasingly being recognized as a serious public health issue (Medic et al., 2017), impacting tens of millions of people in the U.S. alone. There are a wide variety of sleep disorders, which have physiological consequences on their own as well as exacerbating comorbid conditions. Disruption of sleep can come in a variety of forms, including inadequate duration, fragmentation of sleep periods, sleepiness at inappropriate times of day, and inability to fall asleep at a time that fits an individual's lifestyle. Disruption of sleep or circadian rhythms can be conditions on their own, or be comorbid with diseases or other disorders. Examples include Alzheimer's disease and Parkinson's disease (Ju et al., 2017). We have already heard about insomnia, so here we will expand on some other conditions.

Non-24 hour Sleep/wake Disorder

Normally, internal rhythms are synchronized to the external environment through the process of entrainment. An organism's internal clock naturally has a period that might be slightly less than or greater than 24 hours, but is kept synchronized to the 24-hour rotational period of the earth by photic cues present in the daily light/dark cycle. In humans, it is possible that internal (endogenous) rhythms do not get properly synchronized to the 24-hour day (exogenous rhythms). When this happens, the symptoms of non-24 hour sleep/wake disorder can manifest. Non-24 hour sleep/wake disorder is most commonly caused by blindness; in fact it occurs in greater than 50% of all blind people. This condition can occur in people that have blindness caused by the loss of the eye or damage to the retina and the photosensitive retinal ganglion cells (ipRGCs). This damage would eliminate any perception of light and darkness and would prevent such signals from reaching the SCN. If the clock can't set itself to daily cycles of light and darkness, then the body's internal clock remains cyclic but gradually drifts out of phase with the normal light and dark cycle of the day. This is referred to as free-running when the internal and external rhythms are not synchronized. As a result, a person may desire to sleep at 10:30pm, but their internal clock may interpret the time as 3:00pm. As such, they will find it difficult to sleep at bedtime and they may remain alert despite the clock time. If they have school, or a job, that requires them to be active at a consistent time each day, they may find that they are excessively tired due to sleep deprivation. Over the long term, such a condition can also lead to other health problems, including depression. Attempts to use alternative mechanisms to entrain, such as forced sleep schedules or exercise, are not very successful. Non-24 hour sleep/wake disorder is often treated with melatonin or drugs that act on melatonin receptors.

Narcolepsy

Narcolepsy is a sleep disorder in which people feel excessively sleepy at inopportune times throughout the day, even after adequate nocturnal sleep. People can fall asleep even while engaging in activities such as eating or driving, and the normal structure of sleep stages are altered, with an unusually rapid entry into the phase of REM sleep. Figure 15.18 shows polysomnograms of someone with narcolepsy during night sleep and daytime naps where you can see this rapid REM entry along with frequent night wakenings.

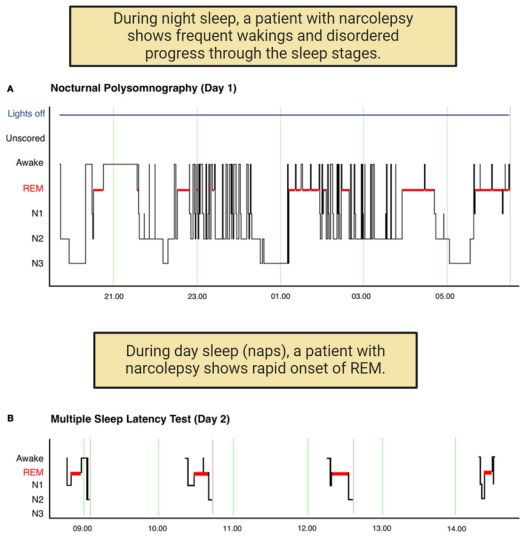


Figure 15.18 Hypnogram of narcolepsy Image credit: Hypnograms from: Rosch RE, Farquhar M, Gringras P and Pal DK (2016) Narcolepsy Following Yellow Fever Vaccination: A Case Report. Front. Neurol. 7:130. doi: 10.3389/fneur.2016.00130. CC BY

Narcolepsy is characterized by 1) excessive daytime sleepiness, 2) a reduction or loss of muscle tone which is known as cataplexy, 3) visual and auditory hallucinations at the time of waking or falling asleep, and 4) sleep paralysis which is a temporary period in which you cannot move or speak. This occurs at waking or onset of sleeping (Tisdale, Yamanaka, and Kilduff; 2021). Narcolepsy is often treated with stimulants and lifestyle adjustments.

One type of narcolepsy is caused by specific gene mutations that alter a neuropeptide called orexin or its receptor. Orexins, also known as hypocretins, are hypothalamic-specific peptides found in the lateral hypothalamus and surrounding nuclei, and have primarily excitatory effects on neurons. They appear to be important in gating the transition between the waking and sleep states, such that when the system is defective it becomes more difficult to sustain wakefulness. Evidence in support of the important role of orexins in this condition comes from animal studies. Mice missing the gene for orexins or its receptors show narcolepsy-like symptoms, and narcolepsy in dogs is the result of a mutation in the orexin receptor 2 gene (Hypocretin receptor 2).

Narcolepsy in Dogs

How did Doberman dogs help sleep research? Narcolepsy was first described in the medical literature in 1877 and 1880 (Mignot, 2014) but it wasn't until the 1980s that scientists began to identify molecular factors that may be playing a role. The Stanford University Sleep Disorders Clinic was studying people with narcolepsy and other diseases in the 1970s. At that time, researchers were also traveling to veterinary colleges and visiting with veterinarians in order to identify dogs that had narcolepsy. A colony of dogs including Beagles and Poodles was established but the researchers were unable to successfully breed additional dogs with the disease. In 1975, they acquired Dobermans that had episodes that resembled human narcolepsy. Furthermore, they were successful at breeding these animals and thus generated more dogs that also expressed narcoleptic-like symptoms (Mignot, 2014). Beginning in the late 1980s, the researchers applied numerous genetic techniques to identify candidate genes for narcolepsy in canines. Finally, in 1999, the team determined that canine narcolepsy was caused by a mutation in the hypocretin receptor 2 gene (HcrtR2). After learning that the hypocretin/orexin system is important to sleep regulation, additional studies were undertaken in human narcoleptic samples. A study in narcoleptic people found that 7 of 9 patients had undetectable levels of the peptide hypocretin 1 in their cerebrospinal fluid, (Nishino et al., 2000) and in samples of postmortem brain tissue, a loss of hypocretin/orexin was found in narcoleptic patients (Peyron et al., 2000). Thus, animal research, particularly in dogs, helped move the field of sleep research forward. A short video describing some of this work in dogs can be found here.

Delayed Sleep-Wake Phase Disorder (DSWPD)

In delayed sleep-wake phase disorder (DSWPD) an individual has difficulty falling asleep at socially appropriate and/or desired times. For example, a person might need to go to bed at 11 pm so that they can get enough sleep for school or work the following

day. However, an individual with DSWPD struggles to fall asleep or wake up at the correct times of day. Sleep in individuals with DSWPD is delayed 2-6 hours later than conventional bed times (Micic et al., 2016). The amount of sleep is compromised, and, when they do wake up, they have sleep inertia or decreased alertness and excessive daytime sleepiness. To diagnose this condition, a patient must keep a prospective sleep diary for at least 7 days and have a discussion with a doctor. In some cases, a patient may wear a wrist device that records the timing of their sleep schedule. This condition may be diagnosed as insomnia. However, if the individual is allowed to set their own sleep and wake schedule then they have no trouble falling asleep or staying asleep, they have normal sleep quality, and they have no daytime sleepiness (Meyer et al., 2022). Thus, it appears that an individual with DSWPD has a circadian rhythm that is delayed relative to the environmental light cycle. The prevalence of this disease is estimated between 0.17-1.54% in children and in adolescent and young adults this can increase to 3.3%-7.3%. However, only about 0.7% of middle aged patients are diagnosed with this disease (Micec et al., 2016). This increase in the number of teenagers that are diagnosed with DSWPD maps onto the "night owl" chronotype that begins to emerge at adolescence (Meyer et al., 2022). While an advancement in the timing of circadian rhythms typically occurs in individuals as they progress through adulthood, some people will retain this significant delay in the timing of their sleep onset. DSWPD can be treated by addressing the underlying biological clock. Specifically, treatments include melatonin, bright light therapy, and light avoidance through the use of blue light blocking glasses at specific times of the day. However, more treatments need to be developed.

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14.6: Parasomnias

Learning Objectives

- Explain NREM sleep arousal disorders (sleepwalking and night terrors)
- Explain REM sleep behavior disorder (RBD)

Parasomnias

A **parasomnia** is one of a group of sleep disorders in which unwanted, disruptive motor activity and/or experiences *during* sleep play a role. Parasomnias can occur in either REM or NREM phases of sleep. Parasomnias include NREM sleep arousal disorders of sleepwalking and sleep terrors, nightmare disorder, REM sleep behavior disorder, and restless leg syndrome.

Link to Learning

Listen to the following clip from NPR's "This American Life" episode "Fear of Sleep" to hear about some experiences of people with parasomnia sleep disorders and how it has affected their lives. Listen specifically to the 1:40–6:25 timeframe.

NREM Sleep Arousal Disorders

Sleepwalking



Figure 14.6.1: Sleepwalking and night terrors take place during non-REM sleep.

In **sleepwalking** or somnambulism, the sleeper engages in relatively complex behaviors ranging from wandering about to driving an automobile. During periods of sleepwalking, sleepers often have their eyes open, but they are not responsive to attempts to communicate with them. Sleepwalking most often occurs during slow-wave sleep, but it can occur at any time during a sleep period in some affected individuals (Mahowald & Schenck, 2000).

Historically, somnambulism has been treated with a variety of pharmacotherapies ranging from benzodiazepines to antidepressants. However, the success rate of such treatments is questionable. Guilleminault et al. (2005) found that sleepwalking was not alleviated with the use of benzodiazepines. However, all their somnambulistic patients who also suffered from sleep-related breathing problems showed a marked decrease in sleepwalking when their breathing problems were effectively treated.

Night Terrors

Night terrors result in a sense of panic in the sufferer and are often accompanied by screams and attempts to escape from

the immediate environment (Mahowald & Schenck, 2000). Although individuals suffering from night terrors appear to be awake, they generally have no memories of the events that occurred and attempts to console them are ineffective. Typically, individuals suffering from night terrors will fall back asleep again within a short time. Night terrors apparently occur during the NREM phase of sleep (Provini, Tinuper, Bisulli, & Lagaresi, 2011). Generally, treatment for night terrors is unnecessary unless there is some underlying medical or psychological condition that is contributing to the night terrors (Mayo Clinic, n.d.).

Nightmare Disorder



Figure 14.6.2: Nightmares occur during REM sleep.

Nightmare disorder is a sleep disorder characterized by frequent nightmares. The nightmares, which often portray the individual in a situation that jeopardizes his or her life or personal safety, usually occur during the REM stages of sleep (unlike night terrors, which occur during NREM sleep and do not follow a storyline in the way that nightmares do). Though most people have experienced at least one nightmare during their life, subjects with nightmare disorder experience them with a greater frequency.

Nightmares also have to be distinguished from bad dreams, which are less emotionally intense. Furthermore, nightmares contain more stories of aggression than bad dreams and more unhappy endings. Finally, people experiencing nightmares feel more fear than for bad dreams.

Comorbidity

Studies have reported that nightmare disorders were present in 50–70% of the cases for PTSD, in 17.5% for depression, in 18.3% for insomnia, in 16.7% for schizophrenia, and in 49% for borderline personality disorder.[1] For all psychiatric disorders taken together, nightmare disorders are present in 29.9% of the cases, a much bigger rate than for the general population, which is 2%-5%. Nightmare disorders can also be associated with sleep disorders such as night terrors, chronic insomnia, and sleep-disordered breathing. The presence of nightmares before a trauma would influence the severity of PTSD symptoms. Furthermore, having nightmares is linked to a significantly higher risk of attempting suicide and of death by suicide.

Nightmares also seem to be correlated with some personality factors. Studies found an association between anxiety, depression, and nightmares in insomnia, while only a small relationship was found in other populations. Neuroticism would be also link to nightmares. Nevertheless, people with a higher score of neuroticism could be better at recalling their nightmares during the self-report assessment, which could have an influence on this association.

Key Takeaways: NREM Sleep Arousal Disorders

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REM Sleep Behavior Disorder (RBD)

REM sleep behavior disorder (RBD) occurs when the muscle paralysis associated with the REM sleep phase does not occur. Individuals who suffer from RBD have high levels of physical activity during REM sleep, especially during disturbing dreams. These behaviors vary widely, but they can include kicking, punching, scratching, yelling, and behaving like an animal that has been frightened or attacked.



Figure 14.6.3: Restless leg syndrome commonly kicks in during the evening hours or during sleep, frustrating a person's ability to relax or get a good night's sleep.

The prevalence of REM sleep behavior disorder (RBD) is approximately 0.5%-1% in the general population and 2% in older adults. A large number of people are undiagnosed. The male to female diagnosis ratio is as high as 9:1. People with REM sleep behavior disorder (RBD) often have a comorbidity with mental health illness like a mood disorder and take anti-depressants or a history of traumatic brain injury.[2] This disorder is associated with a number of neurodegenerative diseases such as Parkinson's disease. In fact, this relationship is so robust that some view the presence of RBD as a potential aid in the diagnosis and treatment of a number of neurodegenerative diseases (Ferini-Strambi, 2011).

Clonazepam, an anti-anxiety medication with sedative properties, is most often used to treat RBD. It is administered alone or in conjunction with doses of melatonin (the hormone secreted by the pineal gland). As part of treatment, the sleeping environment is often modified to make it a safer place for those suffering from RBD (Zangini, Calandra-Buonaura, Grimaldi, & Cortelli, 2011).

Restless Leg Syndrome

A person with **restless leg syndrome** has uncomfortable sensations in the legs during periods of inactivity or when trying to fall asleep. This discomfort is relieved by deliberately moving the legs, which, not surprisingly, contributes to difficulty in falling or staying asleep. Restless leg syndrome is quite common and has been associated with a number of other medical diagnoses, such as chronic kidney disease and diabetes (Mahowald & Schenck, 2000). There are a variety of drugs that treat restless leg syndrome: benzodiazepines, opiates, and anticonvulsants.

Watch It

Watch this video to learn more about the risk factors, symptoms, and treatment options for those with RBD.

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

You can view the transcript for "REM Sleep behavior disorder" here (opens in new window).

Try It

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Dig Deeper: A Sleepwalking Defense?

On January 16, 1997, Scott Falater sat down to dinner with his wife and children and told them about the difficulties he was experiencing on a project at work. After dinner, he prepared some materials to use in leading a church youth group the following morning, and then he attempted to repair the family's swimming pool pump before retiring to bed. The following morning, he awoke to barking dogs and unfamiliar voices from downstairs. As he went to investigate what was going on, he was met by a group of police officers who arrested him for the murder of his wife (Cartwright, 2004; CNN, 1999).

Yarmila Falater's body was found in the family's pool with 44 stab wounds. A neighbor called the police after witnessing Falater standing over his wife's body before dragging her into the pool. Upon a search of the premises, police found blood-stained clothes and a bloody knife in the trunk of Falater's car, and he had blood stains on his neck.

Remarkably, Falater insisted that he had no recollection of hurting his wife in any way. His children and his wife's parents all agreed that Falater had an excellent relationship with his wife and they couldn't think of a reason that would provide any sort of motive to murder her (Cartwright, 2004).

Scott Falater had a history of regular episodes of sleepwalking as a child, and he had even behaved violently toward his sister once when she tried to prevent him from leaving their home in his pajamas during a sleepwalking episode. He suffered from no apparent anatomical brain anomalies or psychological disorders. It appeared that Scott Falater had killed his wife in his sleep, or at least, that is the defense he used when he was tried for his wife's murder (Cartwright, 2004; CNN, 1999). In Falater's case, a jury found him guilty of first degree murder in June of 1999 (CNN, 1999); however, there are other murder cases where the sleepwalking defense has been used successfully. As scary as it sounds, many sleep researchers believe that homicidal sleepwalking is possible in individuals suffering from the types of sleep disorders described below (Broughton et al., 1994; Cartwright, 2004; Mahowald, Schenck, & Cramer Bornemann, 2005; Pressman, 2007).

Try It

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Glossary

parasomnia: a group of sleep disorders where unwanted, disruptive motor activity, or other experiences during sleep play a role in their life

nightmare disorder: the sleep disorder that is characterized by frequent nightmares

night terrors: when a person experiences a sense of panic that is often accompanied by screams and attempts to escape from the immediate environment

REM sleep behavior disorder (RBD): when the muscle paralysis associated with the REM sleep phase does not occur

restless leg syndrome: the sleep disorder where a person has uncomfortable sensations in the legs during periods of inactivity or when trying to fall asleep.

1. Swart, Marijke L.; van Schagen, Annette M.; Lancee, Jaap; van den Bout, Jan (2013). "Prevalence of Nightmare Disorder in Psychiatric Outpatients". *Psychotherapy and Psychosomatics*. 82 (4): 267–268. doi:10.1159/000343590. ISSN 1423-0348. PMID 23735876. ↩
2. UpToDate. https://www.uptodate.com/contents/rapid-eye-movement-sleep-behavior-disorder. ↩

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- REM Sleep behavior disorder. **Provided by**: XpertDox. **Located at**: https://www.youtube.com/watch?v=2nc8jUOQA1c. **License**: *Other*. **License Terms**: Standard YouTube License

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14.7: Circadian Rhythms and Society

Learning Objectives

By the end of this section, you should be able to

- Describe how human biological rhythms of individuals intersect with societal demands and policies.
- Describe how deficits in sleep impact on different measures of human performance.
- Describe how knowledge of biological rhythms of diseases has influenced how we develop therapeutics (chronotherapeutics).

Our biological rhythms can influence our ability to work at certain times of day, the effectiveness of medication, our health, societal practices such as daylight savings time, and educational policies. Disruptions to rhythms such as sleep deprivation have consequences to our health and society.

Daylight Savings Time

In the United States, Canada, Australia, the United Kingdom and the European Union, there is a practice to advance clocks by 1 hour during the warmer months. In the US, we refer to this as Daylight Savings Time (DST) and the concept is to align human activities (and the time on their watch) to the presence of daylight. The change in clock time results in people waking up an hour earlier and conducting their work during an additional daylight hour during the summer. In the cooler months, we return the clocks back to Standard Time.

Recently there has been much debate about DST and its consequences on human health and society. There are numerous reports that in the days following the transition to DST, there is an increase in ischemic strokes and myocardial infarction compared to the week before the time change (Sipila et al., 2016). Following the DST change, there is also a 6% increase in fatal traffic accidents, with the largest increases occurring in the morning hours, although this impact on traffic has not been found in all studies (Fritz et al., 2020). There is also an increase in workplace injuries. The underlying cause for these health consequences and increased risk of accidents is likely due to sleep deprivation. The DST transition typically results in 40 min less sleep the following day and this results in a decrease in sleep quality, fatigue, and a decrease in vigilance. As a result of these negative consequences, there are position statements from the Society for Biological Rhythms and the American Academy of Sleep Medicine that support abolishing DST and maintaining our watches on Standard Time, based on the idea that this clock time best matches the time of day represented by the sun.

Shift Work

In our modern society, shift work has become a necessity and between 18 and 26% of the United States population (26-38 million people) participates in shift work. Shift work can be defined as any work that occurs outside the hours of 7 am to 6 pm. Shift workers are thus working at times when their internal biological clock says they should be sleeping. People work around the clock in transportation and airline travel, health care and medicine, security, hospitality, and manufacturing. Shift work schedules vary widely. Some people may be on a regular schedule even if those working hours occur at night or very early morning; some individuals may have a rotating schedule where they work night shifts in some weeks and day shifts in others. Shift workers are at a higher risk than the general population for a variety of diseases including obesity, metabolic disorder, cancer, insulin resistance, heart disease, and systemic inflammation.

The misalignment between scheduled work times and the internal rhythms may result in restricted sleep times. This sleep deprivation can result in consequences on the job including increased fatigue, decreased alertness, and cognitive decline. This can lead to an increase in mistakes and accidents that occur on the job. One estimate is that night shift workers have a 30-50% increase in the chance of having an accident in the workplace compared to workers on other shifts. Furthermore, night shift workers are significantly more likely to have a fatal accident at their place of employment compared to non-night shift workers (Harrison, 2013).

Endocrine rhythms are also misaligned in shift workers. Normally cortisol (a stress hormone) has a surge at the beginning of the

day and melatonin peaks at night during the dark. These rhythms in hormone secretions are reduced in amplitude or their pattern is altered in shift workers. In fact, there is no sign that these rhythms adapt to the shift work schedule and thus the peak of melatonin, even though reduced, still occurs during the night shift while the individual is at work.

In addition to sleep deprivation, another consideration of shift work is that meals are mistimed relative to internal rhythms. In simulated night shifts in a lab setting, in human studies with light at night, or in studies of a cross section of shift workers, there is increased insulin and disrupted leptin concentrations. The alterations in these hormones can even be detected when the blood is sampled on a day when the individual is not working. These critical hormones are associated with metabolism, glucose homeostasis, and food intake. In animal studies where they model circadian misalignment, these results are duplicated and mice with perturbed rhythms have an increased body weight and altered leptin concentrations. These disruptions to metabolism may be an important factor underlying the increased risk of metabolic disease and obesity that occurs in populations of shift workers.

Sleep Schedules and School Start Times for Adolescents

What time did you wake up to go to High School? What time did school begin? Chances are that your school started between 7 and 8:30 am. In fact, a report by the National Center for Education Statistics finds that over 80% of public high schools in the United States have a start time before 8:30 am (Sawyer & Taie, 2020). Despite having to wake up early for school, teenagers tend to fall asleep relatively late due to underlying circadian biology, homework requirements, job and sports schedules, and distractions from screens. These late bedtimes and early school times mean that teens are not getting enough sleep. A National Sleep Foundation study reveals 56% of teens age 15-17 get less than 7 hours of sleep a night (NSF, 2014). Teens with sleep deprivation experience higher rates of depression, obesity, and daytime sleepiness as well as having lower grades and reduced alertness in school. To increase the amount of sleep teens are getting, The American Academy of Pediatrics and The American Academy of Sleep Medicine recommend that school start times occur at 8:30 am or later. School districts that have adopted a later start time have seen benefits such as improved grades, increased attendance, and reduced tardiness (Dunster et al., 2018). In fact, one school county found that starting school 1 hour later resulted in a greater than 16% reduction in motor vehicle accidents involving teens (Danner and Phillips, 2008). In July of 2022, California passed a law requiring that middle schools start no earlier than 8 am and high schools start no earlier than 8:30 am. Florida passed a similar law in 2023 that will go into effect in 2026. This movement to delay school start times in order to improve student wellbeing is gaining traction. As of May 2023, an additional eight states are considering laws to move school start times later. To read more about these laws, read these press releases.

Long Term Impact of Sleep Deficits on Health

Chronic sleep deprivation refers to a state in which an individual has an insufficient amount of sleep over an extended period of time. According to the American Academy of Sleep Medicine, sleep deprivation becomes chronic when the period of insufficient sleep persists for more than three months. Chronic sleep deficiency is another term that includes sleep deprivation but also covers the case where sleep is fragmented or otherwise disrupted. Such conditions have a direct impact on both cognitive and physical performance and can contribute to an elevated risk of a wide variety of disorders from diabetes to elevated pain sensitivity to several mental health disorders. Fortunately, many types of sleep disorders that cause sleep deprivation or insufficiency are treatable through behavioral interventions.

Naps as Therapy

One theme of this chapter is how disruptions to your circadian clock or sleep cycle can have a negative impact on your health. Can napping during the day alleviate some of these issues? There is a change in the amount of napping which occurs across the lifespan and a change in the type of sleep that occurs during the nap. In infants, naps resemble nighttime sleep because they both contain REM sleep. Naps in young children consist of more non-REM sleep than REM sleep. In young adults, longer naps will contain both REM and non-REM sleep; however naps in older adults consist of lighter sleep stages with a bout of slow wave sleep (non REM stage 3). Napping can be done to counteract sleepiness or recuperate from a reduction in sleep, in anticipation of extended sleep loss such as might occur with a night shift worker, or just for enjoyment or boredom.

There are many documented benefits to naps, with the first being that napping reduces the homeostatic sleep pressure that accumulates with wakefulness. Individuals that nap have both objective and subjective improvement in alertness, enhanced cognition, improved short term memory, and improved mood. The best time to take a nap is in the early afternoon, between 1 and 3 pm (Dutheil et al., 2021). Naps later than this can interfere with your ability to fall asleep that evening. There is an effect of nap

duration on cognitive function after waking. If you take a nap in the afternoon following a normal night of sleep then a short nap is beneficial. Specifically, naps 10-30 min long result in an immediate improvement in alertness and performance on cognitive tasks upon awakening and this effect can last for up to 2 hours (Leong et al., 2023). These shorter naps typically contain stage 1 and stage 2 non-REM sleep. However, longer naps, particularly those that contain slow wave sleep (stage 3 non-REM sleep), result in an initial decrease in alertness that is described as sleep inertia. This grogginess upon waking is associated with a decline in motor performance, cognition, and mood and may last between 30 and 60 minutes. However, after this period passes, there is an increase in alertness and a decrease in fatigue that lasts for several hours. Additionally, longer naps may be more beneficial in individuals that are experiencing sleep deprivation.

Sleep Hygiene and College Students

Being a young adult is an exciting and stressful time with educational, extracurricular, work, and social opportunities. As a result, it may be hard to find the time to get everything accomplished without sacrificing some sleep. In fact, college-aged individuals require about 8-9 hours of sleep a night but between 70-96% report getting less than 8 hours a night. Around 50% of college students report excessive daytime fatigue and sleepiness at least 3 times a week. This sleepiness can be caused by acute lapses in sleep ("all nighters") or chronic partial sleep deprivation. Partial sleep deprivation occurs when students routinely get less sleep than they require, for example college students report getting between 5.7-6.5 hours a night.

What is the consequence of eliminating sleep that you need? It's unlikely that the occasional all-nighter will have significant consequences, but being chronically tired and not getting enough sleep can be detrimental to academic success and mood. For example, students that had a total sleep time of 9 or more hours had an average GPA of 3.24 whereas those with 6 hours or less a night had an average GPA of 2.74 (Kelly, Kelly, and Clanton, 2001). In other studies, sleep patterns played a larger role than total sleep time. Specifically, later bedtimes or later wake up times were associated with lower GPAs (Trockel, Barnes, and Egget, 2000). There is also a relationship between irregular sleep patterns, poor sleep quality and increased anxiety symptoms in university students. In a study of 462 university students, insomnia severity was associated with anxiety severity (Choueiry et al., 2016). Furthermore, when colleges have wellness classes or incentive programs that improve the amount of sleep and sleep schedule, anxiety decreases, and grades improve or stay the same, indicating that students can increase their sleep while maintaining their same GPA.

You can take daytime and evening steps to promote healthy sleep. This is called sleep hygiene. These steps include having a consistent bedtime and wake time, resisting the use of screens in the hour before bed as the blue light emitted by your phone can disrupt your circadian clock, having a period of time before bed where you wind down and relax, and maintaining a dark and cool bedroom. If you have a roommate, this can be difficult but you can try earplugs and eye masks to help. It is also advised that you are careful with alcohol and caffeine use. Alcohol can help you fall asleep but disrupts your restorative sleep, and studies show that caffeine use even 6 hours before bedtime causes problems with sleep quality.

Social Jetlag

As we have described in a previous section, people can exhibit chronotypes such as "night owl" or "lark". These preferences for specific times for sleep/activity can be in conflict with external timing requirements such as work and school. Social jetlag occurs when an individual fits their sleep/wake schedule to match their requirements during the week, but then they allow their internal clock to dictate their sleep/wake schedule on weekends (Figure 15.19). There is a discrepancy between the schedule of sleep during the week and weekend. For example, a college student may get up at 9 am and go to bed at midnight Sunday-Thursday. But on Friday and Saturday they may stay awake until 2 am and get up at 11 am. When Monday morning rolls around, the student would have to readjust their schedule again and wake up 2 hours sooner than they would prefer, as if they were adapting to a new time zone. This phenomena can be worse in night owl chronotypes, as they may experience difficulty falling asleep early, yet they still have to wake up early for school or work.

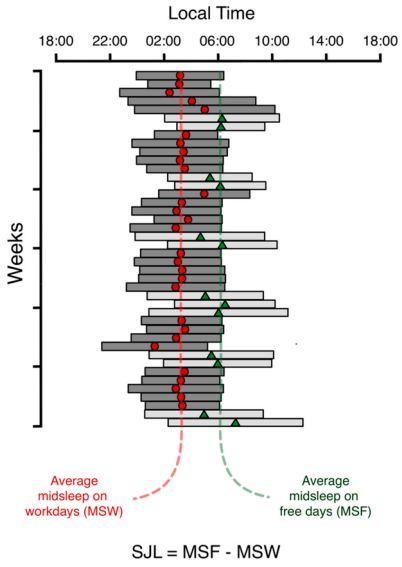


Figure 15.19 Social jet lag Sleep timing varies by days of the week in humans. Image credit: Roenneberg et al., 2019, "Chronotype and social jetlag: A (self-) critical review." Biology, 8(3), 54. https://doi.org/10.3390/biology8030054. CC BY 4.0

Social jet lag can generate poor sleep quality and chronic partial sleep deprivation. As a result, people experiencing social jet lag have reduced attention, increased fatigue, and poor performance at school or work. A variety of studies also find that people experiencing social jet lag have an association with obesity, diabetes, and depression as well as risk factors for metabolic disorder such as high total cholesterol and triglycerides (Castilhoa Beauvalet et al., 2017). As described above, getting healthy sleep on a consistent schedule is key to helping correct social jet lag.

Chronotherapeutics

Chronotherapy, also called chronomedicine, is based on the idea that medicine may be more effective, have fewer side effects, and have higher tolerability, if it is administered at an optimal time of day matching the rhythms of the disease. As we have emphasized throughout this chapter, physiology has many daily rhythms as seen in biochemical reactions, gene changes, and hormone secretion patterns. It makes sense that medication should be administered at a time of day when disease symptoms are expressed at their highest levels. Furthermore, there is evidence that people with consistent and strong circadian rhythms are more likely to have better health than those with rhythms that are disrupted or have low amplitude rhythms. Strengthening rhythms in sleep/wake cycles, mealtimes, or endocrine secretion patterns such as melatonin signaling can reduce health problems and improve health.

Asthma and Bronchodilators

Asthma is a chronic disease characterized by difficulty breathing caused by inflammation and constriction of the airways. Up to 75% of asthma sufferers have "nocturnal asthma" where they report having more significant symptoms during the nighttime hours. Sometimes these symptoms cause disruptions to sleep. Studies of asthma sufferers in the lab reveals that there is a circadian rhythm in pulmonary function, airway resistance, and airway inflammation independent from the influence of sleep, posture, or locomotor activity. Further, there is a daily rhythm in discomfort which peaks at night which corresponds to the daily rhythm in the use of rescue-based inhalers at this time (Litinski, Scheer, and Shea, 2009). In addition to rescue inhalers, people with asthma may also be prescribed a once-daily use of inhaled corticosteroids to help with airflow. In a large meta-analysis of over 1200 patients, it was found that use of this treatment at night led to better pulmonary function compared to use of it in the morning (Song, Park, and Lee, 2018). Asthma is just one example of how therapies for ailments can be optimized by basing the timing of delivery on biological rhythms.

Cancer Therapies

Circadian rhythms have a bidirectional relationship with the development and growth of cancers. Epidemiological studies in humans and laboratory studies using rodent models have linked circadian disruptions to cancer. In fact, this link of disruption of

your clock to cancer prevalence led to the World Health Organization to declare shift work as a "likely carcinogen". In humans, chronic jet lag, shift work, or exposure to light at night are associated with an increased risk for many types of cancer including colon, breast, prostate, and lung. Humans with polymorphisms in the clock genes *Clock* and *Bmal1* have increased susceptibility to certain types of cancers. In animal studies, circadian rhythm disruption can be induced by lesioning the SCN or putting animals in chronic jet lag conditions. When these mice are inoculated with cancer cells that develop into a tumor, the tumor grows both faster and larger in the animals with circadian perturbations. Similarly, mice with mutations in clock related genes also have an increased susceptibility to spontaneous cancers and radiation induced cancers.

Treatment of cancer can be improved by incorporating circadian rhythms into the therapy. Patients that maintain more regular daily patterns of activity have a longer survival rate, and respond to drug treatment better than those with disrupted daily rhythms. In patients with colorectal cancer, time of day of administration of the chemotherapy drug influenced the efficacy of the treatment as well as the ability of the patient to tolerate high doses of the drug (Levi et al., 1994). Interestingly, the time of day of drug effectiveness varies for each drug. Understanding circadian biology of the patient, tumor cell type, and medication effectiveness can be used to tailor cancer therapy that has the maximal anticancer effects, the lowest side effects, and a resultant increase in survival rates.

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15: LATERALIZATION, LANGUAGE, AND THE BRAIN

15.1: Foundations of Language
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15.1: Foundations of Language

Learning Objectives

1. List some of the adaptive functions of animal communication; how do these compare to the adaptive functions of human language
2. Explain why memory is a component of language function
3. List brain structures involved in various types of memory
4. List the stages of speech production during the first 12 months after birth
5. Describe Alzheimer's Disease and the Autism Spectrum Disorders and brain changes associated with each

Overview

In this section, we examine communication in other species, the role of memory in language function, language acquisition, and two disorders, Alzheimer's Disease and Autism, both of which involve language dysfunction as well as other alterations of function.

Communication in Animals

by Kenneth A. Koenigshofer, Ph.D., Chaffey College

Humans are highly social animals, along with many other social species, including social mammals such as wolves, lions, elephants, baboons, chimpanzees, gorillas, water buffalo, dolphins, sea lions, and whales, and social insects such as bees, ants, and wasps. Living in groups has many adaptive advantages such as group hunting, predator defense, food gathering and other forms of cooperation, helping, and, in some mammals such as the mothers in a lion pride, even cooperative nursing of the young within their social group.

Contrast social species with species which are solitary, such as tigers which have no interactions with other tigers except during mating, and when females nurse and care for their offspring. Although both lions and tigers are big cat species, they are highly dissimilar in regard to social life. One reason for this vast difference between lions and tigers is that lions evolved into social creatures because they lived in the open plains of the savannah where group hunting was far more successful than solitary hunting. By contrast, tigers evolved in dense forest where plenty of cover favored quiet stalking and stealth, best accomplished by solitary hunting strategies.

It will come as no surprise to you that animals that live in groups communicate with one another, in part to coordinate their activities, to strengthen social bonds within the group, to warn of danger, to share the location of a food source, to express emotions, to attract mates, to reinforce dominance hierarchies, and so on.

Animal communication can involve any sensory modality. For example, lions of the same group who have been separated greet one another by rubbing their bodies together as they walk past one another. Humans use touch to express affection and sometimes sexual interest. Chimpanzees, like humans, hug and even kiss one another to express affection. Many species mark territory by using the smell of their urine (think of dogs, but male lions do the same, and some species of monkey have scent glands that release a smelly substance on the leaves of the trees they move through). Many animals use visual signals such as bright coloration in many species of birds and tropical fish; other species use visual gestures and facial expressions. For example, chimpanzees raise a hand high above their head and shake it vigorously to signal their displeasure and to threaten other chimps. Bees communicate the direction and distance to a food source by their waggle dance. Wolves and dogs, lions, tigers, primates, and many other species bare their teeth and lower their head as a visual signal communicating threat. Finally, many species utilize auditory means of communication such as screeches, howls, croaks, barks, songs (birds and whales), clicks (dolphins), screams, crying (visual and auditory cues) and laughing in humans, and many other sounds such as those made by crickets or other insects.



Figure 15.1.1: Here a chimpanzee uses visual and auditory signals to communicate threat. A coyote howls to call its pack. (Images from Wikimedia Commons; (left) File:Chimpanzee, Kibale, Uganda (15244558084).jpg; https://commons.wikimedia.org/wiki/F...244558084).jpg; by Rod Waddington; licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (right) File:Howl (cropped).jpg; https://commons.wikimedia.org/wiki/F..._(cropped).jpg; by USFWS Mountain-Prairie; licensed under the Creative Commons Attribution 2.0 Generic license).

All of these various forms of communication use sensory signals received by others who interpret their meaning. However, none have the special properties of human language. Human languages use arbitrary symbols (words do not have innate meaning but acquire meaning by learning; there are approximately 600,000 words in English), and words can be strung into sentences by rules of grammar which permit an infinite number of different and complex meanings to be communicated, a situation which linguists sometimes refer to as "the infinite use of finite means," an infinite number of sentences can be constructed from a finite number of words using a finite number of grammatical rules. Although some animals such as chimpanzees, bonobo chimpanzees, and gorillas have been taught American Sign Language with interesting results, the full bloom of human language appears to require specialized brain circuitry present only in specific, although somewhat widespread, areas of the human brain.

Memory and Language

"You need memory to keep track of the flow of conversation" (Goldstein, 2005).

The interaction between memory and language does not seem very obvious at first, but this interaction is necessary when trying to have a conversation. Memory is also required to know and recall the meanings of words.

This is not a simple process which can be learned within days. In childhood everybody learns to communicate, but it is a process lasting for years.
The connection between memory and language becomes most obvious when an impairment occurs when certain brain areas are damaged.

Basics of Memory and Language Interactions

Memory

Explicit memory, also known as declarative, can be subdivided into semantic and episodic memory. Procedural memory and priming effects are components of the implicit memory.

Table 14.9.1. Brain regions important in memory and language and their interaction.

Brain regions	Memory
Frontal lobe, parietal lobe, dorsolateral prefrontal cortex	Short-term Memory/ Working Memory
Hippocampus	Short-term Memory → Long-term Memory
Medial temporal lobe (neocortex)	Declarative Memory
Amygdala, Cerebellum	Procedural Memory

Language

Language is an essential system for communication which highly influences our life. This system uses sounds, symbols and gestures for the purpose of communication. Visual and auditory systems are the entrance-pathway for language to the brain. The motor system is responsible for speech and writing production, the exit-pathway for language. In this sense, language processing in the brain (like other types of cognition) occurs between processing by the sensory and motor systems. Most of the knowledge about brain mechanism for language comes from studies of language deficits resulting from brain damage. Though there are about 10,000 different languages and dialects in the world, all of them express the subtleties of human experience and emotion.

Acquisition of language

A phenomenon which occurs daily and in everybody's life is the acquisition of language. Theorists like Catherine Snow and Michael Tomasello think that acquisition of language begins at birth. Babbling in the first six months of life activates brain regions later involved in speech production.

The ability to understand the meaning of words begins before the first birthday, and progresses faster than the ability to speak. Babies show comprehension of more complex sentences, even though they may still be in the one-word stage of speech development.

The different stages of speech production in the first year of life are listed in the table below.

Age	Stage of Acquisition	Example
6th month	Stage of babbling: - systematic combining of vowels and consonants	
7th – 10th month	Stage of repetitive syllable-babbling: - higher part of consonants → paired with a vowel – monosyllabic reduplicated babbling	da, ma, ga mama, dada, gaga
11th – 12th month	Stage of variegated babbling: - combination of different consonants and vowels	bada, dadu
12th month	Usage of first words - : - prephonological → consonant-vowel (-consonant)	car, hat

Researchers like Charlotte Bühler (1928), a German psychologist, think that speaking the first word occurs around the tenth month, whereas Elizabeth Bates et al. (1992) proposed a period between eleven and 13 months. The one-word stage described above can last from two to ten months. Until the second year of life a vocabulary of about 50 words develops, four times more than the child

actually uses in speech. Two thirds of the language processed is still babbling. After this stage of learning, vocabulary increases rapidly. The so-called vocabulary spurt causes an increment of about one word every two hours. From that point on children learn to have fluent conversations with a simple grammar usually containing some errors. Over the first three years of life, the length of sentences and the grammatical output improves.

Children first learn to conjugate verbs and to decline nouns using regular rules. To produce irregular forms is more difficult, because they have to be learned and stored in Long-term memory one by one. The observation of speech is important for acquisition of grammatical skills. Around the third birthday the complexity of language increases exponentially.

Disorders

Alzheimer's Disease

Discovered in 1906 by Alois Alzheimer, this disease is the most common type of dementia. Alzheimer's is characterized by symptoms such as loss of memory, loss of language skills and impairments in skilled movements. Additionally, other cognitive functions such as planning or decision-making which are connected to the frontal and temporal lobe can be also be impaired. The correlation between memory and language in this context is very important because the two work together in order to establish and maintain conversations. When both are impaired, communication becomes a difficult task. People with Alzheimer's have reduced working memory capability, so they cannot keep in mind all of the information they have heard during a conversation. They also forget words which they need to denote items, express their desires, and to understand what they are told. Affected persons also change their behavior; they become anxious, suspicious or restless and they may have delusions or hallucinations.

In the early stages of the disorder, affected persons become less energetic and may suffer little loss of memory. They are still able to dress themselves, to eat and to communicate enough to get by. Middle stages of the disease are characterized by problems of navigation and orientation. Affected persons may not be able to find their way home or they may even forget where they live. In the late stages of the disease, the patients' ability to speak, read and write is severely impaired. They are no longer able to denote objects and to talk about their feelings and desires. So their family and the nursing staff have great difficulty finding out what the patients want to tell them. In the end-state, persons with Alzheimer's disease do not show any response or reaction. They lie in bed, have to be fed and are totally helpless. Most of them die after four to six years following diagnosis, although the disease can last from three to twenty years. It is sometimes difficult to distinguish Alzheimer's from other related disorders. Only after death when observing the shrinkage of the brain can one definitely diagnose Alzheimer's disease.

In the Alzheimer brain:
· The cortex shrivels up, damaging areas involved in thinking, planning and remembering.
· Shrinkage is especially severe in the hippocampus, which, as discussed in earlier modules, plays a key role in formation of new memories.
· Ventricles (fluid-filled spaces within the brain) grow larger as the surrounding brain tissue dies away.

Long before the first symptoms appear, nerve cells that store and retrieve information have already begun to degenerate. There are two theories about the causes of Alzheimer's disease. The first describes plaques, protein fragments, which impair the synaptic connections between nerve cells. They arise when little fragments released from nerve cell walls associate with other fragments from outside the cell. These combined fragments, the plaques, attach to the outside of nerve cells and destroy the synaptic connections. Then the nerve cells start to die. The second theory explains that tangles limit the functions of nerve cells. They are twisted fibers of another protein that form inside brain cells and destroy a vital cell transport system made of proteins. But scientists have not yet found out the exact role of plaques and tangles.

- Alzheimer tissue has many fewer nerve cells and synapses than a healthy brain.
- Plaques, abnormal clusters of protein fragments, build up between nerve cells.
- Dead and dying nerve cells contain tangles, which are made up of twisted fibers of another protein.

Alzheimer's progress is separated into three stages: In the early stages (1), tangles and plaques begin to evolve in brain areas where learning, memory, thinking and planning takes place. This may begin 20 years before diagnosis. In the middle stages (2), plaques and tangles start to spread to areas for speaking and understanding speech. The sense of where your body is in relation to objects around you is impaired. This may last from 2–10 years. In advanced Alzheimer's disease (3), most of the cortex is damaged, so that the brain starts to shrink seriously and cells begin to die. The people affected lose their ability to speak and communicate and they do not recognize their family or people they know. This stage may generally last from one to five years.

Today, more than 18 million people suffer from Alzheimer's disease. Alzheimer's is often only related to older people. Five percent of the people older than 65 years and fifteen to twenty percent of the people older than 80 years suffer from Alzheimer's. But people in their late thirties and forties can also be affected by this heritable disease. Though heritable, the probability of getting Alzheimer's when one's parents suffer from the typical older-generation-Alzheimer's is not very high.

Autism

Autism is a condition of neurodevelopment, which causes neurodevelopmental disorders in several ways. For more than a decade, autism has been studied in the context of Autistic Spectrum Disorders, including mild and severe autism, as well as Asperger's syndrome. Individuals with autism, for example, have restricted perception and problems in information processing. The often associated intellectual giftedness (savants) only holds for a minority of people with autism; most possess normal or below average intelligence.

There are different types of autism:

- Asperger's syndrome – usually arising by the age of three years
- infantile autism – arising between nine and eleven months after birth

Two different types of infantile autism are low functioning autism (LFA) and high functioning autism (HFA). LFA describes children with an IQ lower than 80, while HFA refers to those with an IQ higher than 80. The disorders in both types are similar, but they are more severe in children with LFA.

The disorders are mainly defined by the following symptoms:

1. the inability for normal social interaction, e.g. normal relations with other children, perhaps related to impairments in Theory of Mind (TOM), the ability to "read/understand the minds" and intentions of others
2. the inability for ordinary communication, e.g. disorder of spoken language/idiosyncratic language
3. stereotypical behavior, e.g. stereotypical and restricted interests with an atypical content

To investigate the inability of children with autistic disorder to manage normal communication and language, the University of Pittsburgh performed experiments to provide possible explanations for some of their symptoms. Sentences, stories or numbers were presented to children with autism and to normal children. The researchers concluded that the disorders in people with HFA and LFA are caused by an impairment in declarative memory. This impairment leads to difficulties in learning and remembering sentences, stories or personal events, whereas the ability to learn numbers is still available. It has been shown that these children are not able to link words they have heard to their general knowledge, thus the words are only partially learned, often with an idiosyncratic meaning. This may in part explain why LFA and HFA affected children differ in their way of thinking from normal children. It is often difficult for them to understand others and vice versa (perhaps due to deficits in TOM or one or more social processing modules in the brain). Furthermore scientists believe that the process of language learning depends on an initial vocabulary of fully meaningful words. It is assumed that these children do not possess such a vocabulary, thus their language development is impaired. In a few cases the acquisition of language fails completely, therefore in some cases the children are not able to use language in general. The inability to learn and use language may be a consequence of an impairment of declarative memory. This might also cause a low IQ because much of the process of human learning is language-mediated. In HFA the IQ is not significantly lower than the IQ of normal children. This milder form of autism correlates well with their better understanding of word meanings.

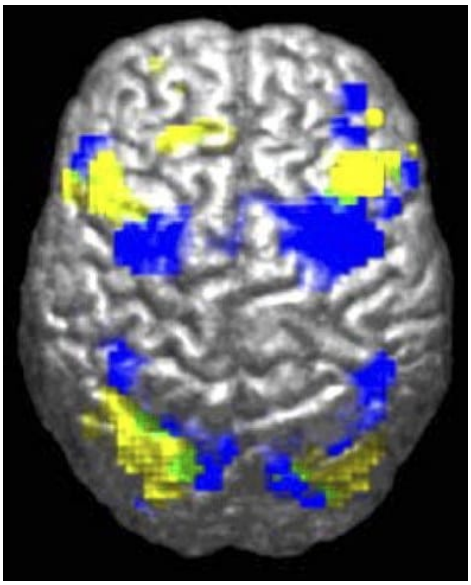


Figure 15.1.2: fMRI-derived image of difference between brains of autistic and control groups. Activation during visuomotor coordination: Autism Group [yellow], Control Group [Blue], Overlap (both groups) [green]. Even researchers who study autism can display a negative bias against people with the condition. For instance, researchers performing functional magnetic resonance imaging (fMRI) scans systematically report changes in the activation of some brain regions as deficits in the autistic group — rather than evidence simply of their alternative, yet sometimes successful, brain organization. (Image and caption from Wikimedia Commons; File:Powell2004Fig1A.jpeg; https://commons.wikimedia.org/wiki/F...2004Fig1A.jpeg; by Ralph-Axel Müller, Modifications made by Eubulides; licensed under the Creative Commons Attribution 2.5 Generic license. Laurent Mottron, *Changing perceptions: The power of autism* ; Nature 479, 33–35 (03 November 2011) ; doi:10.1038/479033a En ligne : 2011-11-02).

The causes of autism are not yet known. It is still not clear whether the Spectrum Disorders are caused by genetic abnormalities, or non-genetic neurological factors such as brain damage or biochemical abnormalities. One possibility is that during brain development prior to birth new neuron migration and/or neural pruning may be impaired leading to atypical brain circuit formation (Koenigshofer, 2011, 2016).

References

Goldstein, E. G. (2005). *Cognitive Psychology - Connecting Mind, Research, and Everyday Experience*, p. 137, Thomson Wadsworth.

Pinker, S. *The Language Instinct*, p.269f

Koenigshofer, K.A. (2011, 2016 revised e-book edition). *Mind Design: The Adaptive Organization of Human Nature, Minds, and Behavior*. Pearson Learning Solutions, Boston.

Resources

Books

Steven Pinker: The Language Instinct; The Penguin Press, 1994, ISBN 0140175296
Gisela Klann-Delius: Spracherwerb; Sammlung Metzler, Bd 325; Verlag J.B.Metzler; Stuttgart, Weimar, 1999; ISBN 3476103218
Arnold Langenmayr: Sprachpsychologie - Ein Lehrbuch; Verlag für Psychologie, Hogrefe, 1997; ISBN 3801710440
Mark F. Bear, Barry W. Connors, Michael A. Paradiso: Neuroscience - Exploring The Brain; Lippincott Williams & Wilkins, 3rd edition, 2006; ISBN 0781760038

Links

http://de.Wikipedia.org/wiki/Ged%C3%A4chtnis

http://en.Wikipedia.org/wiki/Memory
http://www.cogsci.rpi.edu/CSJarchive/proceedings/2006/docs/p822.pdf
http://www.psychology.uiowa.edu/faculty/gupta/pdf/gupta.brain+lang2003.pdf
http://www.cogsci.rpi.edu/CSJarchive/1980v04/i03/p0243p0284/MAIN.PDF
http://www.quarks.de/gedaechtnis/gedaechtnis.pdf
http://www.alz.org/alzheimers_disease_alzheimers_disease.asp
http://en.Wikipedia.org/wiki/Autism
http://www.apa.org/journals/releases/neu20121.pdf
http://www.esrc.ac.uk/ESRCInfoCentre/Plain_English_Summaries/knowledge_communication_learning
/index22.aspx?ComponentId=17702&SourcePageId=11748

Summary

Although forms of communication exist even in species which are primarily solitary, social species communicate more frequently with other members of their species. Animal communication can utilize signals from any of the sensory modalities. Vocal communication is common in many species, however only our species has developed a form of communication with the complexity of human language. Language use requires memory. Different areas of the brain are involved in different types of memory. Normal children begin to comprehend language before the end of their first year. Language expression begins with several stages of babbling typically followed by the production of first words by a year old. Both Alzheimer's and Autism are disorders of the brain that involve language difficulties. fMRI studies reveal that persons with autism have brain organization different from that in persons without autism.

Attributions

"Communication in Animals" is written by Kenneth A. Koenigshofer, Ph.D., Chaffey College

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15.2: Handedness, Language, and Brain Lateralization

Learning Objectives

1. Describe hemispheric asymmetries
2. Describe the role of testosterone and stress in brain lateralization and handedness
3. Describe sex differences in brain lateralization and suggest an explanation
4. Describe lateralization in other species and briefly discuss implications for possible origins of human brain lateralization

Handedness, testosterone, and lateralization for language appear to be related. Approximately 10% of people are left-handed and 2/3 of left-handers are male. 95% of right handed men and women have language lateralized to the left hemisphere. The greatest asymmetries are in the posterior language areas including the temporal planum and angular gyrus. If the left hemisphere is damaged or defective prenatally the right hemisphere can acquire language functions.

Handedness, Language, and Lateralization

The brain's anatomical asymmetry, its lateralization for language, and the phenomenon of handedness are all clearly interrelated, but their influences on one another are complex. Though about 90% of people are right-handed, and about 95% of right-handers have their language areas on the left side of their brains, that still leaves 5% of right-handers who are either right-lateralized for language or have their language areas distributed between their two hemispheres. And then there are the left-handers, among whom all of these patterns can be found , including left-lateralization.

Some scientists suggest that the left hemisphere's dominance for language evolved from this hemisphere's better control over the right hand. The circuits controlling this "skillful hand" may have evolved so as to take control over the motor circuits involved in language. Broca's area, in particular, is basically a premotor module of the neocortex and co-ordinates muscle contraction patterns that are related to other things besides language.

Brain-imaging studies have shown that several structures involved in language processing are larger in the left hemisphere than in the right. For instance, Broca's area in the left frontal lobe is larger than the homologous area in the right hemisphere. But the **greatest asymmetries** are found mainly in the **posterior language areas**, such as the **temporal planum and the angular gyrus**.

Two other notable asymmetries are the larger protrusions of the frontal lobe on the right side and the occipital lobe on the left. These protrusions might, however, be due to a slight rotation of the hemispheres (counterclockwise, as seen from above) rather than to a difference in the volume of these areas. These protrusions are known as the **right-frontal and left-occipital petalias** ("petalias" originally referred to the indentations that these protrusions make on the inside of of the skull).

The **structures involved in producing and understanding language** seem to be laid down in accordance with **genetic instructions** that come into play as **neuronal migration** proceeds in the **human embryo**. Nevertheless, the two hemispheres can remain just about equipotent until language acquisition occurs. Normally, the language specialization develops in the left hemisphere, which matures slightly earlier. The earlier, more intense activity of the neurons in the left hemisphere would then lead both to right-handedness and to the control of language functions by this hemisphere. But **if the left hemisphere is damaged or defective**, **language** can be **acquired by** the **right hemisphere**. An **excess** of **testosterone** in newborns due to stress at the time of birth might well be one of the most common causes of **slower development in the left hemisphere** resulting in **greater participation by the right.**

This hypothesis of a central role for testosterone is supported by experiments which showed that **in rats, cortical asymmetry** is **altered** if the rodents are injected with **testosterone at birth**. This hormonal hypothesis would also explain why **two-thirds of all left-handed persons are males**.

Interindividual variations, which are essential for natural selection, are expressed in various ways in the **human brain**. **Volume and weight can vary by a factor of two** or even more. The **brain's vascular structures are extremely variable**; the deficit caused by an obstruction at a given point in the vascular system can vary greatly from one individual to another. At the macroscopic anatomical level, the **folds and grooves in the brain also vary tremendously from individual to individual**,

especially in the areas associated with language . **Variability in** the language areas can also be observed at the microscopic level, for example, in the **synaptic structure** of the **neurons in Wernicke's area.**

Interindividual variability is also expressed in the brain's functional organization, and particularly in the phenomenon of hemispheric asymmetry. For instance, some data indicate that **language functions may be more bilateral in women than in men**. The percentage of **atypical lateralization for language** also varies with handedness: it is considerably **higher among left-handers** than among right-handers.

Lastly, as if all this were not enough, there is also such a thing as intraindividual variability. In the same individual, a given mental task can sometimes activate different neuronal assemblies in different circumstances—for instance, when the individual is performing this task for the first time, as opposed to when he or she has already performed it many times before.

Even in many species that are quite distant from humans in evolutionary terms (frogs, for example), the brain is left-lateralized for the vocalization function.

In chimpanzees, lateralization for the anatomical areas corresponding to Broca's and Wernicke's areas already exists, even though it does not yet correspond to the language function. And like the majority of humans, the majority of chimpanzees use their right hand in preference to their left.

These asymmetries in the other primates represent persuasive evidence of the **ancient phylogenetic origin of lateralization** in the human brain. The expansion of the prefrontal cortex in humans might in part reflect its role in the production of language.

An asymmetrical lateralized brain may have evolved in order to reduce redundancy of information processing functions in favor of greater processing capacity in a brain whose volume is limited by the size of the human female birth canal (Corballis, 2017). To increase processing capacity if brain volume is fixed, lateralization of function may more efficiently utilize the processing resources available.

Women have the reputation of being able to talk and listen while doing all sorts of things at the same time, whereas men supposedly prefer to talk or hear about various things in succession rather than simultaneously. Brain-imaging studies may now have revealed an anatomical substrate for this behavioural difference, by demonstrating that language functions tend to place more demands on both hemispheres in women while being more lateralized (and mainly left-lateralized) in men. Women also have more nerve fibers connecting the two hemispheres of their brains (via a broader corpus callosum), which also suggests that more information is exchanged between them.

Summary

Most people are right-handed and language in most people is lateralized to the left hemisphere. Lateralization of the brain's functions may have been one way to increase the brain's processing capacity by reducing redundant usage of available processing resources. Vocalization is left-lateralized in species ranging from frogs to chimpanzees, suggesting ancient evolutionary origins of brain lateralization in humans.

References

Corballis, M. C. (2017). The evolution of lateralized brain circuits. *Frontiers in psychology*, *8*, 1021.

Attributions

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15.3: Split-Brain Research

Unique Functions of the Left and Right Hemispheres Using Split-Brain Patients

We learned that the left hemisphere of the brain primarily senses and controls the motor movements on the right side of the body, and vice versa. This fact provides an interesting way to study brain lateralization—the idea that the left and the right hemispheres of the brain are specialized to perform different functions. Gazzaniga, Bogen, and Sperry [9] studied a patient, known as W. J., who had undergone an operation to relieve severe seizures. In this surgery, the region that normally connects the two halves of the brain and supports communication between the hemispheres, known as the corpus callosum, is severed. As a result, the patient essentially becomes a person with two separate brains. Because the left and right hemispheres are separated, each hemisphere develops a mind of its own, with its own sensations, concepts, and motivations. [10]

In their research, Gazzaniga and his colleagues tested the ability of W. J. to recognize and respond to objects and written passages that were presented to only the left or to only the right brain hemispheres. The researchers had W. J. look straight ahead and then flashed, for a fraction of a second, a picture of a geometric shape to the left of where he was looking. By doing so, they assured that—because the two hemispheres had been separated—the image of the shape was experienced only in the right brain hemisphere (remember that sensory input from the left side of the body is sent to the right side of the brain). Gazzaniga and his colleagues found that W. J. was able to identify what he had been shown when he was asked to pick the object from a series of shapes, using his left hand, but that he could not do so when the object was shown in the right visual field. Conversely, W. J. could easily read written material presented in the right visual field (and thus experienced in the left hemisphere) but not when it was presented in the left visual field.

Visual and Verbal Processing in the Split-Brain Patient

The information presented on the left side of our field of vision is transmitted to the right brain hemisphere, and vice versa. In split-brain patients, the severed corpus callosum does not permit information to be transferred between hemispheres, which allows researchers to learn about the functions of each hemisphere.

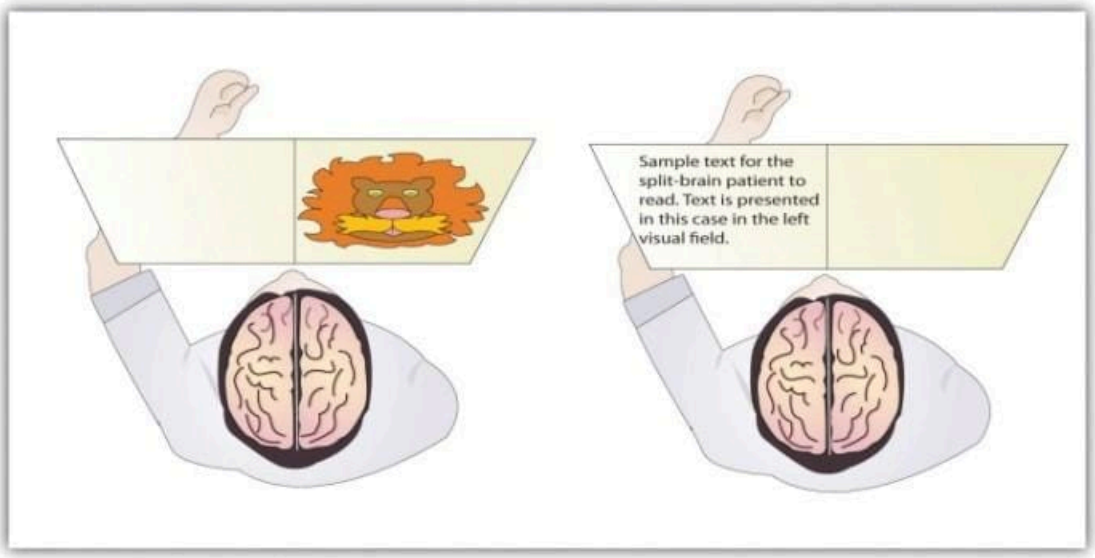


Figure 16. In the sample on the left, the split-brain patient could not choose which image had been presented because the left hemisphere cannot process visual information. In the sample on the right, the patient could not read the passage because the right brain hemisphere cannot process language. From Flat World Knowledge, Introduction to Psychology, v1.0, CC-BY-NC-SA .

This research, and many other studies following it, demonstrated that the two brain hemispheres specialize in different abilities. In most people, the ability to speak, write, and understand language is located in the left hemisphere. This is why W. J. could read passages that were presented on the right side and thus transmitted to the left hemisphere, but could not read passages that were only experienced in the right brain hemisphere. The left hemisphere is also better at math and at judging time and

rhythm. It is also superior in coordinating the order of complex movements—for example, lip movements needed for speech. The right hemisphere has only limited verbal abilities, and yet it excels in perceptual skills. The right hemisphere is able to recognize objects, including faces, patterns, and melodies, and it can put a puzzle together or draw a picture. This is why W. J. could pick out the image when he saw it on the left, but not the right, visual field.

Although Gazzaniga's research demonstrated that the brain is in fact lateralized, such that the two hemispheres specialize in different activities, this does not mean that when people behave in a certain way or perform a certain activity they are using only one hemisphere of their brains at a time. That would be drastically oversimplifying the concept of brain differences. We normally use both hemispheres at the same time, and the difference between the abilities of the two hemispheres is not absolute. [11]

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15.4: Broca's Area, Wernicke's Area, and Additional Language-Processing Areas in the Brain

Learning Objectives

1. Describe the classic Wernicke-Lichtheim-Geschwind model of the neurobiology of language.
2. Identify the temporal planum and specific gyri involved in language processing and list the role of each
3. Explain the idea of a universal grammar and what it implies about human language acquisition and a "language acquisition device" (LAD)
4. On what neuroanatomical basis are the Brodmann areas defined?
5. Describe the functions of the three sub-areas within Wernicke's area
6. Which gyrus gives evidence of involvement of the right hemisphere in language processing and what is that evidence?
7. Briefly describe what is meant by a distributed model of cognitive function; provide examples from neurobiological models of intelligence (from previous modules) and of language function

The Classical Wernicke-Lichtheim-Geschwind model of the neurobiology of language

The brain areas included in the best known model of how language is processed by the brain are **Broca's area** in the frontal lobe, **Wernicke's area** in the temporal lobe, and the **arcuate fasciculus** which connects the two. In this model, Broca's area is associated with language expression and Wernicke's area with language comprehension. Damage to any of these produces various forms of **aphasia** (language disorder) with different symptoms. Damage to Broca's area produces **Broca's aphasia** characterized by difficulties with language expression. **Wernicke's aphasia** involves difficulty with speech and language comprehension. Damage to the arcuate fasciculus produces **conduction aphasia** characterized by impaired ability to repeat simple phrases while expression and comprehension remain otherwise unimpaired.

Table 10.14.1: Features of two forms of aphasia (based on National Aphasia Association; https://www.aphasia.org/aphasia-reso...QaAhX6EALw_wcB).

Broca's (Expressive) aphasia	Speech output is severely reduced and is limited mainly to short utterances of less than four words. Finding the right words is often extremely difficult and clumsy. Comprehension can be relatively preserved. Difficulty producing grammatical sentences. May be able to read but limited in writing. Difficulty understanding complex grammatical sentences. Cognitive capabilities not related to speech and language may be fully preserved.
Wernicke's (Receptive) aphasia Additional forms of aphasia are global, mixed transcortical, transcortical motor, transcortical sensory, and anomic aphasia.	Damage in brain areas important for processing meaning of words and spoken language. Profound language comprehension deficits, even for single words or simple sentences. Reading and writing are often severely impaired. Often speak using grammatically correct sentences with normal rate and prosody but sentences make little sense and may include non-existent or incorrect and irrelevant words. Show little awareness of the lack of meaning of their speech. Cognitive capabilities not related to speech and language may be fully preserved.

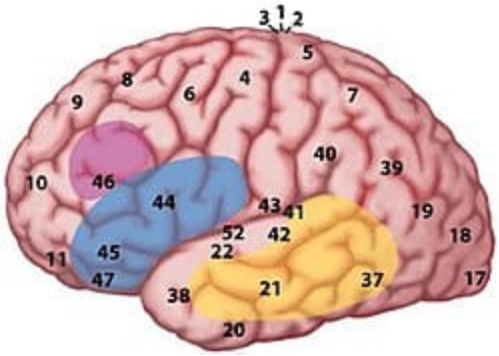


Figure 15.4.1: Lateral view of the human left cerebral cortex. The numbers indicate Brodmann areas. Brodmann areas are cortical regions differentiated by cytoarchitectonics (i.e., composition of cell types).

Broca's area is generally defined as comprising Brodmann areas 44 and 45, which lie anterior to the premotor cortex in the inferior posterior portion of the frontal lobe. Though both area 44 and area 45 contribute to verbal fluency, each seems to have a separate function, so that Broca's area can be divided into two functional units.

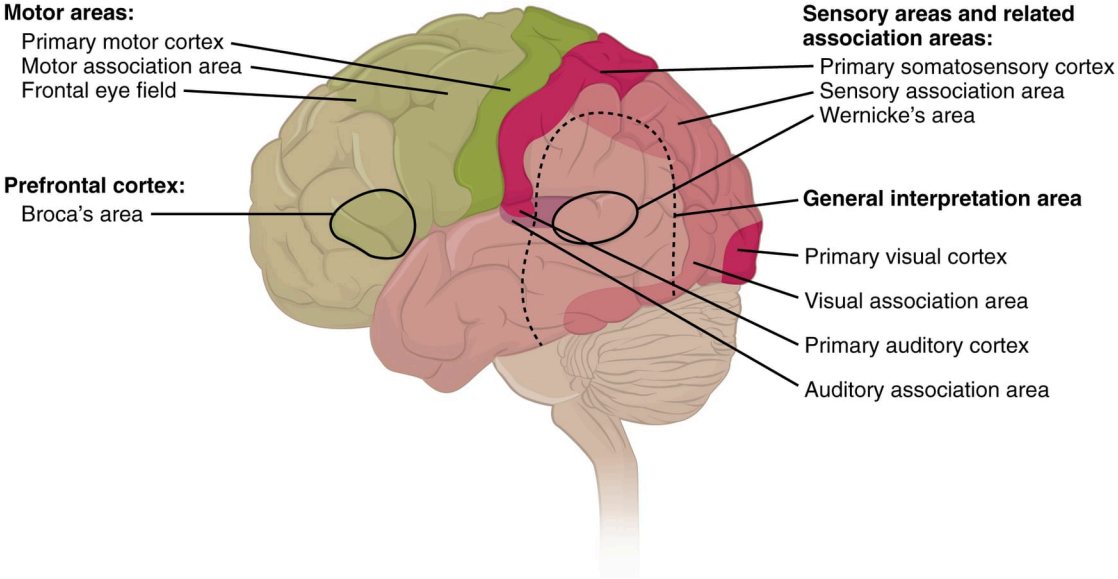


Figure 15.4.2: Locations of Broca's and Wernicke's areas and surrounding cortical regions. (Image from Wikimedia Commons; retrieved 10/18/21).

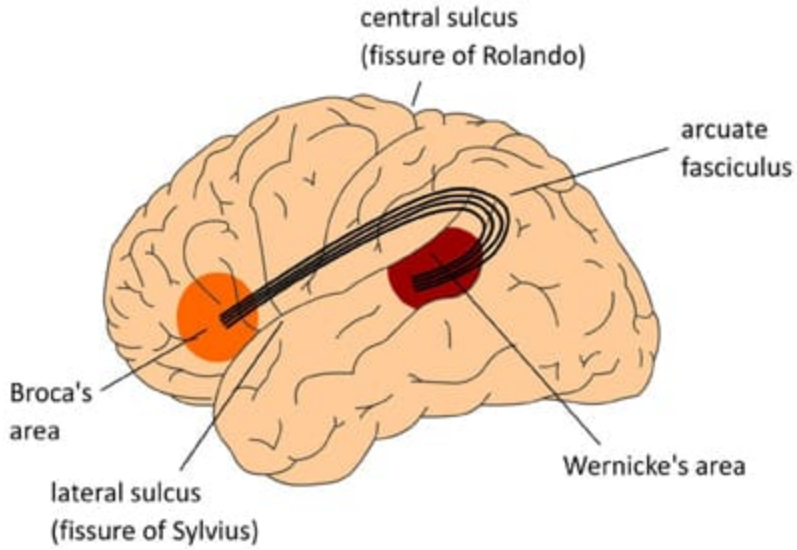


Figure 15.4.3: The classical **Wernicke-Lichtheim-Geschwind model of the neurobiology of language**. In this model Broca's area is crucial for language production, Wernicke's area subserves language comprehension, and the necessary information exchange between these areas (such as in reading aloud) is done via the arcuate fasciculus, a major fiber bundle connecting the language areas in temporal cortex (Wernicke's area) and frontal cortex (Broca's area). The language areas are bordering one of the major fissures in the brain, the so-called Sylvian fissure. Collectively, this part of the brain is often referred to as perisylvian cortex. (Image and caption from Wikimedia Commons; retrieved 10/18/21).

Area 44 (the **posterior** part of the **inferior frontal gyrus**) seems to be involved in phonological processing and in language production as such; this role would be facilitated by its position close to the motor centres for the mouth and the tongue. Area 45 (the **anterior** part of the **inferior frontal gyrus**) seems more involved in the semantic aspects of language. Though not directly involved in accessing meaning, Broca's area therefore plays a role in verbal memory (selecting and manipulating semantic elements).

Wernicke's area lies in the **left temporal lobe** and, **like Broca's area**, is **no longer regarded as a single, uniform anatomical/functional region** of the brain. By analyzing data from numerous brain-imaging experiments, researchers have now distinguished **three sub-areas within Wernicke's area**. The first responds to spoken words (including the individual's own) and other sounds. The second responds only to words spoken by someone else but is also activated when the individual recalls a list of words. The third sub-area seems more closely associated with producing speech than with perceiving it. All of these findings are still compatible, however, with the **general role of Wernicke's area**, which relates to the representation of phonetic sequences, regardless of whether the individual hears them, generates them himself or herself, or recalls them from memory.

Wernicke's area, of which the **temporal planum** is a key anatomical component, is located on the **superior temporal gyrus**, in the superior portion of Brodmann area 22. This is a strategic location, given the language functions that Wernicke's area performs. The temporal planum lies **between** the **primary auditory cortex** (Brodmann areas 41 and 42) **and the inferior parietal lobule**.

This lobule is composed mainly of **two distinct regions:** caudally, the **angular gyrus** (area 39), which itself is bounded by the visual occipital areas (areas 17, 18, and 19), and dorsally, the **supramarginal gyrus** (area 40) which arches over the end of the lateral sulcus, adjacent to the inferior portion of the somatosensory cortex.

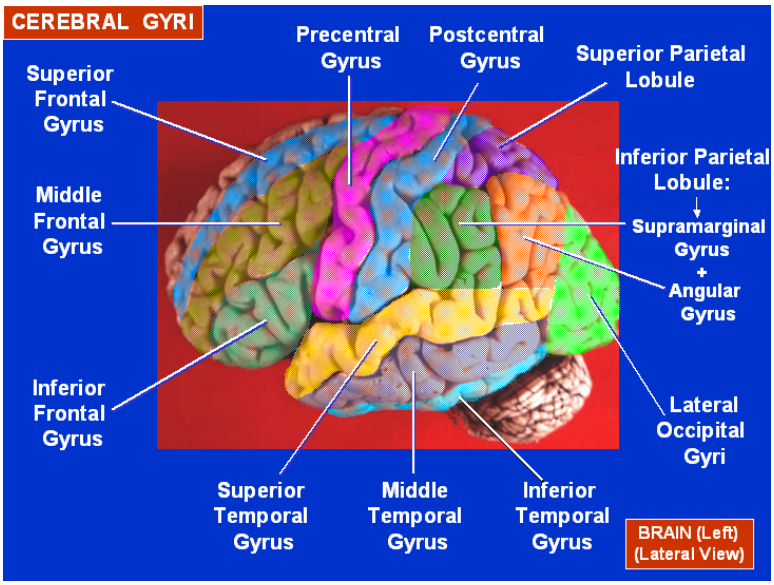


Figure 15.4.4: . Gyri ("hills") on the cerebral cortex, several of which are involved in language processing. (Image from Wikimedia Commons; File:Cerebral Gyri - Lateral Surface.png; https://commons.wikimedia.org/wiki/F...al_Surface.png; by John A Beal, PhD. Dep't. of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport; licensed under the Creative Commons Attribution 2.5 Generic license).

The supramarginal gyrus seems to be involved in phonological and articulatory processing of words, whereas the angular gyrus (together with the **posterior cingulate gyrus**) seems more involved in semantic processing. The **right angular gyrus** appears to be **active as well as the left**, thus revealing that the right hemisphere also contributes to semantic processing of language.

Together, the **angular and supramarginal gyri** constitute a **multimodal associative area** that receives auditory, visual, and somatosensory inputs. The neurons in this area are thus very well positioned to process the phonological and semantic aspect of language that enables us to identify and categorize objects.

The **language areas of the brain are distinct from the circuits responsible for auditory perception of the words we hear or visual perception of the words we read.** The auditory cortex lets us recognize sounds, an essential prerequisite for understanding language. The visual cortex, which lets us consciously see the outside world, is also crucial for language, because it enables us to read words and to recognize objects as the first step in identifying them by a name.

There are wide variations in the size and position of Broca's area and Wernicke's area as described by various authors.

Brain areas such as these, which perform high-level integration functions, are more heterogeneous than areas that perform primary functions. This greater heterogeneity might reflect greater sensitivity to environmental influences and greater plasticity (Links to an external site.) (ability to adapt to the environmental influences). The functional organization of language would even appear to vary within the same individual at various stages of his or her life!

Any attempt to define the precise boundaries of a particular area of the brain, such as Broca's area or Wernicke's area, will involve some serious problems. But we do know that the **cytoarchitectonic areas described by Brodmann provide better anatomical correlates for brain functions than do the shape of the brain's convolutions**. That said, a cortical area such as Broca's cannot be precisely described by reference to Brodmann areas alone. Though many authors regard **Broca's area** as consisting of **Brodmann areas 44 and 45**, other authors say it consists only of area 44, still others only of area 45, and yet others of areas 44, 45, and 47.

Broca's area may also include the most ventral portion of Brodmann area 6, as well as other parts of the cortex lying deep within the lateral sulcus (sulcus is a "valley" between gyri). It is even possible that only certain parts of these areas are actually dedicated to language.

Brain-imaging studies have shown to what a large extent **cognitive tasks** such as those involving language **correspond to a complex pattern of activation of various areas distributed throughout the cortex.** That a particular area of the brain becomes activated when the brain is performing certain tasks therefore does not imply that this area constitutes the only clearly

defined location for a given function. In the more **distributed model of cognitive functions** that is now increasingly accepted by cognitive scientists, all it means is that the neurons in this particular area of the brain are more involved in this particular task than their neighbors. It in no way excludes the possibility that other neurons located elsewhere, and sometimes even quite far from this area, may be just as involved.

Thus, just because the content of a word is encoded in a particular neuronal assembly does not necessarily mean that all of the neurons in this assembly are located at the same place in the brain. On the contrary, **understanding or producing a spoken or written word can require** the simultaneous contribution of several modalities (auditory, visual, somatosensory, and motor). Hence the **interconnected neurons** in the assembly responsible for this task may be **distributed across the various cortexes dedicated to these modalities.**

In contrast, the neuronal assemblies involved in encoding grammatical functions appear to be less widely distributed.

It may therefore be that the **brain processes language functions in two ways simultaneously**: in **parallel** mode by means of **distributed networks**, and in **serial** mode by means of **localized** convergence zones in the brain.

Language Acquisition

Language acquisition in humans is based on our **capacities for abstraction and for applying rules of syntax**—capacities that other animals lack. For example, brain-imaging experiments have shown that Broca's area becomes active when subjects are learning actual rules of grammar in another language, but not when they are exposed to fictitious rules that actually violate the grammar of that language.

These findings suggest that in Broca's area, biological constraints interact with experience to make the acquisition of languages possible. **Broca's area** may thus represent the neuronal substrate of the **"universal grammar"** shared by all of the world's languages. The idea of the universal grammar is that in spite of the great variation in human languages, there still exists basic universal commonalities shared by all human languages and that these basic similarities in grammar reflect **genetically determined** features of the brain areas that acquire language. The linguist, Noam Chomsky, proposed that the **universal grammar** shared by all languages originates from innate brain organization that biologically prepares humans to learn language naturally and easily despite its great complexity. This idea is expressed in Chomsky's proposal of a **Language Acquisition Device (LAD)**--innate, genetically organized brain circuitry found in every normal human specialized for the easy acquisition of a human language that one is exposed to during childhood. Though popular among many psychologists and linguists for some time, more recently others have proposed that language acquisition does not require an LAD and that general learning mechanisms may be sufficient to account for language acquisition (Behme & Deacon, 2008).

Summary

In the classical **Wernicke-Lichtheim-Geschwind model of the neurobiology of language,** Broca's area is crucial for language production, Wernicke's area subserves language comprehension, and the information exchange between these areas (such as in reading aloud) is done via the arcuate fasciculus. Damage to any of these produces various forms of **aphasia**. Distributed models of cognitive function suggest that language function involves many areas of the brain not included in the classic neurobiological model of language function.

References

Behme, C., & Deacon, S. H. (2008). Language learning in infancy: Does the empirical evidence support a domain specific language acquisition device?. *Philosophical Psychology*, *21*(5), 641-671.

Attributions

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15.5: Other Brain Models of Spoken and Written Language

Learning Objectives

1. Contrast Mesulam's model with the Wernicke-Lichtheim-Geschwind model of the brain's processing of language
2. Describe and explain the distributed model of language processing by the brain
3. Explain why in a split brain patient objects presented in the right visual field are processed by the left side of the brain and can be verbally identified and why objects presented in the left visual field cannot be verbally identified
4. Describe the major evidence for and the basic facts of brain lateralization
5. Outline the auditory and visual processing of language
6. Describe the features and anatomical structures involved in three types of aphasia
7. Describe the types of alexia and agraphia and their causes
8. Briefly explain what the processing of sign language, music, and other symbolic systems reveals about language processing

Overview

In this module we consider other models of language representation and function in the brain. The first follows the traditional locationist model which posits specific circuits involved in language processing. The second hypothesizes a non-locationist view which emphasizes distributed networks engaged in parallel processing of language.

An Alternative to the Wernicke-Lichtheim-Geschwind Model

In the 1980s, American neurologist Marsel Mesulam proposed an alternative to the Wernicke-Lichtheim-Geschwind model for understanding the brain's language circuits. Mesulam's model posits a hierarchy of networks in which information is processed by levels of complexity.

For example, when you perform simple language processes such as reciting the months of the year in order, the motor and premotor areas for language are activated directly. But when you make a statement that requires a more extensive semantic and phonological analysis, other areas come into play first.

When you hear words spoken, they are perceived by the **primary auditory cortex**, then processed by unimodal associative areas of the cortex: the **superior and anterior temporal lobes** and the **opercular part of the left inferior frontal gyrus.**

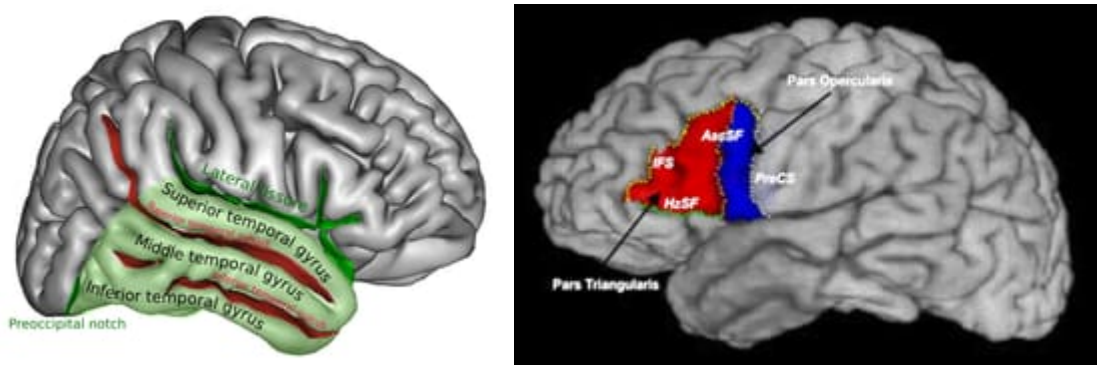


Figure 15.5.1: (Left) Right **temporal lobe**. (Right) Broca's area (left hemisphere) of the **inferior frontal gyrus** divided into the pars triangularis (PTri, red) and pars opercularis (POp, blue). **PreCS**: Precentral sulcus. **IFS**: Inferior frontal sulcus. **AscSF** Ascending ramus of Sylvian fissure. **HzSF** Horizontal ramus of Sylvian fissure (Images and caption for image on the right from Wikimedia Commons, retrieved 10/18/21).

According to Mesulam's model, these unimodal areas then send their information on to two separate sites for integration. One of

these is the temporal pole of the **paralimbic system**, which provides access to the long-term memory system and the emotional system. The other is the posterior terminal portion of the **superior temporal sulcus**, which provides access to meaning. The triangular and orbital portions of the **inferior frontal gyrus** also play a role in semantic processing. One important idea in Mesulam's model is that the function of a brain area dedicated to language is not fixed but rather varies according to the "neural context". In other words, the function of a particular area depends on the task to be performed, because these areas do not always activate the same connections between them. For instance, the left inferior frontal gyrus interacts with different areas depending on whether it is processing the sound of a word or its meaning.

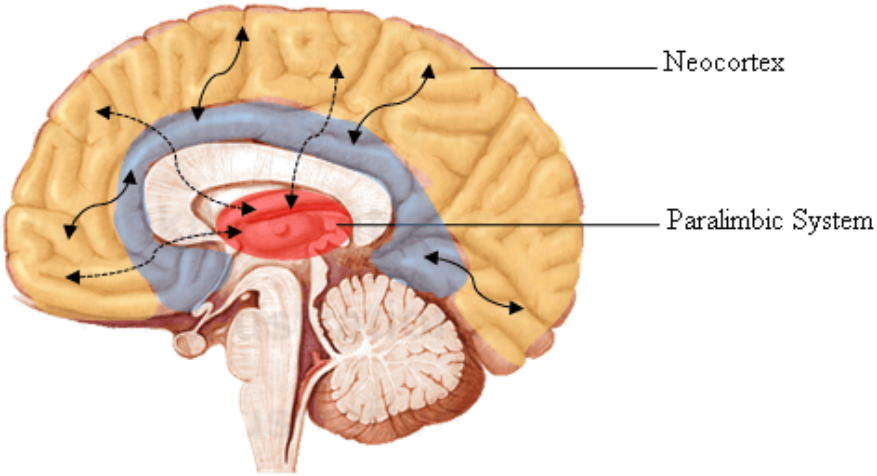


Figure 15.5.2: Paralimbic system, area of three-layered cortex that consists of the pyriform cortex, entorhinal cortex, and parahippocampal cortex on the medial surface of the temporal lobe, and the cingulate cortex just above the corpus callosum. The paralimbic cortex lies close to the limbic structures, and is directly connected with them. (Image, Wikimedia. Caption from Kolb & Whishaw: *Fundamentals of Human Neuropsychology*, 2003).

This networked type of organization takes us beyond the "one area = one function" equation and explains many of the sometimes highly specific language disorders. For example, some people cannot state the names of tools or the colors of objects. Other people can explain an object's function without being able to say its name, and vice versa.

Mesulam does, however, still believe that there are two "epicenters" for semantic processing, i.e., Broca's area and Wernicke's area. This new conception of these two areas is consistent with the fact that they often work synchronously when the brain is performing a word processing task, which supports the idea that there are very strong connections between them.

Mesulam's concept of epicenters resembles that of convergence zones as proposed by other authors: zones where information obtained through various sensory modalities can be combined. This combining process is achieved through the forming of cell assemblies: groups of interconnected neurons whose synapses have been strengthened by their simultaneous firing, in accordance with Hebb's law. This concept of language areas as convergence zones where neuronal assemblies are established thus accords a prominent place to epigenetic influences in the process of learning a language.

Unquestionably, one of these convergence zones is the **left inferior parietal lobule**, which comprises the **angular gyrus and the supramarginal gyrus** . In addition to receiving information from the right hemisphere , the left inferior parietal lobule also integrates emotional associations from the **amygdala** and the **cingulate gyrus**.

Some scientists believe that over the course of evolution, language remained under limbic control until the inferior parietal lobule evolved and became a convergence zone that provides a wealth of inputs to Broca's area . Some scientists also think that it was the emergence of the inferior parietal lobule that gave humans the ability to break down the sounds that they heard so as to make sense of them and, conversely, to express sounds in a sequential manner so as to convey meaning. In this way, primitive emotional and social vocalizations would have eventually come to be governed by grammatical rules of organization to create what we know as modern language.

Distributed Models of Language Function

Lastly, a number of researchers now reject classic locationist models of language such as Geschwind's and Mesulam's. Instead, they conceptualize language, and cognitive functions in general, as being distributed across anatomically separate areas that process information in parallel (simultaneously, rather than serially, from one "language area" to another).

Even those researchers who embrace this view that linguistic information is processed in parallel still accept that the primary language functions, both auditory and articulatory, are localized to some extent.

This concept of a parallel, distributed processing network for linguistic information constitutes a distinctive epistemological paradigm that is leading to the reassessment of certain functional brain imaging (fMRI) studies.

The proponents of this paradigm believe that the extensive activation of various areas in the left hemisphere and the large number of psychological processes involved make it impossible to associate specific language functions with specific anatomical areas of the brain. For example, the single act of **recalling words** involves a highly **distributed network** that is located primarily in the left brain and that includes the **inferolateral temporal lobe,** the **inferior posterior parietal lobule,** the **premotor areas of the frontal lobe,** the **anterior cingulate gyrus,** and the **supplementary motor area.** According to this paradigm, with such a widely distributed, parallel processing network, there is **no way to ascribe specific functions to each of these structures** that contribute to the performance of this task.

The **brain does seem to access meanings by way of categories that it stores in different physical locations**. For example, if the **temporal pole** (the anterior end of the temporal lobe) is damaged, the category "famous people" is lost; if a lesion occurs in the **intermediate and inferior parts of the temporal lobe**, the category "animals" disappears. It also seems that the networks involved in encoding words activate areas in the motor and visual systems. The task of **naming tools** activates the **frontal premotor areas**, while that of **naming animals** activates the **visual areas**. But in both cases, Broca's area and Wernicke's area are not even activated.

Among those scientists who argue that the brain's language processing system is distributed across various structures, some, such as Philip Lieberman, believe that the **basal ganglia** play a very important role in language. These researchers further believe that other subcortical structures traditionally regarded as involved in motor control, such as the **cerebellum** and the **thalamus**, also contribute to language processing. These views stand in opposition to Chomsky's on the exceptional nature of human language and fall squarely within an adaptationist (emphasizing natural selection), evolutionary perspective.

References

Mesulam, 2000 In: M.M. Mesulam, Editor, Principles of Behavioral and Cognitive Neurology (2nd ed.), Oxford University Press, New York (2000)

Lateralization, Auditory and Visual Language Processing

Introduction

What is happening inside my head when I listen to a sentence? How do I process written words? This chapter will take a closer look on brain processes concerned with language comprehension. Dealing with natural language understanding, we distinguish between the neuroscientific and the psycholinguistic approach. As text understanding spreads through the broad field of cognitive psychology, linguistics, and neurosciences, our main focus will lay on the intersection of two latter, which is known as neurolinguistics.

Different brain areas need to be examined in order to find out how words and sentences are being processed. For long time scientist were restricted to draw conclusions from certain brain lesions to the functions of corresponding brain areas. During the last 40 years techniques for brain imaging and ERP-measurement have been established which allow for a more accurate identification of brain parts involved in language processing.

Scientific studies on these phenomena are generally divided into research on auditory and visual language comprehension; we will discuss both. Not to forget is that it is not enough to examine English: To understand language processing in general, we have to look at non-Indo-European and other language systems like sign language. But first of all we will be concerned with a rough

localization of language in the brain.

Lateralization of language

Although functional lateralization studies and analyses find individual differences in personality or cognitive style don't favor one hemisphere or the other, some brain functions occur in one or the other side of the brain. Language tends to be on the left and attention on the right (Nielson, Zielinski, Ferguson, Lainhart & Anderson, 2013). There is a lot of evidence that each brain hemisphere has its own distinct functions in language comprehension. Most often, the right hemisphere is referred to as the non-dominant hemisphere and the left is seen as the dominant hemisphere. This distinction is called lateralization (from the Latin word lateral, meaning sidewise) and reason for it first was raised by experiments with split-brain patients. Following a top-down approach we will then discuss the right hemisphere which might have the mayor role in higher level comprehension, but is not quite well understood. Much research has been done on the left hemisphere and we will discuss why it might be dominant before the following sections discuss the fairly well understood fundamental processing of language in this hemisphere of the brain.

Functional asymmetry

Anatomical differences between left and right hemisphere

Initially we will consider the most apparent part of a differentiation between left and right hemisphere: Their differences in shape and structure. As visible to the naked eye there exists a clear asymmetry between the two halves of the human brain: The right hemisphere typically has a bigger, wider and farther extended frontal region than the left hemisphere, whereas the left hemisphere is bigger, wider and extends farther in it's occipital region (M. T. Banich,"Neuropsychology", ch.3, pg.92). Significantly larger on the left side in most human brains is a certain part of the temporal lobe's surface, which is called the planum temporale. It is localized near Wernicke's area and other auditory association areas, wherefore we can already speculate that the left hemisphere might be stronger involved in processes of language and speech treatment.

In fact such a left laterality of language functions is evident in 97% of the population (D. Purves, "Neuroscience", ch.26, pg.649). But actually the percentage of human brains, in which a "left-dominance" of the planum temporale is traceable, is only 67% (D. Purves, "Neuroscience", ch.26, pg.648). Which other factors play aunsolved yet.

Evidence for functional asymmetry from "split brain" patients

In hard cases of epilepsy a rarely performed but popular surgical method to reduce the frequency of epileptic seizures is the so-called corpus callosotomy. Here a radical cut through the connecting "communication bridge" between right and left hemisphere, the corpus callosum, is done; the result is a "split-brain". For patients whose corpus callosum is cut, the risk of accidental physical injury is mitigated, but the side-effect is striking: Due to this eradicative transection of left and right half of the brain these two are not longer able to communicate adequately. This situation provides the opportunity to study differentiation of functionality between the hemispheres. First experiments with split-brain patients were performed by Roger Sperry and his colleagues at the California Institute of Technology in 1960 and 1970 (D. Purves, "Neuroscience", ch.26, pg.646). They lead researchers to sweeping conclusions about laterality of speech and the organization of the human brain in general.

A digression on the laterality of the visual system

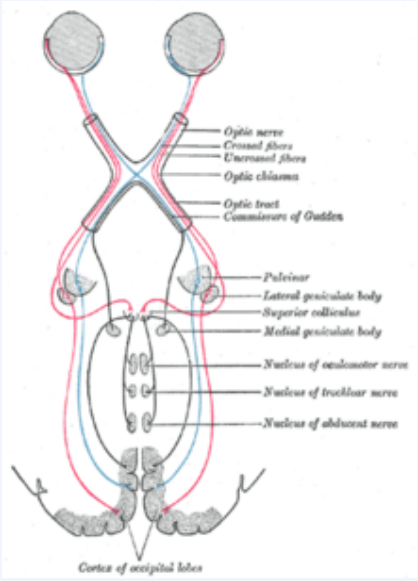


Figure 15.5.3: Visual system showing wiring from each half of the eye to brain. A visual stimulus, located within the left visual field, projects onto the nasal (inner) part of the left eye's retina and onto the temporal (outer) part of the right eye's retina. Images on the temporal retinal region are processed in the visual cortex of the same side of the brain (ipsilateral), whereas nasal retinal information is mapped onto the opposite half of the brain (contralateral). The stimulus within the left visual field will completely arrive in the right visual cortex to be processed and worked up. In "healthy" brains this information furthermore reaches the left hemisphere via the corpus callosum and can be integrated there. In split-brain patients this current of signals is interrupted; the stimulus remains "invisible" for the left hemisphere. (Image from Wikimedia Commons; File:Gray722.png; by Henry Vandyke Carter; This work is in the **public domain** in the United States).



Figure 15.5.4: Split Brain Experiments. (Image from Wikimedia Commons; File:SplitBrainExperiments.jpg; https://commons.wikimedia.org/wiki/F...xperiments.jpg; by TilmanATuos at English Wikibooks; released into the **public domain** by its author).

The experiment we consider now is based on the laterality of the visual system: What is seen in the left half of the visual field will be processed in the right hemisphere and vice versa. Aware of this principle a test operator presents the picture of an object to one half of the visual field while the participant is instructed to name the seen object, and to blindly pick it out of an amount of concrete objects with the contralateral hand.

It can be shown that a picture, for example the drawing of a die, which has only been presented to the left hemisphere, can be named by the participant ("I saw a die"), but is not selectable with the right hand (no idea which object to choose from the table). Contrarily the participant is unable to name the die, if it was recognized in the right hemisphere, but easily picks it out of the heap of objects on the table with the help of the left hand.

These outcomes are clear evidence of the human brain's functional asymmetry. The left hemisphere seems to dominate functions of speech and language processing, but is unable to handle spatial tasks like vision-independent object recognition. The right hemisphere seems to dominate spatial functions, but is unable to process words and meaning independently. In a second experiment evidence arose that a split-brain patient can only follow a written command (like "get up now!"), if it is presented to the left hemisphere. The right hemisphere can only "understand" pictorial instructions.

The following table (D. Purves, "Neuroscience", ch.26, pg.647) gives a rough distinction of functions:

Left Hemisphere	**Right Hemisphere**

• analysis of right visual field
• language processing
  ◦ writing
  ◦ speech
	• analysis of left visual field
	• spatial tasks
	• visuospatial tasks
	• object and face recognition

First it is important to keep in mind that these distinctions comprise only functional dominances, no exclusive competences. In cases of unilateral brain damage, often one half of the brain takes over tasks of the other one. Furthermore it should be mentioned that this experiment works only for stimuli presented for less than a second. This is because not only the corpus callosum, but as well some subcortical comissures serve for interhemispheric transfer. In general both can simultaneously contribute to performance, since they use complement roles in processing.

A digression on handedness

An important issue, when exploring the different brain organization in the two hemispheres, is handedness, which is the tendency to use the left or the right hand to perform activities. Throughout history, left-handers, which only comprise about 10% of the population, have often been considered being something abnormal. They were said to be evil, stubborn, defiant and were, even until the mid 20th century, forced to write with their right hand.

One most commonly accepted idea, as to how handedness affects the hemispheres, is the brain hemisphere division of labour. Since both speaking and handiwork require fine motor skills, the presumption here is that it would be more efficient to have one brain hemisphere do both, rather than having it divided up. Since in most people, the left side of the brain controls speaking, right-handedness predominates. The theory also predicts that left-handed people have a reversed brain division of labour.

In right handers, verbal processing is mostly done in the left hemisphere, whereas visuospatial processing is mostly done in the opposite hemisphere. Therefore, 95% of speech output is controlled by the left brain hemisphere, whereas only 5% of individuals control speech output in their right hemisphere. Left-handers, on the other hand, have a heterogeneous brain organization. Their brain hemisphere is either organized in the same way as right handers, the opposite way, or even such that both hemispheres are used for verbal processing. But usually, in 70% of the cases, speech is controlled by the left-hemisphere, 15% by the right and 15% by either hemisphere. When the average is taken across all types of left-handedness, it appears that left-handers are less lateralized.

After, for example, damage occurs to the left hemisphere, it follows that there is a visuospatial deficit, which is usually more severe in left-handers than in right-handers. Dissimilarities may derive, in part, from differences in brain morphology, which concludes from asymmetries in the planum temporale. Still, it can be assumed that left-handers have less division of labour between their two hemispheres than right-handers do and are more likely to lack neuroanatomical asymmetries.

There have been many theories as to find out why people are left-handed and what its consequences may be. Some people say that left-handers have a shorter life span or higher accident rates or autoimmune disorders. According to the theory of Geschwind and Galaburda, there is a relation to sex hormones, the immune system, and profiles of cognitive abilities that determine, whether a person is left-handed or not. Concludingly, many genetic models have been proposed, yet the causes and consequences still remain a mystery (M.T.Banich, "Neuropsychology", ch.3, pg. 119).

The right hemisphere

The role of the right hemisphere in text comprehension

The experiments with "split-brain" patients and evidence that will be discussed soon suggest that the right hemisphere is usually not (but in some cases, e.g. 15% of left handed people) dominant in language comprehension. What is most often ascribed to the right hemisphere is cognitive functioning. When damage is done to this part of the brain or when temporal regions of the right hemisphere are removed, this can lead to cognitive-communication problems, such as impaired memory, attention problems, and poor reasoning (L. Cherney, 2001). Investigations lead to the conclusion that the right hemisphere processes information in a gestalt and holistic fashion, with a special emphasis on spatial relationships. Here, an advantage arises for differentiating two distinct faces because it examines things in a global manner and it also reacts to lower spatial, and also auditory, frequency. The former point can be undermined with the fact that the right hemisphere is capable of reading most concrete words and can make simple grammatical comparisons (M. T. Banich,“Neuropsychology“, ch.3, pg.97). But in order to function in such a way, there must be some sort of communication between the brain halves.

Prosody - the sound envelope around words

Consider how different the simple statement "She did it again" could be interpreted in the following context taken from Banich: LYNN: Alice is way into this mountain-biking thing. After breaking her arm, you'd think she'd be a little more cautious. But then yesterday, she went out and rode Captain Jack's. That trail is gnarly - narrow with lots of tree roots and rocks. And last night, I heard that she took a bad tumble on her way down. SARA: *She did it again* Does Sara say that with rising pitch or emphatically and with falling intonation? In the first case she would ask whether Alice has injured herself again. In the other case she asserts something she knows or imagines: That Alice managed to hurt herself a second time. Obviously the sound envelope around words - prosody - does matter.

Reason to belief that recognition of prosodic patterns appears in the right hemisphere arises when you take into account patients

that have damage to an anterior region of the right hemisphere. They suffer from **aprosodic** speech, that is, their utterances are all at the same pitch. They might sound like a robot from the 80ties. There is another phenomena appearing from brain damage: **dysprosodic** speech. In that case the patient speaks with disordered intonation. This is not due to a right hemisphere lesion, but arises when damage to the left hemisphere is suffered. The explanation is that the left hemisphere gives ill-timed prosodic cues to the right hemisphere, thus proper intonation is affected.

Beyond words: Inference from a neurological point of view

On the word level, the current studies are mostly consistent with each other and with findings from brain lesion studies. But when it comes to the more complex understanding of whole sentences, texts and storylines, the findings are split. According to E. C. Ferstl's review "The Neuroanatomy of Text Comprehension. What's the story so far?" (2004), there is evidence for and against right hemisphere regions playing the key role in pragmatics and text comprehension. On the current state of knowledge, we cannot exactly say how and where cognitive functions like building situation models and inferencing work together with "pure" language processes.

As this chapter is concerned with the neurology of language, it should be remarked that patients with right hemisphere damage have difficulties with inferencing. Take into account the following sentence:

With mosquitoes, gnats, and grasshoppers flying all about, she came across a small black bug that was being used to eavesdrop on her conversation.

You might have to reinterpret the sentence until you realize that "small black bug" does not refer to an animal but rather to a spy device. People with damage in the right hemisphere have problems to do so. They have difficulty to follow the thread of a story and to make inferences about what has been said. Furthermore they have a hard time understanding non-literal aspects of sentences like metaphors, so they might be really horrified when they hear that someone was "Crying her eyes out".

The left hemisphere

Further evidence for left hemisphere dominance: The Wada technique

Before concerning concrete functionality of the left hemisphere, further evidence for the dominance of the left hemisphere is provided. Of relevance is the so-called Wada technique, allowing testing which hemisphere is responsible for speech output and usually being used in epilepsy patients during surgery. It is not a brain imaging technique, but simulates a brain lesion. One of the hemispheres is anesthetized by injecting a barbiturate (sodium amobarbital) in one of the patient's carotid arteries. Then he is asked to name a number of items on cards. When he is not able to do that, despite the fact that he could do it an hour earlier, the concerned hemisphere is said to be the one responsible for speech output. This test must be done twice, for there is a chance that the patient produces speech bilaterally. The probability for that is not very high, in fact, according to Rasmussen & Milner 1997a (as referred to in Banich, p. 293) it occurs only in 15% of the left-handers and none of the right-handers. (It is still unclear where these differences in left-handers' brains come from.)

That means that in most people, only one hemisphere "produces" speech output – and in 96% of right-handers and 70% of left-handers, it is the left one. The findings of the brain lesion studies about asymmetry were confirmed here: Normally (in healthy right-handers), the left hemisphere controls speech output.

Explanations of left hemisphere dominance

Two theories why the left hemisphere might have special language capacities are still discussed. The first states that dominance of the left hemisphere is due to a specialization for **precise temporal control of oral and manual articulators**. Here the main argument is that gestures related to a story line are most often made with the right and therefore by the left hemisphere controlled hand whilst other hand movements appear equally often with both hands. The other theory says that the left hemisphere is dominant because it is specialized for **linguistic processing** and is due to a single patient - a speaker of American Sign Language with a left hemisphere lesion. He could neither produce nor comprehend ASL, but could still communicate by using gestures in non-linguistic domains.

How innate is the organizational structure of the brain?

Not only cases of left-handers but also brain imaging techniques have shown examples of bilateral language processing: According to ERP studies (by Bellugi et al. 1994 and Neville et al. 1993 as cited in E. Dabrowska, "Language, Mind an Brain" 2004, p. 57), people with the Williams' syndrome (WS) also have no dominant hemisphere for language. WS patients have a lot of

physical and mental disorders, but show, compared to their other (poor) cognitive abilities, very good linguistic skills. And these skills do not rely on one dominant hemisphere, but both of them contribute equally. So, whilst the majority of the population has a dominant left hemisphere for language processing there are a variety of exceptions to that dominance. That there are different “organization possibilities” in individual brains Dabrowska (p. 57) suggests that the organizational structure in the brain could be less innate and fixed as it is commonly thought.

Auditory Language Processing

This section will explain where and how language is processed. To avoid intersections with visual processes we will firstly concentrate on spoken language. Scientists have developed three approaches of conceiving information about this issue. The first two approaches are based upon brain lesions, namely aphasia, whereas the recent approach relies on results of on modern brain-image techniques.

Neurological Perspective

The Neurological Perspective describes which pathways language follows in order to be comprehended. Scientists revealed that there are concrete areas inside the brain where concrete tasks of language processing are taking place. The most known areas are the Broca and the Wernicke Area.

Broca’s aphasia

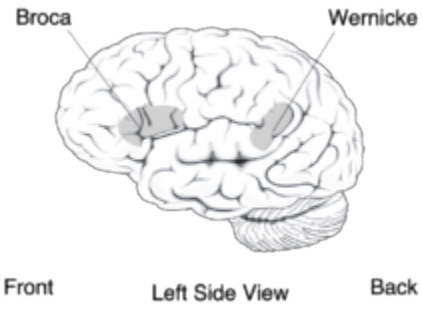


Figure 15.5.5: Broca's and Wernicke's area (Image from Wikimedia Commons; File:BrocasAreaSmall.png; https://commons.wikimedia.org/wiki/F...sAreaSmall.png; **public domain** in the United States because it is a work prepared by an officer or employee of the United States Government as part of that person’s official duties.

One of the most well-known aphasias is Broca’s aphasia that causes patients to be unable to speak fluently. Moreover they have a great difficulty producing words. Comprehension, however, is relatively intact in those patients. Because these symptoms do not result from motoric problems of the vocal musculature, a region in the brain that is responsible for linguistic output must be lesioned. Broca discovered that the brain region causing fluent speech is responsible for linguistic output, must be located ventrally in the frontal lobe, anterior to the motor strip. Recent research suggested that Broca`s aphasia results also from subcortical tissue and white matter and not only cortical tissue.

Example of spontaneous Speech - Task: What do you see on this picture?
„O, yea. Det‘s a boy an‘ girl... an‘ ... a ... car ... house... light po‘ (pole). Dog an‘ a ... boat. ‚N det‘s a ... mm ... a ... coffee, an‘ reading. Det‘s a ... mm ... a ... det‘s a boy ... fishin‘.“ (Adapted from „Principles of Neuroscience“ 4th edition, 2000, p 1178)

Wernicke‘s aphasia

Another very famous aphasia, known as Wernicke`s aphasia, causes opposite syndromes. Patients suffering from Wernicke`s aphasia usually speak very fluently, words are pronounced correctly, but they are combined senselessly – “word salad” is the way it is most often described. Understanding what patients of Wernicke`s aphasia say is especially difficult, because they use paraphasias (substitution of a word in verbal paraphasia, of word with similar meaning in semantic paraphasia, and of a phoneme in phonemic paraphasia) and neologisms. With Wernicke`s aphasia the comprehension of simple sentences is a very difficult task. Moreover their ability to process auditory language input and also written language is impaired. With some knowledge about the brainstructure and their tasks one is able to conclude that the area that causes Wernicke`s aphasia, is situated at the

joint of temporal, parietal and occipital regions, near Heschl`s gyrus (primary auditory area), because all the areas receiving and interpreting sensory information (posterior cortex), and those connecting the sensory information to meaning (parietal lobe) are likely to be involved.

Example of spontaneous Speech - Task: What do you see on this picture?
„Ah, yes, it‘s ah ... several things. It‘s a girl ... uncurl ... on a boat. A dog ... ‘S is another dog ... uh-oh ... long‘s ... on a boat. The lady, it‘s a young lady. An‘ a man a They were eatin‘. ‘S be place there. This ... a tree! A boat. No, this is a ... It‘s a house. Over in here ... a cake. An‘ it‘s, it‘s a lot of water. Ah, all right. I think I mentioned about that boat. I noticed a boat being there. I did mention that before ... Several things down, different things down ... a bat ... a cake ... you have a ...“ (adapted from „Principles of Neuroscience“ 4th edition, 2000, p 1178)

Conduction aphasia

Wernicke supposed that an aphasia between Broca‘s area and Wernicke‘s area, namely conduction aphasia, would lead to severe problems to repeat just heard sentences rather than having problems with the comprehension and production of speech. Indeed patients suffering from this kind of aphasia show an inability to reproduce sentences since they often make phonemic paraphasias, may substitute or leave out words, or might say nothing. Investigations determined that the "connection cable", namely the arcuate fasciculus between Wernicke‘s and Broca‘s area is almost invariably damaged in case of a conduction aphasia. That is why conduction aphasia is also regarded as a disconnection syndrome (the behavioural dysfunction because of a damage to the connection of two connected brain regions).

Example of the repetition of the sentence „The pastry-cook was elated“:
„The baker-er was /vaskerin/ ... uh ...“ (adapted from „Principles of Neuroscience“ 4th edition, 2000, p 1178)

Transcortical motor aphasia and global aphasia

Transcortical motor aphasia, another brain lesion caused by a connection disruption, is very similar to Broca`s aphasia, with the difference that the ability to repeat is kept. In fact people with a transcortical motor aphasia often suffer from echolalia, the need to repeat what they just heard. Usually patients` brain is damaged outside Broca`s area, sometimes more anterior and sometimes more superior. Individuals with transcortical sensory aphasia have similar symptoms as those suffering from Wernicke`s aphasia, except that they show signs of echolalia. Lesions in great parts of the left hemisphere lead to global aphasia, and thus to an inability of both comprehending and producing language, because not only Broca`s or Wenicke`s area is damaged. (Barnich, 1997, pp. 276–282)

Type of Aphasia	Spontaneous Speech	Paraphasia	Comprehension	Repetition	Naming
• Broca`s • Wernicke`s • Conduction • Transcortical motor • Transcortical sensory • Global	• Nonfluent • Fluent • Fluent • Nonfluent • Fluent • Nonfluent	• Uncommon • Common (verbal) • Common (literal) • Uncommon • Common • Variable	• Good • Poor • Good • Good • Poor • Poor	• Poor • Poor • Poor • Good (echolalia) • Good (echolalia) • Poor	• Poor • Poor • Poor • Poor • Poor • Poor

Overview of the effects of aphasia from the neurological perspective

(Adapted from Benson, 1985,p. 32 as cited in Barnich, 1997, p. 287)

Psychological Perspective

Since the 1960‘s psychologists and psycholinguists tried to resolve how language is organized and represented inside the brain. Patients with aphasias gave good evidence for location and discrimination of the three main parts of language comprehension

and production, namely phonology, syntax and semantics.

Phonology

Phonology deals with the processing of meaningful parts of speech resulting from the mere sound. More over there exists a differentiation between a phonemic representation of a speech sound which are the smallest units of sounds that leads to different meanings (e.g. the /b/ and /p/ in bet and pat) and phonetic representation. The latter means that a speech sound may be produced in a different manner at different situations. For instance the /p/ in pill sounds different than the /p/ in spill since the former /p/ is aspirated and the latter is not.

Examining which parts are responsible for phonetic representation, patients with Broca`s or Wernicke`s aphasia can be compared. As the speech characteristic for patients with Broca`s aphasia is non-fluent, i.e. they have problems producing the correct phonetic and phonemic representation of a sound, and people with Wernicke`s aphasia do not show any problems speaking fluently, but also have problems producing the right phoneme. This indicates that Broca`s area is mainly involved in phonological production and also, that phonemic and phonetic representation do not take place in the same part of the brain. Scientists examined on a more precise level the speech production, on the level of the distinctive features of phonemes, to see in which features patients with aphasia made mistakes.

A distinctive feature describes the different manners and places of articulation. /t/ (like in touch) and /s/ (like in such) for example are created at the same place but produced in different manner. /t/ and /d/ are created at the same place and in the same manner but they differ in voicing.

Results show that in fluent as well as in non-fluent aphasia patients usually mix up only one distinctive feature, not two. In general it can be said that errors connected to the place of articulation are more common than those linked to voicing. Interestingly some aphasia patients are well aware of the different features of two phonemes, yet they are unable to produce the right sound. This suggests that though patients have great difficulty pronouncing words correctly, their comprehension of words is still quite good. This is characteristic for patients with Broca`s aphasia, while those with Wernicke`s aphasia show contrary symptoms: they are able to pronounce words correctly, but cannot understand what the words mean. That is why they often utter phonologically correct words (neologisms) that are not real words with a meaning.

Syntax

Syntax describes the rules of how words must be arranged to result in meaningful sentences. Humans in general usually know the syntax of their mother tongue and thus slip their tongue if a word happens to be out of order in a sentence. People with aphasia, however, often have problems with parsing of sentences, not only with respect to the production of language but also with respect to comprehension of sentences. Patients showing an inability of comprehension and production of sentences usually have some kind of anterior aphasia, also called agrammatical aphasia. This can be revealed in tests with sentences. These patients cannot distinguish between active and passive voice easily if both agent and object could play an active part. For example patients do not see a difference between “The boy chased the girl” and “The boy was chased by the girl”, but they do understand both “The boy saw the apple” and “The apple was seen by the boy”, because they can seek help of semantics and do not have to rely on syntax alone. Patients with posterior aphasia, like for example Wernicke`s aphasia, do not show these symptoms, as their speech is fluent. Comprehension by mere syntactic means would be possible as well, but the semantic aspect must be considered as well. This will be discussed in the next part.

Semantics

Semantics deals with the meaning of words and sentences. It has been shown that patients suffering from posterior aphasia have severe problems understanding simple texts, although their knowledge of syntax is intact. The semantic shortcoming is often examined by a Token Test, a test in which patients have to point to objects referred to in simple sentences. As might have been guessed, people with anterior aphasia have no problems with semantics, yet they might not be able to understand longer sentences because the knowledge of syntax then is involved as well.

	anterior Aphasia (e.g. Broca)	**posterior Aphasia (e.g. Wernicke)**
Phonology	phonetic and phonemic representation affected	phonemic representation affected
Syntax	affected	no effect
Syntax	no effect	affected

In general studies with lesioned people have shown that anterior areas are needed for speech output and posterior regions for speech comprehension. As mentioned above anterior regions are also more important for syntactic processing, while posterior regions are involved in semantic processing. But such a strict division of the parts of the brain and their responsibilities is not possible, because posterior regions must be important for more than just sentence comprehension, as patients with lesions in this area can neither comprehend nor produce any speech. (Barnich, 1997, pp. 283–293)

Evidence from Advanced Neuroscience Methods

Measuring the functions of both normal and damaged brains has been possible since the 1970s, when the first brain imaging techniques were developed. With them, we are able to "watch the brain working" while the subject is e.g. listening to a joke. These methods show whether the earlier findings are correct and precise.

Generally, imaging shows that certain functional brain regions are much smaller than estimated in brain lesion studies, and that their boundaries are more distinct (cf. Banich p. 294). The exact location varies individually, therefore bringing the results of many brain lesion studies together caused too big estimated functional regions before. For example, stimulating brain tissue electrically (during epilepsy surgery) and observing the outcome (e.g. errors in naming tasks) led to a much better knowledge where language processing areas are located.

PET studies (Fiez & Petersen, 1993, as cited in Banich, p. 295) have shown that in fact both anterior and posterior regions were activated in language comprehension and processing, but with different strengths – in agreement with the lesion studies. The more active speech production is required in experiments, the more frontal is the main activation: For example, when the presented words must be repeated.

Another result (Raichle et al. 1994, as referred to in Banich, p. 295) was that the familiarity of the stimuli plays a big role. When the subjects were presented well-known stimuli sets in well-known experimental tasks and had to repeat them, anterior regions were activated. Those regions were known to cause conduction aphasia when damaged. But when the words were new ones, and/or the subjects never had to do a task like this before, the activation was recorded more posterior. That means, when you repeat an unexpected word, the heaviest working brain tissue is about somewhere under your upper left earlap, but when you knew this word that would be the next to repeat before, it is a bit nearer to your left eye.

Visual Language Processing

The processing of written language is performed when we are reading or writing and is thought to happen in a distinct neural processing unit than auditory language processing. Reading and writing respectively rely on vision whereas spoken language is first mediated by the auditory system. Language systems responsible for written language processing have to interact with a sensory system different from the one involved in spoken language processing.

Visual language processing in general begins when the visual forms of letters ("c" or "C" or "c") are mapped onto abstract letter identities. These are then mapped onto a word form and the corresponding semantic representation (the "meaning" of the word, i.e. the concept behind it). Observations of patients that lost a language ability due to a brain damage led to different disease patterns that indicated a difference between perception (reading) and production (writing) of visual language just like it is found in non-visual language processing.

Alexic patients possess the ability to write while not being able to read whereas patients with agraphia are able to read but cannot write. Though alexia and agraphia often occur together as a result of damage to the angular gyrus, there were patients found having alexia without agraphia (e.g. Greenblatt 1973, as cited in M. T. Banich, "Neuropsychology", p. 296) or having agraphia without alexia (e.g. Hécaen & Kremin, 1976, as cited in M. T. Banich, "Neuropsychology", p. 296). This is a double dissociation that suggests separate neural control systems for reading and writing.

Since double dissociations are also found in phonological and surface dyslexia, experimental results support the theory that language production and perception respectively are subdivided into separate neural circuits. The two route model shows how these two neural circuits are believed to provide pathways from written words to thoughts and from thoughts to written words.

Two routes model

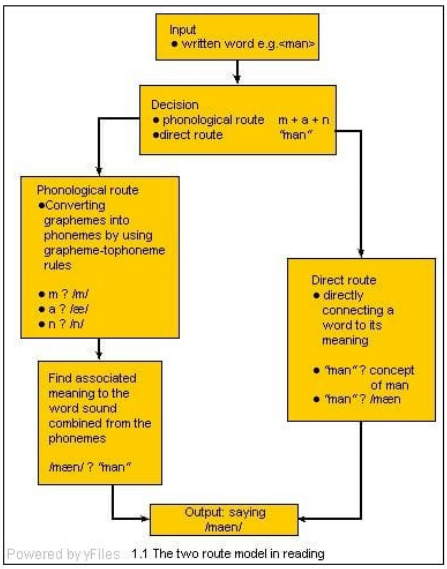


Figure 15.5.6: Each route derives the meaning of a word or the word of a meaning in a different way, depending on word familiarity. (Image from Wikimedia Commons; File:1 1 twoRouteModelInReading.JPG; https://commons.wikimedia.org/wiki/F...lInReading.JPG; by TilmanATuos at en.wikibooks; licensed under *GNU Free Documentation License*.).

In essence, the two routes model contains two routes. Each of them derives the meaning of a word or the word of a meaning in a different way, depending on how familiar we are with the word.

Using the **phonological route** means having an intermediate step between perceiving and comprehending of written language. This intermediate step takes places when we are making use of grapheme-to-phoneme rules. Grapheme-to-phoneme rules are a way of determining the phonological representation for a given grapheme. A grapheme is the smallest written unit of a word (e.g. “sh” in “shore”) that represents a phoneme. A phoneme on the other hand is the smallest phonological unit of a word distinguishing it from another word that otherwise sounds the same (e.g. “bat” and “cat”). People learning to read or are encountering new words often use the phonological route to arrive at a meaning representation. They construct phonemes for each grapheme and then combine the individual phonemes to a sound pattern that is associated with a certain meaning (see 1.1).

The **direct route** is supposed to work without an intermediate phonological representation, so that print is directly associated with word-meaning. A situation in which the direct route has to be taken is when reading an irregular word like “colonel”. Application of grapheme-to-phoneme rules would lead to an incorrect phonological representation.

According to Taft (1982, as referred to in M. T. Banich,“Neuropsychology“, p. 297) and others the direct route is supposed to be faster than the phonological route since it does not make use of a “phonological detour” and is therefore said to be used for known words (see 1.1). However, this is just one point of view and others, like Chastain (1987, as referred to in M. T. Banich, “Neuropsychology“, p. 297), postulate a reliance on the phonological route even in skilled readers.

The processing of written language in reading

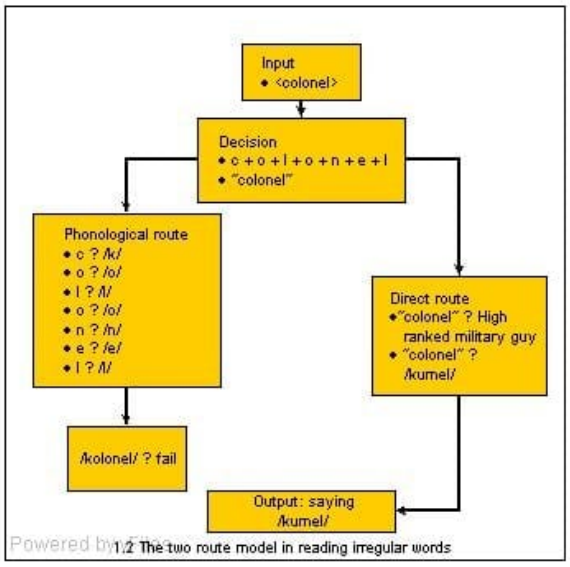


Figure 15.5.7: Regularity effects are common in cases of surface alexia. (Image from Wikimedia Commons; File:1 2 TwoRouteModelIrregularWords.JPG; https://commons.wikimedia.org/wiki/F...gularWords.JPG; by TilmanATuos at en.wikibooks; licensed under *GNU Free Documentation License*.).

Several kinds of alexia could be differentiated, often depending on whether the phonological or the direct route was impaired. Patients with brain lesions participated in experiments where they had to read out words and non-words as well as irregular words. Reading of non-words for example requires access to the phonological route since there cannot be a “stored” meaning or a sound representation for this combination of letters.

Patients with a lesion in temporal structures of the left hemisphere (the exact location varies) suffer from so called **surface alexia**. They show the following characteristic symptoms that suggest a strong reliance on the phonological route: Very common are regularity effects, that is a mispronunciation of words in which the spelling is irregular like "colonel" or "yacht" (see 1.2). These words are pronounced according to grapheme-to-phoneme rules, although high-frequency irregularly spelled words may be preserved in some cases, the pronunciation according to the phonological route is just wrong.

Furthermore, the would-be pronunciation of a word is reflected in reading-comprehension errors. When asked to describe the meaning of the word “bear”, people suffering from surface alexia would answer something like “a beverage” because the resulting sound pattern of “bear” was the same for these people as that for “beer”. This characteristic goes along with a tendency to confuse homophones (words that sound the same but are spelled differently and have different meanings associated). However, these people are still able to read non-words with a regular spelling since they can apply grapheme-to-phoneme rules to them.

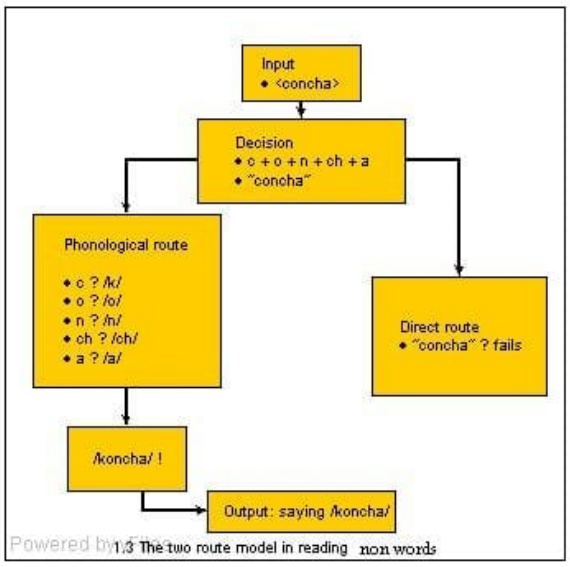


Figure 15.5.8: Patients with phonological alexia have to rely on the direct route. (Image from Wikimedia Commons; File:1 3 TwoRouteModelNonWords.JPG; https://commons.wikimedia.org/wiki/F...elNonWords.JPG; by TilmanATuos at en.wikibooks; licensed under *GNU Free Documentation License*.).

In contrast, **phonological alexia** is characterized by a disruption in the phonological route due to lesions in more posterior temporal structures of the left hemisphere. Patients can read familiar regular and irregular words by making use of stored information about the meaning associated with that particular visual form (so there is no regularity effect like in surface alexia). However, they are unable to process unknown words or non-words, since they have to rely on the direct route (see 1.3).

Word class effects and morphological errors are common, too. Nouns, for example, are read better than function words and sometimes even better than verbs. Affixes which do not change the grammatical class or meaning of a word (inflectional affixes) are often substituted (e.g. “farmer” instead of “farming”). Furthermore, concrete words are read with a lower error rate than abstract ones like “freedom” (concreteness effect).

Deep Alexia shares many symptomatic features with phonological alexia such as an inability to read out non-words. Just as in phonological alexia, patients make mistakes on word inflections as well as function words and show visually based errors on abstract words (“desire” → “desert”). In addition to that, people with deep alexia misread words as different words with a strongly related meaning (“woods” instead of “forest”), a phenomenon referred to as semantic paralexia. Coltheart (as referred to in the “Handbook of Neurolinguistics”, ch.41-3, p. 563) postulates that reading in deep dyslexia is mediated by the right hemisphere. He suggests that when large lesions affecting language abilities other than reading prevent access to the left hemisphere, the right-hemispheric language store is used. Lexical entries stored there are accessed and used as input to left-hemisphere output systems.

	Ability to read non-words	Ability to read irregular words	Ability to read regular words	Rely on	Disruption in	Other symptoms
Surface alexia	Ok	No	Ok	Phonological route	Direct route	-Confuse homophones - errors in word inflection
Phonological alexia	No	Ok	Ok	Direct route	Phonological route	-word class effects -morphological errors (e.g. farmer- farming) - concretness effect
Deep alexia	No	Ok	Ok	Direct route	Phonological route	-Confuse Homophones (e.g. pane -pain) -semantic paralexia (e.g. woods -forest)

Figure 15.5.9: Overview of alexia. (Image from Wikimedia Commons; File:Overview alexia.JPG; https://commons.wikimedia.org/wiki/F...iew_alexia.JPG; by TilmanATuos at en.wikibooks; licensed under *GNU Free Documentation License*.).

The processing of written language in spelling

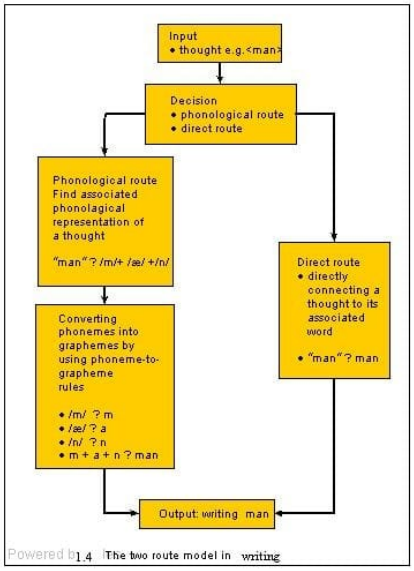


Figure 15.5.10: The phonological route is supposed to make use of phoneme-to-grapheme rules while the direct route links thought to writing without an intermediary phonetic representation. (Image from Wikimedia Commons; File:1 4 TwoRoutesModelWritig.JPG; https://commons.wikimedia.org/wiki/F...odelWritig.JPG; by TilmanATuos at en.wikibooks; licensed under *GNU Free Documentation License*).

Just like in reading, two separate routes –a phonological and a direct route- are thought to exist. The phonological route is supposed to make use of phoneme-to-grapheme rules while the direct route links thought to writing without an intermediary phonetic representation (see 1.4).

It should be noted here that there is a difference between phoneme-to-grapheme rules (used for spelling) and grapheme-to-phoneme rules in that one is not simply the reverse of the other. In case of the grapheme “k” the most common phoneme for it is /k/. The most common grapheme for the phoneme /k/, however, is “c”. **Phonological agraphia** is caused by a **lesion in the left supramarginal gyrus**, which is located **in the parietal lobe above** the **posterior** section of the **Sylvian fissure** (M. T. Banich,

"Neuropsychology", p. 299). The ability to write regular and irregular words is preserved while the ability to write non-words is not. This, together with a poor retrieval of affixes (which are not stored lexically), indicates an inability to associate spoken words with their orthographic form via phoneme-to-grapheme rules. Patients rely on the direct route, which means that they use orthographic word-form representations that are stored in lexical memory. **Lesions at** the **conjunction of the posterior parietal lobe** and the parieto-occipital junction cause so called **lexical agraphia** that is sometimes also referred to as **surface agraphia**. As the name already indicates, it parallels surface alexia in that patients have difficulty to access lexical-orthographic representations of words. Lexical agraphia is characterized by a poor spelling of irregular words but good spelling for regular and non-words. When asked to spell irregular words, patients often commit regularization errors, so that the word is spelled phonologically correct (for example, "whisk" would be written as "wisque").

	Ability to write non-words	Ability to write irregular words	Ability to write regular words	Rely on	Disruption in	Other symptoms
Phonological agraphia	No	Ok	Ok	Direct route	Phonological route	poor retrieval of affixes
Lexical agraphia	Ok	No	Ok	Phonological route	Direct route	

Figure 15.5.11: Overview of agraphia. (Image from Wikimedia Commons; File:Overview agraphia.JPG; https://commons.wikimedia.org/wiki/F...w_agraphia.JPG; by TilmanATuos at en.wikibooks; licensed under *GNU Free Documentation License*).

Evidence from Advanced Neuroscience Methods

How can we find evidence for the theory of the two routes. Until now neuroscientific research is not able to ascertain that there are neural circuits representing a system like the one described above. The problem of finding evidence for visual language processing on two routes in contrast to one route (as stated by e.g. from Seidenberg & McClelland as referred to in M. T. Banich,"Neuropsychology", p. 308) is that it is not clear what characteristic brain activation would indicate that it is either happening on two or one routes. To investigate whether there are one or two systems, neuroimaging studies examine correlations between the activations of the **angular gyrus**, which is thought to be a crucial brain area in **written language processing**, and other brain regions. It was found out that during reading of non- words (which would strongly engage the phonological route) the activation is mostly correlated with brain regions which are involved in phonological processing e.g. **superior temporal regions** (BA 22) and **Broca's area**. During reading of normal words (which would strongly engage the direct route) the highest activation was found in **occipital and ventral cortex**. That at least can imply that there are two distinct routes. However, these are conclusions drawn from highest correlations which do not ensure this suggestion. What neuroimaging studies do show is that the usage of a phonological and a direct route strongly overlap, which is rather unspectacular since it is quiet reasonable that fluent speakers mix both of the routes. Other studies additionally provide data in which the activated brain regions during reading of non-words and reading of normal words differ. ERP studies suggest that the left hemisphere possesses some sort of mechanism which responds to combinations of letters in a string, or to its orthography and/or to the phonological representation of the string. ERP waves differ, during early analysis of the visual form of the string, if the string represents a correct word or just pronounceable nonsense (Posner & McCandliss, 1993 as referred in M.T. Banich, "Neuropsychology," p. 307-308). That indicates that this mechanism is sensitive to correct or incorrect words.

The opposite hemisphere, the **right hemisphere**, in contrast to the left hemisphere, is not involved in abstract mapping of word meaning but is rather responsible for **encoding word specific visual forms**. ERP and PET studies provide evidence that the right hemisphere responds in a stronger manner than the left hemisphere to letter-like strings. Moreover divided visual field studies reveal that the right hemisphere can better distinguish between different shapes of the same letter (e.g. in different handwritings) than the left hemisphere. The contribution of visual language processing by both hemispheres is that the **right hemisphere first recognizes** a **written word as letter sequences**, no matter how exactly they look like, **then the language network in the left hemisphere builds** up an **abstract representation** of the word, **which is the comprehension of the word**.

Other symbolic systems

Most neurolinguistic research is concerned with production and comprehension of English language, either written or spoken.

However, looking at different language systems from a neuroscientific perspective can substantiate as well as differentiate acknowledged theories of language processing. The following section shows how neurological research of three symbolic systems, each different from English in some aspect, has made it possible to distinguish - at least to some extent - between brain regions that deal with the modality of the language (and therefore may vary from language to language, depending on whether the language in question is e.g. spoken or signed) from brain regions that seem to be necessary to language processing in general - regardless whether we are dealing with signed, spoken, or even musical language.

Kana and Kanji

Kana and Kanji are the two writing systems used parallel in the Japanese language. Since different approaches are used in them to represent words, studying Japanese patients with alexia is a great possibility to test the hypothesis about the existence of two different routes to meaning, discussed in the previous section.

The English writing system is phonological – each grapheme in written English roughly represents one speech sound – a consonant or a vowel. There are, however, other possible approaches to writing down a spoken language. In syllabic systems like the Japanese kana, one grapheme stands for one syllable. If written English were syllabic, it could e.g. (for example) include a symbol for the syllable “nut”, appearing both in the words “donut” and “peanut”. Syllabic systems are sound-based – since the graphemes represent units of spoken words rather than meaning directly, an auditory representation of the word has to be created in order to arrive at the meaning. Therefore, reading of syllabic systems should require an intact phonological route. In addition to kana, Japanese also use a logographic writing system called kanji, in which one grapheme represents a whole word or a concept. Different from phonological and syllabic systems, logographic systems don’t comprise systematical relationships between visual forms and the way they’re pronounced – instead, visual form is directly associated with the pronunciation and meaning of the corresponding word. Reading kanji should therefore require the direct route to meaning to be intact.

The hypothesis about the existence of two different routes to meaning has been confirmed by the fact that after brain damage, there can be a double dissociation between kana and kanji. Some Japanese patients can thus read kana but not kanji (surface alexia), whereas other can read kanji but not kana (phonological alexia). In addition, there is evidence that different brain regions of Japanese native speakers are active while reading kana and kanji, although like in the case of English native speakers, these regions also overlap.

Since the distinction between direct and phonological route also makes sense in case of Japanese, it may be a general principle common to all written languages that reading them relies on two independent (at least partially) systems, both using different strategies to catch the meaning of a written word – either associating the visual form directly with the meaning (the direct route), or using the auditory representation as an intermediary between the visual form and the meaning of the word (the phonological route).



The Japanese Kana sign for the syllable "mu"



The Japanese Kanji sign for the concept "Book", "writing", or "calligraphy

Figure 15.5.12: Two forms of Japanese writing elicit activity in different regions of the brain in native speakers.

Sign Language

From a linguistic perspective, sign languages share many features of spoken languages – there are many regionally bounded sign languages, each with a distinct grammar and lexicon. Since at the same time, sign languages differ from spoken languages in the way the words are “uttered”, i.e. in the modality, neuroscientific research in them can yield valuable insights into the question whether there are general neural mechanisms dealing with language, regardless of its modality.

Structure of SL

Sign languages are phonological languages - every meaningful sign consists of several phonemes (phonemes used to be called cheremes (Greek χερι: hand) until their cognitive equivalence to phonemes in spoken languages was realized) that carry no meaning as such, but are nevertheless important to distinguish the meaning of the sign. One distinctive feature of SL phonemes is the place of articulation – one hand shape can have different meanings depending on whether it’s produced at the eye-, nose-, or chin-level. Other features determining the meaning of a sign are hand shape, palm orientation, movement, and non-manual markers (e.g. facial expressions).

To express syntactic relationships, Sign Languages exploit the advantages of the visuo-spatial medium in which the signs are produced – the syntactic structure of sign languages therefore often differs from that of spoken languages. Two important features of most sign language's grammars (including American Sign Language (ASL), Deutsche Gebärdensprache (DGS) and several other major sign languages) are directionality and simultaneous encoding of elements of information:

- Directionality

The direction in which the sign is made often determines the subject and the object of a sentence. Nouns in SL can be 'linked' to a particular point in space, and later in the discourse they can be referred to by pointing to that same spot again (this is functionally related to pronouns in English). The object and the subject can then be switched by changing the direction in which the sign for a transitive verb is made.

- Simultaneous encoding of elements of information

The visual medium also makes it possible to encode several pieces of information simultaneously. Consider e.g. the sentence "The flight was long and I didn't enjoy it". In English, the information about the duration and unpleasantness of the flight have to be encoded sequentially by adding more words to the sentence. To enrich the utterance "The flight was long” with the information about the unpleasantness of the flight, another sentence (“I did not enjoy it") has to be added to the original one. So, in order to convey more information, the length of the original sentence must grow. In sign language, however, the increase of information in an utterance doesn’t necessarily increase the length of the utterance. To convey information about the unpleasantness of a long flight experienced in the past, one can just use the single sign for "flight" with the past tense marker, moved in a way that represents the attribute "long", combined with the facial expression of disaffection. Since all these features are signed simultaneously, no additional time is needed to utter "The flight was long" as compared to "The flight was long and I didn't enjoy it".

Neurology of SL

Since sentences in SL are encoded visually, and since its grammar is often based on visual rather than sequential relationships among different signs, it could be suggested that the processing of SL mainly depends on the right hemisphere, which is mainly concerned with the performance on visual and spatial tasks. However, there is evidence suggesting that processing of SL and spoken language might be equally dependent on the left hemisphere, i.e. that the same basic neural mechanism may be responsible for all language functioning, regardless of its modality (i.e. whether the language is spoken or signed).

The importance of the left hemisphere in SL processing indicated e.g. by the fact that signers with a damaged right hemisphere may not be aphasiacs, whereas as in case of hearing subjects, lesions in the left hemisphere of signers can result in subtle linguistic difficulties (Gordon, 2003). Furthermore, studies of aphasic native signers have shown that **damage to anterior portions of the left hemisphere (Broca’s area) result in a syndrome similar to Broca’s aphasia** – the patients lose fluency of communication, they aren’t able to correctly use syntactic markers and inflect verbs, although the words they sign are semantically appropriate. In contrast, patients with **damages to posterior portions of the superior temporal gyrus (Wernicke’s area)** can still properly inflect verbs, set up and retrieve nouns from a discourse locus, but **the sequences they sign have no meaning** (Poizner, Klima & Bellugi, 1987). So, **like in the case of spoken languages, anterior and posterior portions of the left hemisphere seem to be responsible for the syntax and semantics of the language respectively.** Hence, it’s not essential for the "syntax processing mechanisms" of the brain whether the syntax is conveyed simultaneously through spatial markers or

successively through word order and morphemes added to words - the **same underlying mechanisms might be responsible for syntax in both cases**.

Further evidence for the same underlying mechanisms for spoken and signed languages comes from studies in which fMRI has been used to compare the language processing of:

- 1. congenitally deaf native signers of British Sign Language,
- 2. hearing native signers of BSL (usually hearing children of deaf parents)
- 3. hearing signers who have learned BSL after puberty
- 4. non-signing subjects

Investigating language processing in these different groups allows making some distinctions between different factors influencing language organization in the brain - e.g. to what amount does deafness influences the organization of language in the brain as compared to just having SL as a first language(1 vs. 2), or to what amount does learning of SL as a first language differ from learning SL as native language (1,2 vs.3), or to what amount is language organized in speakers as compared to signers (1,2,3 vs.4).

These studies have shown that **typical areas in the left hemisphere** are activated in both native English speakers given written stimuli and native signers given signs as stimuli. Moreover, there are also areas that are equally activated both in case of deaf subjects processing sign language and hearing subjects processing spoken language – a finding which **suggests that these areas constitute the core language system regardless of the language modality** (Gordon, 2003).

Different from speakers, however, signers also show a strong activation of the right hemisphere. This is partly due to the necessity to process visuo-spatial information. Some of those areas, however (e.g. the **angular gyrus**) are only activated in native signers and not in hearing subjects that learned SL after puberty. This **suggests that the way of learning sign languages (and languages in general) changes with time:** Late learner's brains are unable to recruit certain brain regions specialized for processing this language (Newman et al., 1998).]

We have seen that evidence from aphasias as well as from neuroimaging suggest the **same underlying neural mechanisms to be responsible for sign and spoken languages.** It ‘s natural to ask whether these neural mechanisms are even more general, i.e. whether they are able to process any type of symbolic system underlying some syntax and semantics. One example of this kind of more general symbolic system is music.

Music

Like language, music is a human universal involving some combinatorial principles that govern the organizing of discrete elements (tones) into structures (phrases) that convey some meaning – music is a symbolic system with a special kind of **syntax and semantics**. It’s therefore interesting to ask whether music and natural language share some neural mechanisms: whether processing of music is dependent on processing of language or the other way round, or whether the underlying mechanisms underlying them are completely separate. By investigating the neural mechanisms underlying music we might find out whether the neural processes behind language are unique to the domain of natural language, i.e. whether language is modular. Up to now, research in the neurobiology of music has yielded contradicting evidence regarding these questions.

On the one hand, there is evidence that there is a double **dissociation of language and music abilities**. People suffering from **amusia** are unable to perceive harmony, to remember and to recognize even very simple melodies; at the same time they have **no problems in comprehending or producing speech**. There is even a case of a patient who developed amusia without aprosodia, i.e. although she couldn't recognize tone in musical sequences, she nevertheless could still make use of pitch, loudness, rate, or rhythm to convey meanings in spoken language (Pearce, 2005). This highly selective **problem in processing music (amusia)** can occur as a result of **brain damage**, or be inborn; in some cases it runs on families, suggesting a **genetic** component. The complement syndrome of amusia also exists – after suffering a **brain damage in the left hemisphere**, the Russian composer Shebalin **lost** his **speech** functions, **but** his **musical abilities remained** intact (Zatorre, McGill, 2005).

On the other hand, **neuroimaging** data suggest that **language and music** have a **common mechanism for processing syntactical structures**. The P600 ERP`s in the Broca area, measured as a response to ungrammatical sentences, is also elicited in subjects listening to musical chord sequences lacking harmony (Patel, 2003) – the expectation of typical sequences in music could therefore be mediated by the same neural mechanisms as the expectation of grammatical sequences in language.

A possible solution to this apparent contradiction is the dual system approach (Patel, 2003) according to which music and language share some procedural mechanisms (frontal brain areas) responsible for processing the general aspects of syntax, but

in both cases these mechanisms operate on different representations (posterior brain areas) – notes in case of music and words in case of language.

Summary

Many questions are yet to be answered. It is still unclear whether there is a distinct language module (that you could cut out without affecting anything in other brain functions) or not. As Evely C. Ferstl points out in her review, the next step after exploring distinct small regions responsible for subtasks of language processing will be to find out how they work together and build up the language network.

References & Further Reading

Books

- Brigitte Stemmer, Harry A. Whitaker. Handbook of Neurolinguistics. Academic Press (1998). ISBN 0126660557
- Marie T. Banich: Neuropsychology. The neural bases of mental function (1997).
- Ewa Dąbrowska: Language, Mind and Brain. Edinburgh University press Ltd.(2004)
- *a review:* Evelyn C. Ferstl, The functional neuroanatomy of text comprehension. What's the story so far?" from: Schmalhofer, F. & Perfetti, C. A. (Eds.), Higher Level Language Processes in the Brain:Inference and Comprehension Processes. Lawrence Erlbaum. (2004)
- Müller,H.M.& Rickert,G. (Hrsg.): Neurokognition der Sprache. Stauffenberg Verlag (2003)
- Poizner, Klima & Bellugi: What the hands reveal about the brain. MIT Press (1987)
- N. Chomsky: Aspects of the Theory of Syntax. MIT Press (1965). ISBN 0262530074
- Neville & Bavelier: Variability in the effects of experience on the development of cerebral specializations: Insights from the study of deaf individuals. Washington, D.C.: US Government Printing Office (1998)
- Newman et al.: Effects of Age of Acquisition on Cortical Organization for American Sign Language: an fMRI Study. NeuroImage, 7(4), part 2 (1998)

Links - english

- Robert A. Mason and Marcel Adam Just: How the Brain Processes Causal Inferences in Text
- Neal J. Pearlmutter and Aurora Alma Mendelsohn: Serial versus Parallel Sentence Comprehension
- Brain Processes of Relating a Statement to a Previously Read Text: Memory Resonance and Situational Constructions
- Clahsen, Harald: Lexical Entries and Rules of Language: A Multidisciplinary Study of German Inflection.
- Cherney, Leora (2001): Right Hemisphere Brain Damage
- Grodzinsky, Yosef (2000): The neurology of syntax: Language use without Broca's area.
- Müller, H.M. & Kutas, M. (1996). What's in a name? Electrophysiological differences between spoken nouns, proper names and one's own name. NeuroReport 8:221-225.
- Müller, H. M., King, J. W. & Kutas, M. (1997). Event-related potentials elicited by spoken relative clauses Cognitive Brain Research 4:193-203.

Attributions

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15.6: Dorsal and Ventral Language Streams

Contemporary Models of Speech Processing and Production

Contemporary researchers generally understand language as the product of multiple interacting brain systems rather than a single pathway connecting a few specialized regions. One of the most influential frameworks is the dual-stream model of speech processing, developed by Gregory Hickok and David Poeppel in the early 2000s (Hickok, 2009; Hickok & Poeppel, 2004, 2007). This model builds on the classical Wernicke–Lichtheim model but proposes that spoken language is processed through two partially distinct pathways: a dorsal stream and a ventral stream. Although these streams perform different functions, they work together whenever we listen to, understand, or produce speech.

The dorsal stream connects auditory information with the motor processes needed to produce speech. In other words, it helps the brain translate heard speech sounds into patterns of movement involving the mouth, tongue, and vocal tract. This pathway includes the posterior superior temporal gyrus, the planum temporale, and portions of the inferior parietal lobule. It then projects toward frontal regions, including the inferior frontal gyrus. The dorsal stream is especially important when people repeat unfamiliar words, learn new speech sounds, monitor their own speech, or compare the sounds they produce with the sounds they intended to produce.

The ventral stream supports speech comprehension by connecting speech sounds with meaning. It includes portions of the middle and inferior temporal gyri and extends toward anterior temporal and frontal regions. When a listener hears a familiar word, the ventral stream helps connect its sound pattern with stored knowledge about what that word means. The ventral pathway therefore contributes to recognizing words, accessing concepts, and understanding spoken sentences.

The dual-stream model has been valuable because it moves beyond the idea that language depends on a single route between Wernicke's area and Broca's area. It also helps explain why damage to different portions of the language network can produce different patterns of impairment. However, the model remains an approximation of a much more complicated system. Its division of language processing into two streams can make the organization of language appear more clearly separated than it actually is. The model also does not fully explain individual differences, the effects of language experience, multilingualism, learning, or the influence of social and conversational context. Consequently, researchers continue to refine the model as new evidence becomes available.

Researchers have also developed more detailed models of how the brain plans and produces speech. Levelt's model of speech production describes several stages that occur before a person speaks (Levelt, 1993, 1999; Indefrey & Levelt, 1999). A speaker must first decide what they want to communicate, select appropriate words, arrange those words into a grammatical structure, retrieve the necessary speech sounds, and prepare the resulting sequence for articulation. This model provides a detailed explanation of linguistic planning, but it is less specific about how the brain controls the physical movements required for speech and how speech production relates to the motor system more generally.

The Directions Into Velocities of Articulators, or DIVA, model addresses these motor components of speech production (Guenther et al., 1998; Tourville & Guenther, 2010; Guenther, 2016). DIVA proposes that speech depends on interactions between feedforward and feedback control systems. Feedforward commands are previously learned motor instructions that allow familiar speech sounds to be produced quickly. Feedback systems compare the sounds and movements actually produced with the speaker's intended target. When the system detects a mismatch, it can make corrections and update future motor commands. This process helps explain how people learn to pronounce new sounds and how they maintain accurate speech despite changes in the voice, mouth, or surrounding environment.

The Goal-Oriented Dynamics of Articulators, or GODIVA, model extends this framework by explaining how the brain selects, sequences, and produces more complex combinations of speech sounds (Bohland et al., 2010). GODIVA incorporates the timing and coordination required to produce syllables and longer speech sequences. Within this model, the primary motor cortex generates commands controlling speech movements, while the ventral premotor cortex contains learned representations of speech sounds. The inferior frontal gyrus contributes to the organization and sequencing of linguistic information. The basal ganglia assist with selecting and initiating appropriate motor programs, and the cerebellum helps regulate timing, coordination, and the correction of movement errors.

An important contribution of the DIVA and GODIVA models is that they place speech within the broader motor system. Speaking

is a language behavior, but it is also a highly practiced motor behavior requiring precise coordination among respiration, vocalization, and movements of the jaw, lips, and tongue. These models therefore connect research on language with what is known about motor planning, motor learning, sensory feedback, and error correction.

Together, the dual-stream, Levelt, DIVA, and GODIVA models describe different but complementary parts of spoken language. The dual-stream model focuses primarily on how speech sounds are processed and connected with meaning or motor representations. Levelt's model explains the stages of linguistic planning that occur before articulation. DIVA and GODIVA provide more detailed accounts of speech motor learning, sequencing, and control. Despite these substantial advances, researchers have not yet developed a single model that fully integrates speech perception, language comprehension, linguistic planning, and speech production. Current research therefore increasingly examines language as a flexible, distributed network in which auditory, linguistic, cognitive, and motor systems continuously interact.

Tremblay P and Brambati SM (2024) A historical perspective on the neurobiology of speech and language: from the 19th century to the present. Front. Psychol. 15:1420133. doi: 10.3389/fpsyg.2024.1420133

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15.7: The Right Hemisphere's Contribution to Language

Learning Objectives

1. Describe the cause and symptoms of hemineglect (unilateral neglect)
2. Describe the primary contributions of the right hemisphere to human language expression and comprehension
3. Identify and describe language pragmatics and its disorders
4. Describe theory of mind and how it is related to autism

Overview

Hemineglect, also known as unilateral neglect, following damage in the right parietal cortex is characterized by inability to attend to sensory inputs on the left side of the body leading to lack of awareness and emotional indifference to these inputs. Because of the disorder, such patients can "lose track" of the left side of their body and limbs because of the lack of attention to inputs from the left side of space including the left side of their own bodies. Some of these patients may fail to understand that the left side of their bodies belong to them. Right hemisphere damage can disrupt the emotional and contextual aspects of language use, suggesting that the right hemisphere is more emotional than the left and that normally the right hemisphere contributes the emotional aspects of human speech.

The Role of the Right Hemisphere in Language

To follow a conversation, a written document, or an exchange of witticisms, you must be able not only to understand the syntax of sentences and the meanings of words, but also to interrelate multiple elements and interpret them with respect to a given context. While various types of damage to the left hemisphere produce the many documented forms of aphasia, right hemisphere damage (RHD) causes a variety of communication deficits involving the interpretation of context. These deficits can be divided into two main categories.

The first category of RHD-induced deficits affect communication indirectly, by disrupting people's ability to interact effectively with their environment. One example of a deficit that can be caused by RHD is **hemineglect (unilateral neglect)**, in which an individual pays no attention to stimuli presented to the various sensory modalities on the left side of the body. The individual may also suffer from **anosognosia**: unawareness of such deficits. For instance, some people who have damage just posterior to the central sulcus in their **parietal lobe** in their **right** hemispheres cannot even recognize certain parts of their own bodies as being their own. Thus this type of RHD produces a kind of indifference that is the opposite of the minimum emotional investment required to establish harmonious communication.

The other major family of RHD-induced deficits affect communication and cognition directly. These deficits can be grouped under the heading of pragmatic communication disorders, pragmatics being the discipline that studies the relationships between language and the way that people use it in context. **Pragmatic disorders can be subdivided into disorders in prosody, discourse organization, and understanding of non-literal language.**

Prosody refers to the **intonation and stress** with which the phonemes of a language are **pronounced**. People with **aprosodia**—**RHD** that **impairs** their use of **prosody—cannot use intonation and stress to effectively express** the **emotions** they actually feel. As a result, they speak and behave in a way that seems flat and emotionless.

The **second category of pragmatic communication disorders** that can be caused by RHD affect the organization of discourse according to the rules that govern its construction. In some individuals, these disorders take the form of a **reduced ability to interpret** the signs that establish the **context** for a communication, or the nuances conveyed by certain words, **or the speaker's intentions or body language**, or the applicable **social conventions**. With regard to social conventions, for example, people generally do not address their boss the same way they would their brother, but people with certain kinds of RHD have difficulty in making this distinction.

Last but not least among the **types of pragmatic communication disorders caused by RHD** are **disorders** in the **understanding of non-literal language**. It is estimated that fewer than half of the sentences that we speak express our meaning

literally, or at least they do not do so entirely. For instance, whenever we use **irony, or metaphors, or other forms of indirect language**, people's ability to understand our actual meaning depends on their ability to interpret our intentions.

To understand irony, for example, people must apply two levels of awareness, just as they must do to understand jokes. First, they must understand the speaker's state of mind, and second, they **must understand the speaker's intentions** as to how his or her words should be construed. Someone who is telling a joke wants these words not to be taken seriously, while someone who is speaking ironically wants the listener to perceive their actual meaning as the opposite of their literal one.

Metaphors too express an intention that belies a literal interpretation of the words concerned. If a student turns to a classmate and says "This prof is a real sleeping pill", the classmate will understand the implicit analogy between the pill and the prof and realize that the other student finds this prof boring. But someone with RHD that affects their understanding of non-literal language might not get this message.

Lastly, the various indirect ways that we commonly use language in everyday life can cause problems for people with RHD. In such cases, the speaker's actual intention underlies their oral statement as such. For example, someone who says "I wonder what the time is now " is indirectly asking for someone to tell them the time, but a person with RHD may not understand that.

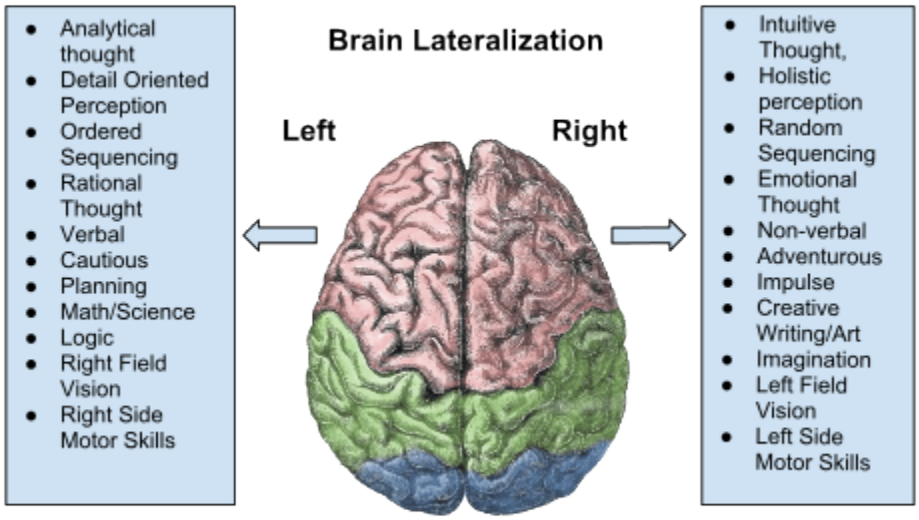


Figure 15.7.1: The oversimplification of lateralization in pop psychology. This belief was widely held even in the scientific community for some years. The left brain controls functions that have to do with logic and reason, while the right brain controls functions involving creativity and emotion. This simplified view of brain lateralization is no longer considered accurate by neuroscientists. Instead, new research using brain imaging shows that the two halves of the brain work together much more than earlier research had implied. (Image and first two sentences of caption from Wikimedia Commons, remainer of caption by Kenneth A. Koenigshofer, Ph.D.; File:Brain Lateralization.svg; https://commons.wikimedia.org/wiki/F...ralization.svg; by Chickensaresocute; licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license).

Though the **left hemisphere** is still regarded as the **dominant hemisphere for language**, the role of the **right hemisphere** in understanding the **context** in which language is used is now well established. We know that in the absence of the left hemisphere (for example, when Wada's test is performed which temporarily inactivates targeted brain tissue), the **right hemisphere can produce some rudimentary language.** But lesion studies have shown that the right hemisphere's role in language appears to be far wider—so much so that it is now more accurate to think of the **two hemispheres' language specializations** not as separate functions, but rather as a variety of abilities that **operate in parallel** and whose interaction makes human language in all its complexity possible.

Many theories have been offered to explain people's ability to adapt their use of language to the interpersonal context. One of these is the theory of mind. According to Premack and Woodruff (1978), the **theory of mind is the ability that lets people ascribe mental processes to other people**, to reason on the basis of these ascribed processes, and to understand the behaviors that arise from them. Premack and Woodruff were the first authors to use the term "theory of mind". They did so in a study on the ability of chimpanzees to ascribe beliefs and intentions to human beings. Since the time of this study, the theory of mind has been applied mainly in studies comparing the cognitive development of normal children and **autistic children**, because the latter represent a population that is known to display **deficits in social reasoning** from the very earliest age. In normal children,

theory of mind (ToM) develops between 3 and 4 years of age and is fully developed by 5 years of age (Roth & Dicke, 2012).

When experimental subjects are asked to **identify the emotional content of recorded sentences** that are played back into only one of their ears, they perform **better if these sentences are played into their left ear (which sends them to the right hemisphere)** than into their right (which sends them to the left hemisphere). These results confirm that the right hemisphere has a role in processing the emotional content of speech.

Summary

Hemineglect, also known as unilateral neglect, caused by damage to the right parietal lobe, is a disorder of attention to sensory inputs from the left side of space including the left side of one's own body. Language in patients with this disorder, reflects indifference to sensory inputs from the left half of space. The right hemisphere is involved in understanding the speaker's intentions and the emotional components of language. Language pragmatics including prosody and indirect language appear to be at least in part dependent upon processing by the right hemisphere. Some researchers suggest that damage to the right hemisphere may interfere with theory of mind, the ability to understand that others have minds, beliefs and intentions, and that persons with autism may have impairments in theory of mind.

References

Premack, D., & Woodruff, G. (1978). Does the chimpanzee have a theory of mind?. *Behavioral and brain sciences*, *1*(4), 515-526.

Roth, G., & Dicke, U. (2012). Evolution of the brain and intelligence in primates. *Progress in brain research*, *195*, 413-430.

Attributions

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16: EMOTION AND STRESS

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16.1: Affective Neuroscience-What is it?

Affect, in psychology, refers to the experience of emotions, moods, and feelings, so **affective neuroscience** examines how the brain creates emotional responses. Emotions are psychological phenomena that involve changes to the body (e.g., facial expression), changes in autonomic nervous system activity, feeling states (subjective responses), and urges to act in specific ways (motivations; Izard, 2010). Affective neuroscience aims to understand how matter (brain structures and chemicals) creates one of the most fascinating aspects of the mind—emotions. Affective neuroscience uses unbiased, observable measures that provide credible evidence to other scientists and laypersons on the importance of emotions. It also leads to biologically based treatments for affective disorders, such as depression and bipolar disorder.

Photo of a cap to detect changes in human emotion.

Figure 1. Although we experience emotions all the time, they are very difficult to describe and study. Fortunately, technological advances and the tools of neuroscience are making this easier.

The human brain and its emotional processes are complex and flexible. In order to study emotions in humans, human neuroscience must rely primarily on noninvasive techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) and on studies of individuals with brain lesions caused by accident or disease. Invasive neuroscience techniques, such as electrode implantation, lesioning, and hormone administration, are more powerful experimental tools but can only readily be used in nonhuman animals. While nonhuman animals possess simpler nervous systems and arguably more basic emotional responses than humans, affective circuits found in other species, particularly social mammals such as rats, dogs, and monkeys, function similarly to human affective networks. Thus, animal research serves as a valuable model for understanding affective processes in humans.

In humans, emotions and their associated neural systems have additional layers of complexity and flexibility. Compared to animals, humans experience a vast variety of nuanced and sometimes conflicting emotions. Humans also respond to these emotions in complex ways, such that conscious goals, values, and other cognitions influence behavior in addition to emotional responses. However, in this chapter, we focus on the similarities between organisms rather than the differences. We often use the term “organism” to refer to the individual who is experiencing an emotion or showing evidence of particular neural activations. An organism could be a rat, a monkey, or a human.

Across species, emotional responses are organized around the organism’s survival and reproductive needs. Emotions influence perception, cognition, and behavior to help organisms survive and thrive (Farb et al., 2013). Networks of structures in the brain respond to different needs, with some overlap between different emotions. Specific emotions are not located in a single structure of the brain. Instead, emotional responses involve networks of activation, with many parts of the brain activated during any emotional process. In fact, the brain circuits involved in emotional reactions include nearly the entire brain (Berridge & Kringelbach, 2013). Brain circuits located deep within the brain below the cerebral cortex are primarily responsible for generating basic emotions (Berridge & Kringelbach, 2013; Panksepp & Biven, 2012). In the past, research attention was focused on specific brain structures that will be reviewed here, but future research may find that additional areas of the brain are also important in these processes.

Illustration of the cross section of the brain and its structure

Figure 2: Some of the many structures involved in emotion processing in the brain.

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- structure in the brain © Noba is licensed under a CC BY-NC-SA (Attribution NonCommercial ShareAlike) license

definition

An emotional process that includes moods, subjective feelings, and discrete emotions.

×Close definition

The study of how the brain and nervous system process emotions

×Close definition

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16.2: Foundational and Contemporary Theories of Emotion

Learning Objectives

By the end of this section, you should be able to

- Discuss the similarities and differences between the early theories of emotion.
- Understand the shortcomings of early theories of emotion and list some specific behavioral conditions that early theories cannot adequately explain.
- Describe how the shortcomings of early theories led to more contemporary theories of emotion that describe emotions as complex interactions between cognitive, neural and physiological changes to external events

Three interrelated variables are presented repeatedly throughout this chapter to discuss the most important factors underlying emotions. The first involves the environmental context we inhabit. The environmental context is the source of ever-changing external stimuli and events that are perceived by the organism. Second, stimuli encompassing a given context possess the capacity to elevate or reduce bodily or physiological states by their impact on sympathetic or parasympathetic divisions of the autonomic nervous system, respectively. Third, autonomic changes, in turn, influence brain systems that appraise environment-body interactions, and provide cognitive resources to generate the broad range of conscious emotions and the behavioral responses to adapt appropriately to environmental events. Although each variable is vital in the generation of emotions, we shall see below that the major theories differ in their explanations of how each component of this triad, contributes to the conscious development of feelings, mood and emotions.

James Lange

William James (1884) and Carl Lange (1885) independently proposed a theory to explain how the experience of emotion influences behavior. Their collective views became known as the James-Lange theory of emotion. According to their understanding, “the conscious experience of emotion develops, only after an organism’s perception of its body’s level of autonomic arousal” to some external stimulus or event (see Step #3 in Figure 13.3).

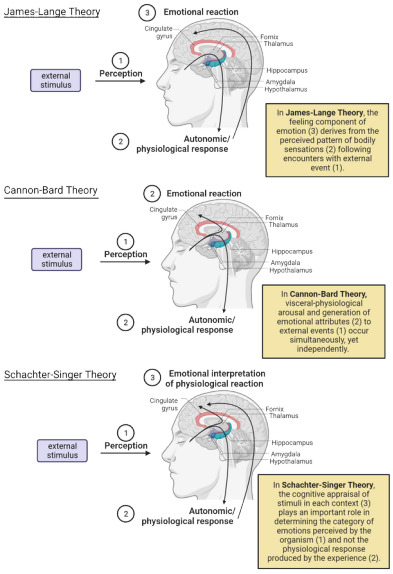


Figure 13.3 Theories of emotion

One common example to describe their theory concerns the cause of why fear is generated during an encounter with any of the three pictures in the second row of Figure 13.2. Contrary to common sense interpretations, the James-Lange theory posits that the emotion of fear is not developed because you are naturally afraid of any of the dangerous or threatening stimuli in those contexts. Rather, the feeling of fear is generated *after* an organism perceives the increased physiological and visceral changes generated

by the autonomic nervous system following direct experience with those events. Put simply, we become afraid not because of the stimulus, but because of the internal physiological changes the stimulus produces within us. *That is, the feeling component of emotion derives from the perceived pattern of bodily sensations following encounters with external events.*The James-Lange theory places an emphasis on autonomic specificity, which assumes that different patterns of physiological arousal shown as Step #2 in Figure 13.3 (e.g. elevations or reductions in heart rate, respiration, blood pressure, skin conductance, secretion of adrenal hormones, etc.) are the basis for the experience of distinct emotional states or feelings that are given the labels of fear, happiness, anger, sadness or the like. Several empirical studies report that discrete patterns of autonomic nervous system responses to a given external stimulus are correlated with the differentiation of separate emotion categories (Stephens, Christie and Friedman, 2010). For example, it is well-documented that the emotions of sadness or fear can be produced by exposing human participants to visual film clips or auditory stimuli. These types of experiments report that the emotion of fear is accompanied by predicted changes in heart rate acceleration, elevated blood pressure, increased skin conductance and faster respiration (Kreibig et al., 2007; Bosch et al., 2001). In contrast, laboratory conditions that induce the emotion of sadness produce consistent decelerations in cardiac functioning, deep and slow breathing and increased activation of the corrugator supercilii and zygomaticus facial muscles that have a dedicated role in producing frowning and other related facial expressions that correspond to suppressed mood states (Bosch et al., 2001; Ritz, et al., 2005).

The James-Lange theory is known as a bottom-up theory because, as Figure 13.3 illustrates, exposure to external stimuli (1) directly impacts physiological activity in the peripheral autonomic nervous system (2), that in turn is projected to the brain (3) to produce emotional reactions. Thus, the behavioral responses of fleeing from, or completely freezing to, some threatening stimulus will, according to James, elicit heightened visceral activity. Perception of these elevated bodily changes is the critical factor, James assumes, that leads to the direct *feeling of fear*. James supported his argument by stating that when emotions are stripped of their *bodily manifestations*, they are no longer emotions, but simply cold and neutral states of intellection perception (James, 1884, p. 193). Moreover, James suggested to imagine feeling sad without tears or sighing; feeling angry in the absence of muscle tension or heat in the face; experiencing fear when there is no racing of the heart or unsettling reactions in the stomach. Because this is not possible, James contends that *bodily responses* are necessary for the subjective feelings and play a causal role in generating those feelings that are commonly known as emotions.

Cannon-Bard

An extension of the James-Lange theory was proposed by Walter Cannon and his graduate student Philp Bard. Their theory came from observations of experiments in physiology and emotion in cats. The Cannon-Bard theory challenged James' initial propositions on three separate grounds. First, they asserted that autonomic and visceral changes that follow exposure to external stimuli develop much too slowly to generate the type of emotional feelings that occur almost instantaneously when organisms are exposed to emotion-provoking stimuli. Second, artificially generating visceral changes in the body by injecting the stress hormone adrenaline to increase sympathetic drive does not always induce discrete conscious emotions (Schachter and Singer 1962). Moreover, when visceral reactions are blocked pharmacologically with drugs, the perception and feeling of emotional reactions are not abolished (Reisenzein, 1983). The Cannon-Bard position was also strengthened by the finding that their cats continued to display species typical emotional reactions to threatening stimuli, even when signals representing heightened physiological states were blocked. They interrupted the flow of updated information from the viscera to the brain by severing visceral and spinal nerves that normally transmit important fluctuations in bodily states to discrete brain structures. Despite the absence of intact nerves to relay elevated changes in the viscera to the brain, Cannon and Bard observed that presentation of a threatening canine still elicited emotional reactions such as hissing, fighting responses or reflexive muscular responses leading to piloerection in their denervated cats. Similar findings are reported in humans who continue to display appropriate emotional reactions to events, even after spinal cord transections from accidents or surgery interrupt the flow of communication regarding changes in autonomic activity to the brain (Bermond, Niewenhuyse, Fasotti & Schuerman, 1991).

Cannon and Bard also noted the extensive number of visceral organs in the autonomic nervous system that show changes in activity to salient stimuli from the environment (e.g. heart, lungs, adrenals, stomach, liver, etc). As such, they concluded that the body's anatomy contains an insufficient number of nerves to convey the multiple changes across these organs to brain systems involved in generating conscious differences in emotional experiences. Based upon these limitations, the Cannon-Bard theory took issue with the neat sequential three-stage explanations of James-Lang and as depicted in Figure 13.3. They expanded this view by asserting that during an encounter with external stimuli (1), the thalamus is activated by the external event. The thalamus then sends the information in two simultaneous directions. It relays the specifics of the encounter to cerebral cortical structures (e.g. prefrontal, cingulate and insula cortex) to appraise the possible danger, safety or other emotional features of an experience (3). It also sends neural signals to subcortical structures such as the hypothalamus and amygdala to initiate physiological reactions in the body to adapt to the specific nature of the experience (2).

The Cannon-Bard theory of emotion introduces the idea that visceral-physiological arousal and generation of emotional

attributes to external events occur simultaneously, yet independently. Therefore, exposure to an alerting event such as a vicious canine or hissing snake will result in the feeling of fear during the same time that the body shows adaptive increases in sympathetic activation to initiate the behavioral response of fleeing or freezing to the external event. In contrast to the James-Lange theory, this viewpoint is considered a top-down theory since the initiation of emotional states are generated in cortical regions of the brain, and downstream projections from the thalamus to hypothalamus are attributed a role in producing the visceral physiological reactions in the organs of the body.

Schachter-Singer Two-Factor view

Stanley Schacter and Jerome Singer developed a theory of how human emotions evolve by incorporating the main premises from both Cannon-Bard and James-Lange. As such, it was named the two-factor theory since emotions were proposed to develop from interactions between autonomic physiological changes in the body with cognitive appraisals generated in the brain. According to the Two-Factor theory, (1) encounters with broad categories of external stimuli will (2) elicit increased autonomic activity within the body. However, (3) the brain plays an important role in *interpreting the context* in which the changes are elicited, before assigning a label or discrete emotion to the feelings that are experienced. This appraisal process involves obtaining knowledge regarding the nature of the immediate context and evaluating the personal significance (i.e. beneficial, harmful, rewarding, etc.) of what is happening in the environment. For example, encountering a hissing snake that jumps into the air will unmistakably evoke increased physiological arousal whether it is encountered in the woods, or while viewing an exhibit with a snake handler at a zoo. The Two-Factor theory proposes that although bodily changes are heightened in both circumstances, cognitive appraisal of the respective contexts will determine whether the emotion of fear and responses of startle and fleeing are generated in the woods, or the emotion of amazement or being astounded, surprised and entertained develops in the context of the zoo. Thus, cognitive interpretations of the actual items, events or stimuli in a context interact cooperatively with changes in body physiology to determine the exact label the brain assigns as a bona-fide emotion. It is these interactions that capture the true essence of any meaning we derive from a given experience.

The significance of cognitive processes and their importance in interpreting contextual attributes prior to assigning emotional labels was nicely illustrated in a well-cited study by the authors of this theory (Schacter & Singer, 1962). *Contextual influences* were assessed by assigning human participants to groups that completed a survey of subjective emotional reactions. Participants were assigned to either a pleasant context containing a euphoric actor or an unpleasant context where the actor was instructed to display a great deal of anger, pessimism, or discontent (Figure 13.4). *Physiological changes* were induced in participants by injecting either a placebo drug consisting of saline (0.9% NaCl) or the stress hormone epinephrine to produce arousal and physiological changes (i.e. increased heart rate, sweating, etc.) via the autonomic nervous system. The relative impact of *cognitive interpretive processing* on emotional perception was assessed by informing one group of the reactions to expect from the injection (i.e. you will experience a change in heart rate), while providing no information regarding the effects of the stress hormone to a second group.

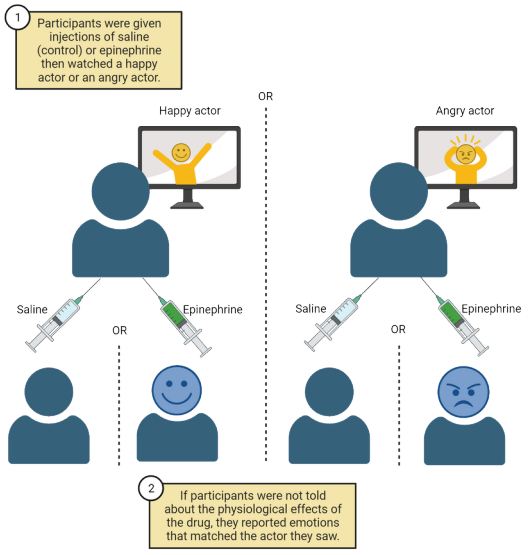


Figure 13.4 Schachter-Singer experiment

The most striking finding from this experiment is that the group given adrenaline and not informed about its effects reported

intense emotional reactions. This finding supports the James-Lange viewpoint. However, the specific emotion experienced (i.e. euphoria or anger) actually matched the *emotion displayed by the actor placed in the CONTEXT* where unsuspecting participants completed the subjective emotional questionnaires. Thus, epinephrine-injected participants placed with the euphoric actor reported intense pleasant feelings, whereas epinephrine-injected participants grouped with the angry actor experienced intense anger. It should be noted that only mild emotional responses were reported in participants *informed about the reactions of the adrenaline injection* and placed in either the happy or angry context. The authors noted that only mild responses were reported in these participants because they attributed the changes in physiological and emotional state directly to their knowledge (i.e. cognitive appraisal) regarding the actions of the injection *and not to the actors*. Taken together, both findings reveal that bodily/physiological changes may intensify any emotional experience but more importantly, *the cognitive appraisals of the context* in which these bodily changes occur has a direct impact on the type of emotion attributed to any given experience and the corresponding behaviors that are manifested therein.

To shed light on the distinctions between the Schachter-Singer and James-Lange models, consider how the experience of riding a thrilling roller coaster versus enduring extreme turbulence while flying in an airplane, may lead to completely opposing emotional reactions. Both conditions involve rapid changes in velocity or speed, unsteady elevated and dropping movements that lead to a bumpy uncomfortable ride. Both conditions also produce profound elevations in cardiac output, blood pressure and a number of other autonomic physiological variables. Despite the similarity in physiological changes produced by both conditions, most individuals experience emotions of joy, excitement and exhilaration after a roller coaster ride, while the emotions of fear, helplessness and worry are generally attributed to undergoing turbulence during an airplane flight. Notice that both experiences produce similar physiological outcomes. Yet, the emotions attributed to each are totally dependent on how the brain *interprets the context* that physiological changes occur in, prior to assigning labels to the conscious emotion that is experienced. In the context of the roller coaster, you are likely to view others laughing, raising their arms in excitement, and smiling widely. In contrast, the context of the turbulent flight may be filled with others displaying facial signs of distress and fear, as well as auditory signs such as sighs or moans, etc. This example reveals a shortcoming of the James-Lange theory of autonomic specificity that assumes specific categories of subjective emotions are produced by distinct physiological signatures. *According to the Schachter-Singer model, the cognitive appraisal of stimuli in each context, plays an important role in determining the category of emotions perceived by the organism and not the physiological response produced by the experience*.

Appraisal Theory Perspectives

There are several other viewpoints of emotion that belong to the category of appraisal-based theories. These theories are similar to the Schacter-Singer model in stressing that the same external event will not produce identical emotions across all individuals. Appraisal theories assert that emotional reactions are very different from one individual to another because of several complex processes that are initiated collectively to produce a final emotion. The foundation of these theories stress that what produces emotional reactions *is not the stimuli we encounter externally*, but how we *subjectively interpret or appraise* these stimuli relative to several personal variables. These variables include the meaning that external stimuli present in terms of our goals in life and concerns regarding our own well-being, as well as that of others, our job, country, etc.

Magda Arnold (1960) was one of the first Appraisal theorists who believed that physiological changes are not the only basis for emotional feelings. Rather, the act of cognitive appraisal of daily experiences is the defining feature and cause of emotional reactions. This view was later echoed by Richard Lazarus (1977) who also advanced the idea that appraisal *causes emotions*. The emotions are then ultimately expressed internally through physiological and motivational changes, and externally through behavioral responses. A defining feature of most of Appraisal theories is the insistence that emotions are not generated solely as reactions to events faced on a daily basis in the world. Instead, emotions are responses to our "ongoing relationships with the environment", that result in our evaluation of whether a given array of stimuli and events will serve to benefit or harm us (Lazarus, 1991). Lazarus viewed the Appraisal process in terms of two separate themes. The first identifies emotions as a consequence of forming evaluative judgments that renders meaning to our circumstances. The second concerns the role of emotions, as Appraisal theories provide a nice extension to the propositions developed by Schacter-Singer. They do so by defining the category or types of appraisals employed to evaluate the significance and relevance of circumstances we find ourselves in daily.

Here is how Lazarus describes these processes:

"This approach to emotion contains two basic themes: First, emotion is a response to evaluative judgments or meaning; second, these judgments are about ongoing relationships with the environment, namely how one is doing in the agenda of living and whether the encounter of the environment is one of harm or benefit."

The following list is not exhaustive but summarizes the types of appraisal dimensions organisms consider while appraising not only the context, but also the potential value any new experience presents to them. Appraisal theories assert that, for any

environmental encounter, the resulting emotion is a product of the individual evaluating the present situation relative to 1) *novelty*, or whether or not we have ever experienced this set of features before, 2) *expectedness*, is this event predictable based upon the configuration of environmental events, 3) *pleasantness*, is the circumstance one that will be positive and beneficial or aversive and bad for me, 4) *goal oriented*, is the situation congruent with my present goals or a distraction, 5) *fairness*, is the circumstance fair and just or dishonest and deceitful, 6) *control*, can I control the present events or is the locus of control outside of my responding, 7) *certainty*, which is similar to *expectedness* in being capable of predicting the outcome of this encounter, 8) *morality*, is the event in line with my concepts of what is or is not morally acceptable, and 9) *self-concept relevance*, will this event influence how I feel or view myself.

Answers derived from evaluating how new events rate on these, or a subset of these, dimensions determine how a given event will produce the emotion of happiness, sadness, fear, anger, same, disgust, or any combination of these states. Richard Lazarus (1991) categorized the list of appraisal dimensions into either primary appraisals or secondary appraisals. The former term is used to denote the type of assessments that directly influence an organism's well-being such as whether a given encounter is *goal oriented*, *pleasant*, *fair*, has *relevance to self-concept* or grouped collectively will impact how an organism will feel about itself. As such, primary appraisals determine the type of emotional response to any new encounter. *Secondary* appraisals assess how well one may be able to cope with a new encounter. These evaluations are derived by considering the appraisal dimensions of *expectedness*, *fairness* , *control* and *certainty*. Assessment of these dimensions allows organisms to reach the conclusion of whether they are competent enough to address the conditions of a new experience, or alternatively, if the present circumstances will require some form of emotion regulation to accept the lack of control of any given event.

Constructionist Theory view

Constructionist theories of emotion believe the memories representing your previous encounters with natural or inanimate objects, living organisms or personal episodes involving these events play an important role in generating emotions. According to this view, the vast reservoir of stored information regarding previously experienced stimuli, your reaction to these events, and the outcome of your responses is used by the brain to provide some of the conceptual meaning or perceptions to any new experiences an organism will face. The Constructionist's perspective is a bit different from those of previously discussed theories. Those viewpoints consider the brain as a passive medium to transduce or convert auditory, visual, tactile, etc. components of new events into neural activity. It is this constellation of inputs from various sensory modalities that provide an internal representation of what you are currently experiencing in the external or real world.

In contrast to these views, constructionist theory asserts a primary role of the brain in combining stimuli within your immediate context with past episodes saved in memory. These two sources of information are then used to construct a hypothesis or prediction of what an organism is experiencing. The point made with constructionist theories of emotion is that the brain itself, rather than individual features of environmental stimuli, is what *constructs* meaning to, or predictions of, what is occurring in our immediate circumstances. In essence, the brain is viewed as actively creating explanations for the sensory input it receives during new events, by generating internal models to infer the nature or causes of what we experience from the environment.

The merit of this concept explains why a single event may produce variations or totally different emotional reactions from one individual to the next. If the brain simply played a role in converting sound, sight, smells, taste and touch into neural patterns of activity to represent the features of environmental stimuli, then everyone would experience the same reactions. The constructionist's viewpoint readily accounts for why variations of emotional reactions occur to identical circumstances. Their premise is that the brain uses both previously stored knowledge, along with the configuration of newly imposed environmental stimuli, to create *simulations* or hypotheses about your immediate circumstances. Since the content of stored knowledge and memory varies from one individual to the next, it is conceivable that the actual perceptions everyone creates from environmental events will also vary.

This point is illustrated in Figure 13.5; where the same event (i.e. a funeral) creates opposing emotional reactions due to how the brain constructs the actual meaning to be attributed to any environmental encounter.



Celebration at a funeral



Sadness at a funeral

Figure 13.5 Differences in emotional reactivity to the same event, a funeral Constructionist theories assert the brain combines memory of previous events (we celebrate vs mourn death) with stimuli representing your immediate circumstances (funeral attendance) to construct emotions appropriate for honoring the death of a loved one at a funeral. Note the difference in emotional reactions to the same category of emotional experience. Image credit: Right: Picture provided by Carl and Lorraine Aveni and their world travels. From aveniadventure.weebly.com/blo...-jazz-funerals. CC BY NC SA 4.0; Left: By Eric Draper - White House Photo Essay, Public Domain, commons.wikimedia.org/w/inde...?curid=25500424

The image on the left depicts a traditional funeral in New Orleans, where many inhabitants have learned from an early age that death is actually celebrated. The response of celebration, rather than of mourning, evolves from learned *cultural beliefs or concepts*, that through death, their loved ones are advancing, graduating, or moving on to a much better place than the present earth. Contrast the emotions observed in this image with those in the image on the right, where individuals display sad and solemn emotions. Here, the *brain's learned concept* of funerals generates these opposing emotions because loved ones have learned that funerals are where you mourn the permanent loss or absence of the valuable roles they remember the deceased played in their lives. Thus, concepts learned through experience and embedded within memory are used by the brain as a foundation for guessing or predicting what is occurring in the world and in selecting the most appropriate behavioral responses to adapt flexibly to any given event.

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16.3: Basic Emotions

Desire: The neural systems of reward-seeking

One of the most important affective neuronal systems relates to feelings of desire or the appetite for rewards. Researchers refer to these appetitive processes using terms such as “wanting” (Berridge & Kringelbach, 2008), “seeking” (Panksepp & Biven, 2012), or “behavioral activation sensitivity” (Gray, 1987). When the appetitive system is aroused, the organism shows enthusiasm, interest, and curiosity. These neural circuits motivate the animal to move through its environment in search of rewards such as appetizing foods, attractive sex partners, and other pleasurable stimuli. When the appetitive system is underaroused, the organism appears depressed and helpless.

Much evidence for the structures involved in this system comes from animal research using direct brain stimulation. When an electrode is implanted in the lateral hypothalamus or in cortical or mesencephalic regions to which the **hypothalamus** is connected, animals will press a lever to deliver electrical stimulation, suggesting that they find the stimulation pleasurable. Other regions in the desire system also include the amygdala, nucleus accumbens, and **frontal cortex** (Panksepp & Biven, 2012). The neurotransmitter dopamine, produced in the mesolimbic and mesocortical dopamine circuits, activates these regions. It creates a sense of excitement, meaningfulness, and anticipation. These structures are also sensitive to drugs such as cocaine and amphetamines, chemicals that have similar effects to dopamine (Panksepp & Biven, 2012).

Photo of an ice cream sundae with a cherry on top

Figure 3. Just looking at an image of appealing food should increase the activity in your left frontal cortex. Yum!

Research in both humans and nonhuman animals shows that the left frontal cortex (compared to the right frontal cortex) is more active during appetitive emotions such as desire and interest. Early researchers noted that persons who suffered damage to the left frontal cortex developed depression, whereas those with damage to the right frontal cortex developed mania (Goldstein, 1939). The relationship between left frontal activation and approach-related emotions has been confirmed in healthy individuals using EEG and fMRI (Berkman & Lieberman, 2010). For example, increased left frontal activation occurs in 2- to 3-day-old infants when sucrose is placed on their tongues (Fox & Davidson, 1986), and in hungry adults as they view pictures of desirable desserts (Gable & Harmon-Jones, 2008). In addition, greater left frontal activity in appetitive situations has been found to relate to dopamine (Wacker et al., 2013).

“Liking”: The neural circuits of pleasure and enjoyment

Surprisingly, the amount of desire an individual feels toward a reward need not correspond to how much they like that reward. The neural structures responsible for enjoying rewards differ from those involved in desiring rewards. “Liking” (e.g., enjoyment of a sweet liquid) can be measured in babies and nonhuman animals by measuring licking speed, tongue protrusions, and happy facial expressions, whereas “wanting” (desire) is shown by the willingness to work hard to obtain a reward (Berridge & Kringelbach, 2008). Liking has been distinguished from wanting in research on topics such as drug abuse. For example, drug addicts often desire drugs even when they know that the ones available will not provide pleasure (Stewart et al., 1984).

Research on liking has focused on a small area within the **nucleus accumbens** and on the posterior half of the ventral pallidum. These brain regions are sensitive to opioids and endocannabinoids. Stimulation of other regions of the reward system increases wanting but does not increase liking and, in some cases, even decreases liking. The research on the distinction between desire and enjoyment contributes to the understanding of human addiction, particularly why individuals often continue to frantically pursue rewards such as cocaine, opiates, gambling, or sex, even when they no longer experience pleasure from obtaining these rewards due to habituation.

The experience of pleasure also involves the **orbitofrontal cortex**. Neurons in this region fire when monkeys taste or merely see pictures of desirable foods. In humans, this region is activated by pleasant stimuli, including money, pleasant smells, and attractive faces (Gottfried et al., 2002; O’Doherty et al., 2001; 2002; 2003).

Fear: The neural system of freezing and fleeing

Photo of a snake coiled on a tree branch.

Figure 4. Because fear is so important for our survival (i.e., fear informs us when something threatens us), our brains are able to "recognize" frightening stimuli before we are even consciously aware of them.

Fear is an unpleasant emotion that motivates avoidance of potentially harmful situations. Slight stimulation of fear-related brain areas causes animals to freeze, whereas intense stimulation causes them to flee. The fear circuit extends from the central amygdala to the **periaqueductal gray** in the midbrain. These structures are sensitive to glutamate, corticotrophin-releasing factor, adreno-cortico-trophic hormone, and several different neuropeptides. Benzodiazepines and other tranquilizers inhibit activation in these areas (Panksepp & Biven, 2012).

The role of the amygdala in fear responses has been extensively studied. Perhaps because fear is so important to survival, two pathways send signals to the **amygdala** from the sensory organs. When an individual sees a snake, for example, the sensory information travels from the eye to the **thalamus** and then to the **visual cortex**. The visual cortex sends the information on to the amygdala, provoking a fear response. However, the thalamus also quickly sends the information straight to the amygdala so that the organism can react before consciously perceiving the snake (LeDoux et al., 1990). The pathway from the thalamus to the amygdala is fast but less accurate than the slower pathway from the visual cortex. Damage to the amygdala or areas of the ventral hippocampus interferes with fear conditioning in both humans and nonhuman animals (LeDoux, 1996).

Rage: The circuits of anger and attack

Anger or rage is an arousing, unpleasant emotion that motivates organisms to approach and attack (Harmon-Jones et al., 2013). Anger can be evoked through goal frustration, physical pain, or physical restraint. In territorial animals, anger is provoked by a stranger entering the organism's home territory (Blanchard & Blanchard, 2003). The neural networks for anger and fear are near one another but separate (Panksepp & Biven, 2012). They extend from the medial amygdala, through specific parts of the hypothalamus, and into the periaqueductal gray of the midbrain. The anger circuits are linked to the appetitive circuits, such that lack of an anticipated reward can provoke rage. In addition, when humans are angered, they show increased left frontal cortical activation, supporting the idea that anger is an approach-related emotion (Harmon-Jones et al., 2013). The neurotransmitters involved in rage are not yet well understood, but the neurotransmitter and neuromodulator Substance P (also involved in pain and stress) may play an important role (Panksepp & Biven, 2012). Other neurochemicals that may be involved in anger include testosterone (Peterson & Harmon-Jones, 2012) and arginine-vasopressin (Heinrichs et al., 2009). Several chemicals inhibit the rage system, including opioids and high doses of antipsychotics, such as chlorpromazine (Panksepp & Biven, 2012).

Love: The neural systems of care and attachment

Black and white of of a teenage school boy and a girl about to kiss

Figure 5. Just as scientists today distinguish between types of love like "romantic" and "parental," so did the ancient Greeks, who used the terms "eros" and "storge."

For social animals such as humans, attachment to other members of the same species produces the positive emotions of attachment: love, warm feelings, and affection. The emotions that motivate nurturing behavior (e.g., maternal care) are distinguishable from those that motivate staying close to an attachment figure in order to receive care and protection (e.g., infant attachment). Important regions for maternal nurturing include the dorsal **preoptic area** (Numan & Insel, 2003) and the bed nucleus of the **stria terminalis** (Panksepp, 1998). These regions overlap with the areas involved in sexual desire and are sensitive to some of the same neurotransmitters, including oxytocin, arginine-vasopressin, and **endogenous** opioids (endorphins and enkephalins).

Grief: The neural networks of loneliness and panic

The neural networks involved in infant attachment are also sensitive to separation. These regions produce the painful emotions of grief, panic, and loneliness. When infant humans or other infant mammals are separated from their mothers, they produce distress vocalizations or crying. The attachment circuits are those that cause organisms to produce distress vocalizations when electrically stimulated.

The attachment system begins in the midbrain periaqueductal gray, very close to the area that produces physical pain responses, suggesting that it may have originated from the pain circuits (Panksepp, 1998). Separation distress can also be evoked by

stimulating the dorsomedial thalamus, ventral septum, dorsal preoptic region, and areas in the bed nucleus of stria terminalis (near sexual and maternal circuits; Panksepp et al., 1988).

These regions are sensitive to endogenous opiates, oxytocin, and prolactin. All of these neurotransmitters prevent separation distress. Opiate drugs such as morphine and heroin, as well as nicotine, artificially produce feelings of pleasure and gratification similar to those normally produced during positive social interactions. This may explain why these drugs are addictive. Panic attacks appear to be an intense form of separation distress triggered by the attachment system, and panic can be relieved by opiates. Testosterone also reduces separation distress, perhaps by reducing attachment needs. Consistent with this, panic attacks are more common in women than in men.

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definition

Part of the diencephalon. Regulates biological drives with pituitary gland.

×Close definition

The frontal cortex contains four main gyri.

×Close definition

A region of the basal forebrain located in front of the preoptic region.

×Close definition

A region of the frontal lobes of the brain above the eye sockets.

×Close definition

The gray matter in the midbrain near the cerebral aqueduct.

×Close definition

Almond-shaped neural structure that is primarily responsible for regulating emotional responses, especially fear.

×Close definition

A part of the diencephalon that works as a gateway for incoming and outgoing information.

×Close definition

The part of the brain that processes visual information that is located in the back of the brain.

×Close definition

A part of the anterior hypothalamus.

×Close definition

A band of fibers that runs along the top surface of the thalamus.

×Close definition

Originating from within an organism. For example, endogenous opioids such as endorphins are produced in the brain.

×Close definition

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16.4: Brain Structures Involved in Emotional States

Learning Objectives

By the end of this section, you should be able to

- Describe how information conveyed from sensory systems and autonomic nervous system inputs to the CNS influence the functioning of limbic areas to generate emotions.
- Discuss how the coordination of neural input into limbic brain structures are integrated to produce characteristic patterns of physiological and neural changes that evolve into appropriate emotional responses to a given external stimulus.
- Describe an example of a limitation in generalizing findings from animal studies to humans.
- Define the roles of specific cortical limbic structures in appraisal of emotionally-salient stimuli, generating the “feelings” from appraisals to develop adaptive strategies, and generating decisions and motor plans for responding to emotional stimuli.

An extensive amount of research is directed toward identifying the source or substrate of individual emotions in the brain. These efforts are quite challenging since distinct brain regions have multiple inter-connections with a diffuse set of other regions that in themselves process different types of internal and external stimuli. Thus, the search for a specific “neural signature or fingerprint” for each category of emotions has been a difficult process. The large variation in neural patterns observed within brain circuits during different states of internal arousal may explain why individual emotions are perceived as feeling different from one another. Still, decades of research in animal models and in humans have given us some insight into the major structures that mediate the experience of emotion and our behavioral/physiological responses to it. In this section, you will then learn how the brain integrates information from both internal systems and external sensory perception to form cognitive appraisal and evaluative functions to generate emotions that are appropriate for any given circumstance.

Papez circuit overview

The complicated but essential process of emotional experience and expression is regulated in part by an assembly of brain structures that comprise the Papez Circuit (Papez, 1937; MacLean, 1952). The important contributors to this neural system include the thalamus, hypothalamus, amygdala, hippocampus, anterior cingulate cortex , orbitofrontal cortex, insula cortex and striatum. This interconnected circuit of cortical and subcortical brain regions takes inputs from the internal and external environment and helps to evaluate those cues to generate emotional responses to them. Figure 13.11 shows the anatomical location of several of these major structures, as well as a schematic for how they connect to one another.

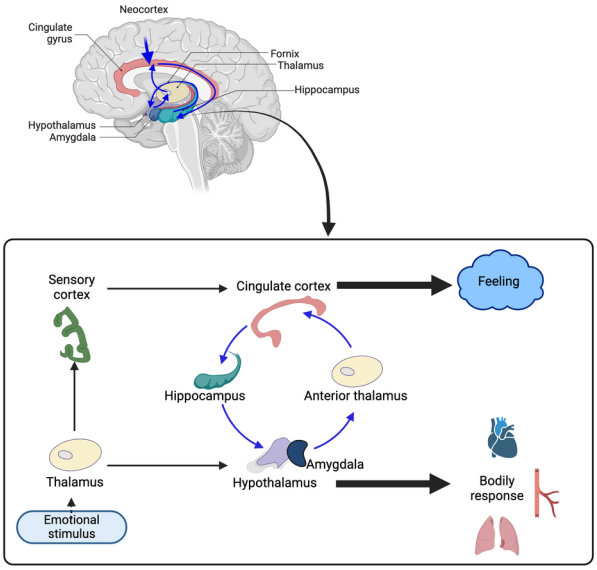


Figure 13.11 Papez circuit and interrelated structures The limbic and subcortical structures of the Papez circuit allow organisms to adapt to changes in the environment. These structures initiate neural and behavioral programs that return internal physiological and psychological states to an ideal balance. Image inspired by work of Dalgleish, T. The emotional brain. (2004). Nature Reviews Neuroscience, 5, 583–589.

The initial evidence that structures in the Papez circuit are involved in constructing emotions was provided by Heinrich Klüver and Paul Bucy (1938). These scientists removed large parts of the temporal lobe in monkeys that included the amygdala, hippocampus and selective white matter tracts or nerve bundles that connect some of the components comprising the Papez circuit. The range of behavioral and emotional deficits produced by removing these critical brain areas is now commonly known as the Kluver-Bucy Syndrome. One key deficit in Kluver-Bucy syndrome that pointed to the importance of these temporal lobe regions in emotion is a complete absence of the agonistic emotions of anger or fear to threatening stimuli (placidity). Appetitive-related emotional responses involving feeding are also severely impaired as subjects that have been satiated by a previous meal will still eat excessive quantities of food or other objects that do not even resemble food. Other perceptual and behavioral impairments included difficulty in identifying objects by sight, the sound of stimuli or touch, even when there is no damage to brain areas that process these three stimulus modalities. There is also severe global amnesia manifested by the inability to convert short-term memory into long-term memory, most likely due to the selective damage to the amygdala or hippocampus. Compulsive-like interests in exploring the immediate environment (hypermetamorphosis) is also frequently observed in Kluver-Bucy syndrome. These types of impairments were first observed in early studies of monkeys and cats and then were later observed clinically in humans with temporal lobe damage from accidents or following bilateral temporal lobe surgery to alleviate the debilitating symptoms of epilepsy.

Kluver-Bucy syndrome provided some clues to the functions of several components of the Papez circuitry. We now have a more detailed understanding of the unique roles that each brain area in the Papez circuit plays. In the subsequent sections, we will walk through the specific roles of several of these regions.

The thalamus relays interoceptive and exteroceptive sensory information

We will begin our tour of the individual components of the Papez circuit by first understanding the sensory information inputs that generate emotional responses. According to a recent view, emotions are constructed when internal physiological sensations are so intense that they are in the foreground of our awareness. This process of monitoring internal physiological conditions is called interoception. It stands in contrast to exteroception, which is our sensory perception of the external environment (Figure 13.12). Both of these senses contribute to our emotions. The converted signals from collective receptor cells of both forms of sensation (interoceptors and exteroceptors) are conveyed by different nerve pathways to individual regions of the thalamus. The thalamus, in turn, relays this information to both the hypothalamus and amygdala as shown in Figure 13.11. Both of these downstream structures are considered reflexive in nature, in that thalamic activation of particular regions within either structure automatically initiates behavioral, emotional and physiological responses without conscious awareness or thought.

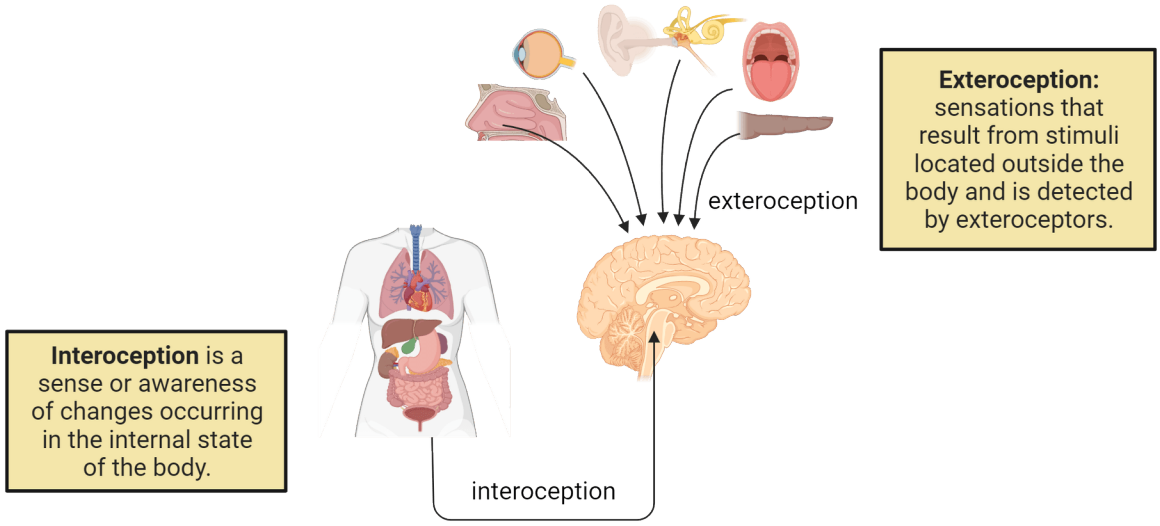


Figure 13.12 Interoception and exteroception

The reflexive emotional responses generated by the hypothalamus

The hypothalamus is critical to coordinating our bodily and psychological responses to the changing demands of our environment. Organisms must constantly adapt to changing environmental conditions in order to survive and reproduce. Fortunately, humans and animals are successful in adapting to dynamic external changes through the aid of body machinery and selective behavioral programs that return internal physiological and psychological states to some comfortable, ideal balance when a change in the environment occurs. We refer to the desired, ideal balance as homeostasis. The hypothalamus receives interoceptive input from throughout the body, via the relays in the thalamus, which it then uses to direct a number of physiological and behavioral responses.

The hypothalamus is composed of many individual nuclei, each of which can elicit specific emotion-related behaviors and their accompanying physiological changes. These behaviors fall broadly in to 3 categories:appetitive responses (*e.g. energy needs, replacement of nutrients and temperature regulation)*, agonistic behaviors (*e.g. self-protecting defending or attack behaviors)* and reproductive mating instincts. The early German researcher Walter Hess (1933) demonstrated in awake cats how applying electrical stimulation to activate neurons in discrete regions of the hypothalamus would produce a host of agonistic, appetitive or autonomic changes. For example, stimulation directed at one group of hypothalamic nuclei could cause the appearance of the emotions of fear and anger (agonistic behaviors). These readily observable emotional signs were accompanied by intense physiological changes in autonomic functioning (e.g. increased heart rate), as well as motor signs and instinctive behaviors where the stimulated cat would attack the first available object in its environment. Moreover, this set of bodily, emotional and behavioral changes persisted as long as the stimulation was applied and ceased only when the stimulation was terminated. In contrast, stimulation applied to other divisions of the hypothalamus slowed down the cat's heart rate and rendered the animal calm, tame, and sleepy (appetitive responses). These and other related findings of the provocation of physiological, emotional and behavioral changes by artificial stimulation of the brain strengthened the belief that physiological changes in the body lead to the development of discrete emotions that in turn determined the nature of behavioral responses an organism will emit on external environmental stimuli. These new discoveries also pointed to a critical contribution of the hypothalamus as a major initiator of behavior and physiological response to emotional stimuli.

The amygdala's reflexive role in emotional learning and fear

The response profiles in the amygdala are similar to those in the hypothalamus. One characteristic distinction between the two is that subdivisions of nuclei within the amygdala may produce reflexive changes not only to important external stimuli that are immediately threatening or rewarding, but also to neutral or once *unattended stimuli* that occur in concert with important events. In other words, the amygdala can form memories about the relationships between two or more stimuli that occur together or even in some sequential fashion during our daily interactions if one of the stimuli has emotional importance. For example, the hypothalamus may initiate feelings of hunger when children are in a classroom simply through olfactory stimuli associated with the smell of food from the cafeteria. The amygdala, however, may generate the same feelings of hunger by simply seeing

students from an adjacent class line up in the hallway to head to the cafeteria. This extension is produced by the capacity of amygdala neurons to form associations between previously neutral stimuli (i.e. students from a neighboring class proceeding to the cafeteria to eat) that serve to predict the eventual satisfaction of a meal you will eventually encounter in the cafeteria. The previous scenario is an example of associative learning that takes place in the amygdala, yet not in the hypothalamus. These learned associations equip humans and animals to use the predictive value of once *unattended stimuli* to anticipate appetitive or aversive events.

In addition to mediating emotion-related learning, the amygdala also appears to have a particular importance for generating the emotion of fear. Key evidence for the necessity of the amygdala for generating fear in humans has come from study of rare disorders that impair amygdala function, such as Urbach-Wiethe's disease. Urbach-Wiethe's disease is a rare disorder that causes a slow bilateral calcification and destruction of the amygdala starting around age 10 (Markowitsch, 1994) in roughly 50 to 75% of cases examined thus far (Staut & Naidich, 1998).

One of the most extensive case studies of Urbach-Wiethe's disease involves patient SM who was first documented by Tranel & Hyman in 1990. The late onset of the disease (starting in later childhood and progressing slowly from there) may explain why patient SM failed to notice that she did not feel the emotion of fear or threat until she went to the hospital for treatment of epilepsy at age 20. It was during these exams that SM was given brain scans with computed tomography (CT), and later magnetic resonance imaging (MRI), to reveal severe atrophy and destruction of the amygdala in both hemispheres.

Further neuropsychological exams revealed that SM showed unique highly specialized deficits associated with the expression of fear (Adolphs, Tranel & Damasio, 1994). She also failed to recognize facial expressions of fear in photographs similar to those used in the research discussed by Ekman and Pulchik discussed in 13.2 What Category of Feelings Are Considered as the "Basic Emotions"?. She had difficulty discerning what fearful facial expressions mean, yet expressions of happiness, disgust or joy were easily identified. SM is actually an experienced artist, but could not draw or sketch a scared face, since she expressed no knowledge of what such a face would look like. One researcher noted that SM displayed little if any emotional reactions when discussing highly emotional and traumatic life experiences (Tranel et al., 2006). The apparent damage to each of SM's amygdala was also manifested by major impairments in memory for nonverbal visual information, social behavior, and executive control functions, however, other specialized test confirmed that SM's general intelligence and language were no different than normal healthy adults (Tranel and Hyman, 1990). You can read more about the kinds of test done with SM in Diagnostic tests of patient SM.

Diagnostic tests of patient SM

Patient SM had a rare genetic disorder that caused her bilateral amygdala to be destroyed. Careful study of her emotional responses helped reveal a specific deficit in experiencing or expressing fear in a variety of contexts. In a study conducted by Feinstein, Adolphs, Damasio, and Tranel (2011), the emotional reactions of SM were examined under three conditions that produce moderate to extreme fear in normal adults. As shown in the top of Figure 13.13, SM was taken to an exotic pet store and actually handled both a large threatening snake and frightening tarantula spider. Despite her stated hate for snakes and spiders, when asked to rate her fear during these encounters from "0" (no fear) to "10" (intense fear), her fear levels never exceeded the rating of 2. Although, she did express the feeling of extreme curiosity, rather than fear. She also was accompanied by researchers into the building shown in top right of Figure 13.13, the previous Waverly Hills Sanatorium, one of the most notorious "naturally haunted" buildings in existence. It is converted into a tourist attraction during Halloween. This tourist attraction-made-"lab test" for SM was complete with haunting noises, monsters, and actors dressed in horrifying costumes that would often jump out from hidden locations to scare and frighten visitors. SM failed to display the slightest emotion of fright or fear during the tour but rather was observed laughing and scaring the monsters by poking them in the head. In a separate component of the study, Feinstein's group also documented SM's emotional response to a series of short movies that elicit different emotional reactions and included ten video clips from notable horror films. As shown in the middle of Figure 13.13, the maximum amount of fear elicited by these scary film clips in SM involved a rating of "1". Note how different the emotion of fear was expressed in SM relative to healthy controls who rated their subjective feelings of being frightened by the scary clips from "5 to 8".

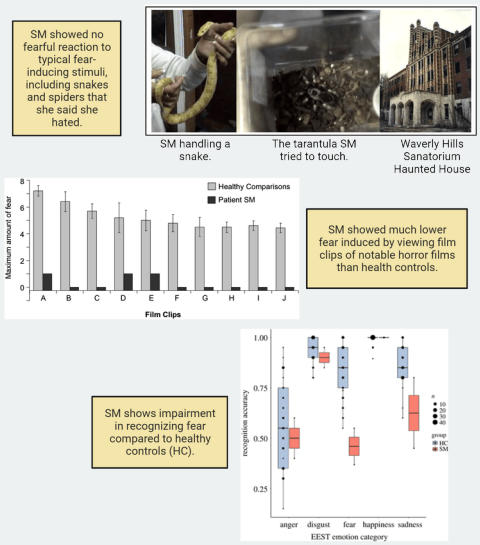


Figure 13.13 The human amygdala and the induction and experience of fear Image credit: Top photo and middle graph: Reprinted from Current Biology, Vol 21, Feinstein, J. S., Adolphs, R., Damasio, A., Tranel, D. The Human Amygdala and the Induction and Experience of Fear, Pages No. 34-38, Copyright 2011, with permission from Elsevier; Bottom box plot: Cardinale, E. M., Rever, J., O'Cpnnell, K., Turkeltaub, P. E., Trancel, D., Buchanan, T. W., Marsh, A.A. (2021). Bilateral amygdala damage linked to impaired ability to predict others' fear but preserved moral judgements about causing others fear. Proceedings of the Royal Society B. Vol 288 (1943). doi.org/10.1098/rspb.2020.2651. Reproduced with permission

More recent findings with patient SM verified a role of the amygdala in recognizing and appraising fear related stimuli in social conditions (Cardinale, et al., 2021). SM and healthy controls were given a series of 100 written statements previously shown to cause the reader to experience different levels of fear. The phrases included statements such as *('I could easily hurt you', 'I don't want to be friends anymore')*. Both SM and controls were tasked with predicting which emotion category (i.e. anger, disgust, fear, happiness or sadness) someone would experience when a given statement was directed to them. The results, displayed in the bottom of Figure 13.13, confirm the essential nature of the amygdala in registering and generating emotional responses to fear and threat-related environment stimuli. SM's ability to accurately recognize verbal stimuli that generates fear and sadness was significantly poorer than controls. In contrast, her capacity to identify statements leading to the emotions of happiness, disgust or anger were no different than the control group. The reliability of these results was demonstrated by documenting SM's performance across two separate test sessions. She displayed consistent poor emotion recognition performance for fear-eliciting statements in both sessions with a score of 55% accuracy relative to controls performance of 98% in the first session and an even worse 36% accuracy vs the control performance of 99% during the final testing session. The documented inability to experience fear as a result of bilateral and almost complete destruction of the amygdala in the case study involving SM provides convincing support for the important role played by the amygdala in both the appraisal and expression of one category of emotions involving both fear and sadness. These findings are supported by the growing amount of evidence showing a critical role of the amygdala in emotion-related disorders such as post-traumatic stress disorder (PTSD), anxiety and depression.

Neuroscience in the Lab

Neuroscientific Approaches in examining Fear/Threat Conditioning: An animal model of fear and anxiety in humans

The section above highlighted the role of the amygdala in producing the emotion of fear in response to threat related stimuli from the environment. In addition to studying diseases like Urbach-Weithe's disease, a great deal of animal research has confirmed the role of the amygdala in fear by showing that experimental lesions of parts of this brain region led to the apparent absence of fear. Today, more sophisticated approaches such as optogenetics are now available to study how brain regions mediate emotions in animal models. Optogenetics takes advantage of the finding that light sensitive proteins known as Channelrhodopsins-2 (ChR2) become active when exposed to light and release a number of excitatory ions that can be used to activate neurons in specific neural circuits. Methods: Optogenetics has more details about this method, but in short, by genetically expressing ChR2 in neurons and then shining a fiberoptic light on those neurons researchers can make neurons fire and then study what kinds of behavioral responses they see.

A study conducted by Kwon and colleagues (Kwon et al., 2014) employed the optogenetic technique to reveal how associative learning (*i.e. forming learned associations between 2 or more events that occur together in space or time*) in a fear conditioning task produces specific, plastic changes within the amygdala that results in the emotional expression of fear. In traditional forms of fear conditioning (top of Figure 13.14), a neutral tone is presented at a decibel that does not scare or induce any fear reactions in an animal. After 30 seconds of tone presentation, a mildly aversive footshock is administered to the animal's paws through the metal grid panels in the floor. Generally, only 5 to 6 "tone-footshock" pairings are necessary before the animal learns the predictive value of the "once-neutral" tone and begins to exhibit extreme emotional fear responses to the neutral tone, even before the footshock appears. The characteristic response indicative of the emotion of fear is the agonistic "freezing response". This form of associative learning discussed earlier is produced by the amygdala forming associations between the external auditory "tone" stimulus with the threatening and painful "footshock" stimulus applied to the animal's paws.

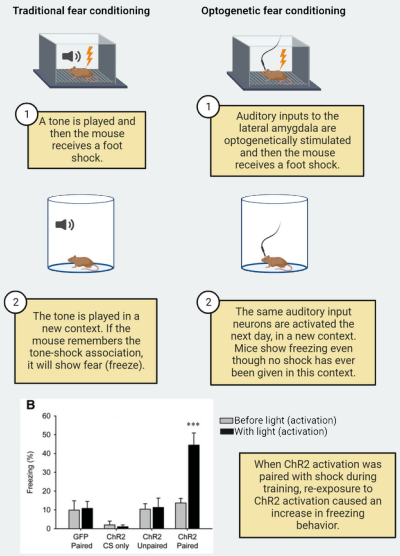


Figure 13.14 Optogenetic activation of fear memory Data from: Kwon et al., "Optogenetic activation of presynaptic inputs in lateral amygdala forms associative fear memory." Learn Mem. 2014 Nov; 21(11): 627–633. CC BY-NC 4.0

Kwon's group used optogenetics to determine if the amygdala is the actual site where associations between the tone is formed with the footshock during the generation of fear to neutral stimuli. The main manipulation involved using viral vectors to incorporate ChR2 within the parts of the auditory cortex that provide one source of auditory input to the lateral amygdala. The clever part of this study involved substituting the neutral tone with optogenetic activation of the auditory projections. To produce associative learning in this study, experimental animals received six pairings of optogenetic stimulation of auditory axons innervating the amygdala with a footshock, *rather than tone*-shock pairings (middle of Figure 13.14). The main question of interest here is whether associative memories develop following this artificial form of simulating auditory stimuli and pairing this experience with a threatening event.

This question was assessed twenty-four hours later by placing the animals in a new context (Context B), void of any previous associations and essentially fearless since no footshock was presented during this memory test. While in this neutral context, auditory inputs innervating the lateral amygdala were activated once again with optogenetic blue lights to represent the stimulus that was previously paired with the fearful footshock. The authors found that reactivating the connections between auditory inputs and the lateral amygdala (i.e. ChR2 paired group) was sufficient to produce the emotional response of fear even though no footshock was given in this new context. Notice in the graph in the bottom of Figure 13.14, the low level of fear learning observed in mice that received only optogenetic stimulation without footshock (ChR2 CS only) or those given optogenetic activation of auditory inputs that were not paired directly with footshock delivery (i.e. ChR2 Unpaired). The absence of associative learning in these group reveal that stimulation of inputs to the amygdala is not sufficient to produce emotional learning. Associative processes leading to learning in the lateral amygdala occurs only when auditory stimulation is paired with some emotion provoking event such as footshock delivery. The findings demonstrate that activation of auditory signals in the lateral amygdala serve as a potent conditioned stimulus that forms long term memories with the footshock to produce emotional responses of fear.

Insula Cortex

Thus far, we have discussed more reflexive regions of the Papez circuit, the amygdala and hypothalamus. Now, we will move on to brain regions that form cognitive appraisal and evaluative functions to generate emotions that are appropriate for any given circumstance. One major area that is involved in this process is the insula cortex. Insula cortex activity leads to an awareness of affective feelings and eventual emotions. Early studies conducted by the famous neurosurgeon Walter Penfield established that patients receiving electrical stimulation in the insula cortex reported unusual visceral sensations consistent with the experience of disgust associated with uneasy sensations in the stomach or throat, smelling or tasting something bad, and the experience of nausea (Penfield & Faulk 1955). In subsequent studies, it was found that insula stimulation produces a range of other emotions including feelings of empathy, intuition, unfairness, risk and uncertainty, trust and cooperation. The unique behavioral deficits that emerge after damage to the anterior insula cortex provide even greater clues to its function in emotions. Following insula lesions, patients do not express the emotion of disgust to unpleasant scenes involving body products, mutilations, etc. that are evoked in humans with an intact insula (Adolphs et al. 2003). They are also impaired in identifying signs of other emotions from either the facial expressions or inflections in voice produced by others.

The clinical and empirical observations discussed above make sense, given that the insula receives representations of the current state of internal bodily sensations (interoception) along with recreated replicas of the external environment (exteroception). The insula also has bi-directional communication with a variety of other cortical brain regions involved in emotion, memory, language and reasoning, such as the amygdala, ventral striatum, ventral medial prefrontal cortex, dorsolateral prefrontal cortex and anterior cingulate cortex. These connections are shown in Figure 13.15. Together, communication between these regions permit the insula to form appraisals of each emotional event by incorporating interoceptive and exteroceptive changes already processed in this area, with subjective feelings, personal reflections on the feelings and the cognitive resources to express them.

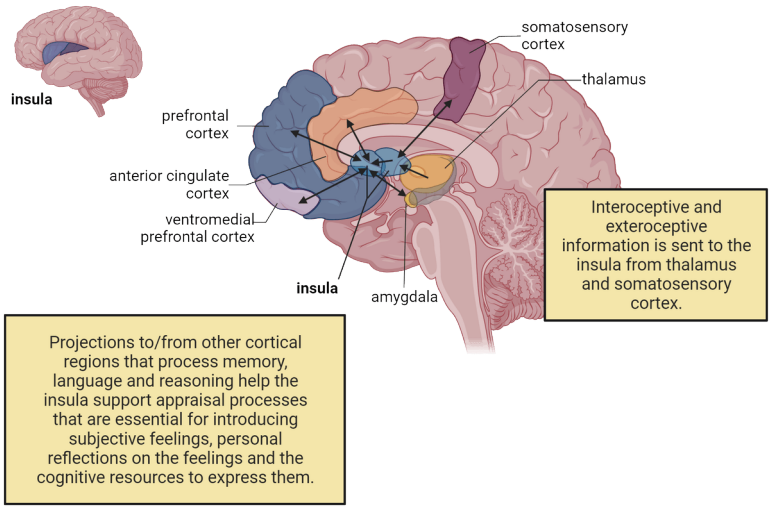


Figure 13.15 Insula cortex connections and function

Prefrontal Cortex

The prefrontal cortex can be functionally divided into two major areas: the orbitofrontal cortex and the dorsolateral prefrontal cortex. Figure 13.16 shows the relative locations of these regions on a 3D human brain surface rendering. Each of these regions has distinct functions in emotions.

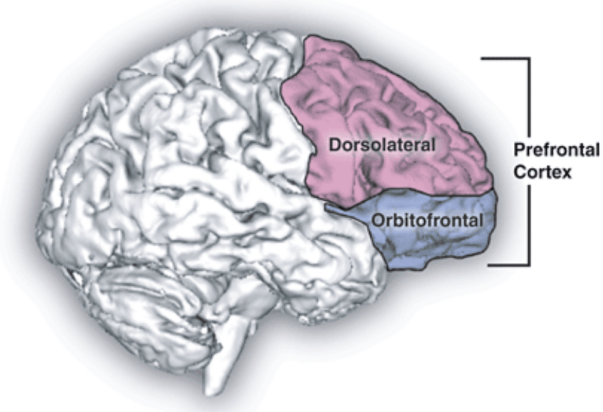


Figure 13.16 Prefrontal cortex regions Image By Natalie M. Zahr, Ph.D., and Edith V. Sullivan, Ph.D. - Natalie M. Zahr, Ph.D., and Edith V. Sullivan, Ph.D. "Translational Studies of Alcoholism Bridging the Gap" Alcohol Research & Health, Volume 31, Number 3, p.215-(2008)[1], Public Domain, https://commons.wikimedia.org/w/inde...?curid=8663554

Orbitofrontal cortex

As shown in Figure 13.17, the ventromedial prefrontal cortex is a part of the prefrontal cortex, located just above the eye sockets (or orbits). This location is why it is also called the orbitofrontal cortex.

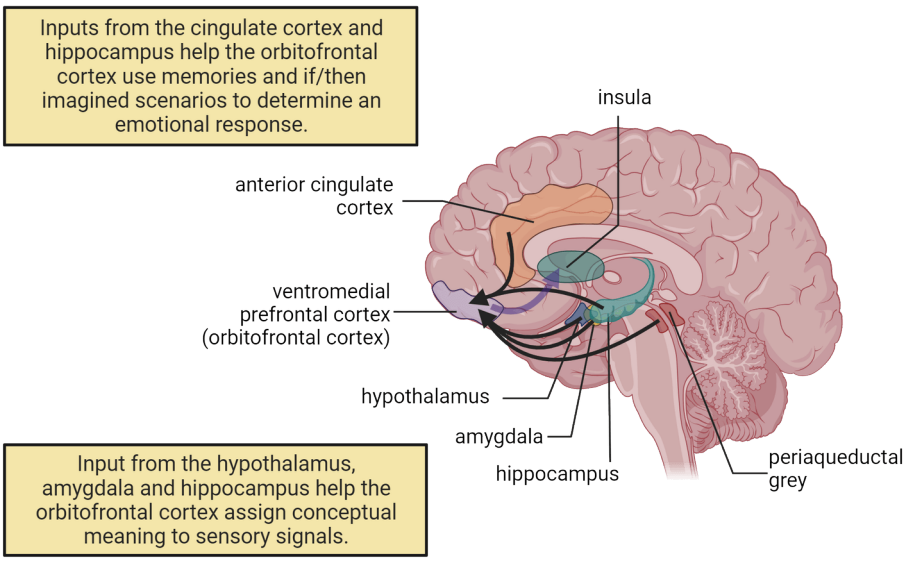


Figure 13.17 Ventromedial prefrontal cortex

The orbitofrontal cortex has multiple reported roles in emotion but we will focus here on 2 major ones: 1) assessing the goal-relevance of exteroceptive signals from the environment and 2) using internally generated thoughts pertaining to both episodic memories (*i.e. memory for personal events*) and imagined future events to determine the types of responses an organism should display to maintain allostasis in the face of new circumstances. The product of these internally generated processes in the orbitofrontal cortex is submitted to the insula to assist in the appraisal of new events. The importance of this evaluative process makes it easier to understand why humans that lack the vital contribution of the orbitofrontal cortex due to damage or surgery display extreme states of anger, lack self-control, and are more prone to rapid aggression without thinking about the consequences of these negative responses. Below, we discuss some of the connections in the brain that facilitate these two functions, which are also exemplified in Figure 13.17.

- *Assessing goal-relevance of exteroceptive signals*: Orbitofrontal cortex neurons are supplied with neural signals representing

every stimulus modality (exteroceptors) in the outer world. This arrangement may explain why neural activity in the orbitofrontal cortex is elevated when humans are exposed to somatosensory stimulation, visually presented scenes of erotic images, or facial expression involving either rewarding stimuli such as smiles or aversive stimuli in the form of angry expressions (for a review see, Dixon, Thiruchselvam, Todd, & Christoff, 2017). Interconnections with the amygdala, hypothalamus, and periaqueductal gray then help with assessing the goal-relevance of these exteroceptive signals. These areas provide information regarding rewards, punishment, current physiological needs and the agonistic or appetitive behaviors to exert on the environment to achieve these goals. The orbitofrontal cortex uses this information to assign positive or negative emotional labels to exteroceptive stimuli by considering how responses exerted on the environment in the past led to either favorable or undesirable consequences for the organism. The assessment role of the orbitofrontal cortex is in many ways an extension of the role of the amygdala in assigning affective value to sensory stimuli. The orbitofrontal cortex extends the role of the amygdala by learning the ever-changing relationships between sensory features of exteroceptive stimuli.

- *Using internal thoughts, memories and imagined events to determine a response*: The orbitofrontal cortex receives a great deal of information from brain structures involved in planning and simulating "if/then" scenarios of the possible outcomes of a given response. It is also the recipient of inputs from brain regions that store long term episodic memories of the outcomes of responses made in the past to exteroceptive stimuli including the hippocampus and cingulate cortex. These kinds of connections are the reason that activity of some orbitofrontal cortex neurons are more readily observed when humans are engaged in internally oriented thinking, but inhibited when it is necessary to focus attention on externally presented stimuli. The orbitofrontal cortex draws on these connections to contribute to an organism's personal appraisal of higher-order internal events, self-reflection of thoughts and memories triggered by a given event.

Dorsolateral Prefrontal Cortex.

The dorsolateral prefrontal cortex is a separate structure attributed a role in the process of emotional appraisal. Cognitive mechanisms in the dorsolateral prefrontal cortex are quite complex and perform a range of high-level computations on the behavioral actions an organism makes. Dorsolateral prefrontal cortex neurons are given the executive task of understanding the rules governing any given social environment, the goals of the organism in terms of allostasis and performing continuous updates or corrections of one's ongoing emotional state. This highly complex responsibility is a necessary component of emotion regulation, the process where value is assigned to emotional feelings created by initial appraisal processes and the behavioral actions that were generated as a result. The dorsolateral prefrontal cortex sits in the "executive's seat" by attending to the emotional evaluation process occurring in the cortical and subcortical structures discussed above. It uses this information to guide responses in specific contexts away from non-adaptive, short term payoffs of immediate rewards, towards more favorable behavioral actions that materialize into beneficial future outcomes.

Anterior Cingulate Cortex

The theories proposed by James-Lange and Cannon-Bard both stressed the importance of physiological reactions within the body as contributors to the development of emotions. We now know that this component of both theories is mediated by neural activation of the anterior cingulate cortex. The functions of the anterior cingulate cortex can be divided into 3 domains, summarized in Figure 13.18.

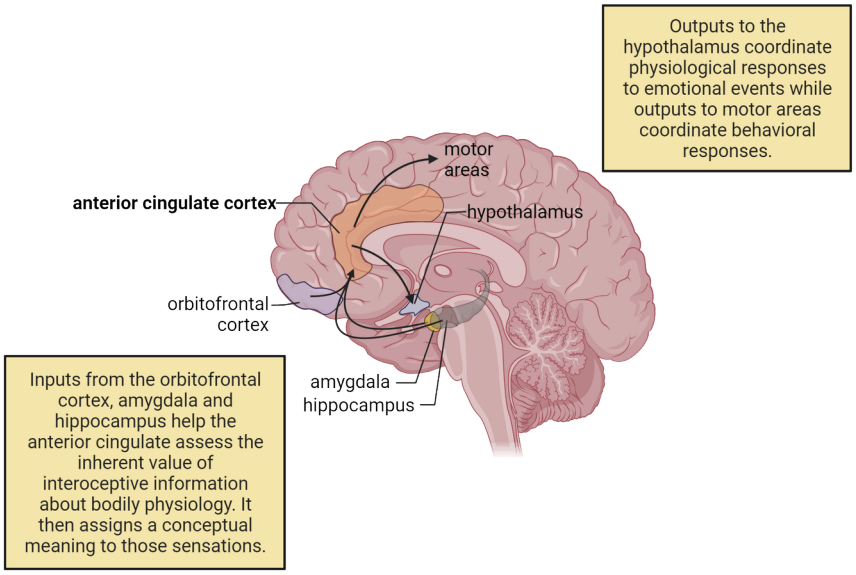


Figure 13.18 Anterior cingulate cortex and emotion

First, the anterior cingulate monitors internal physiology (e.g. heart rate, respiration) and makes evaluations to determine what level or intensity of physiological bodily adjustments are necessary to cope with the challenges posed by new experiences. To make these assessments, it uses important inputs from the orbitofrontal cortex, amygdala and hippocampus that project understanding of the inherent value, meaning, and also anticipated outcomes of a given situation. Downstream connections to the hypothalamus and other brainstem regions then allow it to influence internal physiological reactions.

Second, the cingulate cortex gives conceptual meaning to the physiological information it receives. It generates feelings of satisfaction when it deems the physiological information to reflect adaptation to external events, or states of displeasure when it assesses the behavioral and internal changes as not beneficial to the organism. Please note that the previous sections identified other brainstem and cortical structures that also process interoceptive signals. The contribution of the anterior cingulate cortex to emotions is somewhat different, however, since the appraisal processes undertaken in this area results in organisms developing*conceptual meanings* to the bodily sensations they experience. For example, many individuals avoid public speaking and the anticipation of even being in the stimulus context of an audience produces heightened levels of arousal and a number of unwanted interoceptive changes including raised heart rate, heavy breathing, tight feeling in the stomach or butterflies. These interoceptive changes also occur in experienced speakers, yet the*conceptual meaning* they apply to these changes may not be fear, anxiety or fright, but simply a suite of necessary signals to mark or denote the significance of the behavioral responses they are about to exert on the environment (i.e. public audience). The same application of *conceptual meaning* to internal changes is what distinguishes experienced, accomplished athletes from those who crumble under the stress and anxiety produced by these same interoceptive changes. The cognitive processing that takes place in the anterior cingulate cortex is what engenders one to not only to be aware of fluctuations in their interoceptive sensations, but to use conceptual knowledge to understand and regulate their emotional feelings that emerge in different contextual settings.

Third, the anterior cingulate cortex also assigns some positive or negative value to potential actions. It does this by assessing the degree of effort required to produce any potential action and maintaining a record of the observed consequences of the behavioral response (i.e. favorable or unfavorable) during an emotional encounter (Rangel, Camerer, & Montague, 2008). Direct anatomical connections with areas of the motor system allow the cingulate to create action or response plans.

Neuroscience Across Species

Generalization of findings of fear, threat and anxiety across species

Much of our study of emotions has been informed by animal studies, especially in rodents. While animal studies have greatly advanced our understanding of neural circuitry underlying emotion, not all results from animals have generalized well to humans. The neural circuitry supporting fear provides a good example of the challenges of generalizing from animal models to humans. Fear is a particularly well-studied emotion in rodent models because rodents have characteristic fear-related behaviors that are easy to observe, such as freezing. Early work in animal studies generated the idea that a dedicated fear

circuit exists in the brains of both rodents and humans to serve an evolutionary function of survival. The key to the fear circuit idea is that it is a single system and each piece is necessary to produce fear. Numerous animal studies have supported the existence of a fear circuit in rodent models with the amygdala performing a particularly critical role in generating fear.

More contemporary viewpoints challenge the fear circuitry position and propose that emotional responses are generated by a network of brain systems which differ in humans and rodents. Evidence against the fear circuit view in humans was obtained by studies demonstrating that humans with amygdala damage continued to display emotions of fear and threat despite an absence of the primary structure involved in the “fear circuit”. This study permitted three amygdala-lesioned participants to inhale 35% carbon dioxide CO2, which is known to produce panic attacks and fear in normal participants. Despite having extensive amygdala damage as a result of Urbach-Wieth disease, all three participants displayed excessive fear responses, panic attacks, and elevated physiological markers of fear such as increased respiration and heart rate (Feinstein, et al., 2013). These findings are unique in that previous studies reported a complete absence of fear or threat in Urbach-Wieth participants during presentation of fearful external stimuli including live snakes, spiders, tour of a haunted house or emotionally evocative horror films (Feinstein, Adolphs, Damasio & Tranel, 2011). These findings support the idea of a network of brain emotional systems in humans. This network is capable of responding to external threats (mediated via the amygdala). In addition, other brain emotion systems may elicit fear and threat through connections with acid-detecting chemoreceptors that are sensitive to internal changes produced by elevated concentrations of CO2 within the body.

The network position considers that, in humans, subjective feelings are mental states of *feeling* that are generated by higher order brain structures such as the prefrontal cortex, insula and cingulate cortices. These cortical structures are involved in planning, decision making, emotional regulation and emotional appraisal processing. According to this view, brain systems that generate*feelings* are completely separate from subcortical structures such as the amygdala and hypothalamus that play primary roles in detecting fear or threat. The major function of the subcortical systems are to prepare the organism by directing physiological changes in the body and defensive behavioral responses when organisms detect immediate sources of harm or danger such as those depicted in Figure 13.2, (or *a rapidly approaching vehicle, animal or human; a surprise quiz*), or when these uncomfortable states are uncertain or implied by some form of environmental stimuli (*e.g. plummeting economy that directly affects your line of employment; changes in the criteria for acceptance into graduate, medical, law or business school*).

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16.5: Experiences Can Alter the Brain

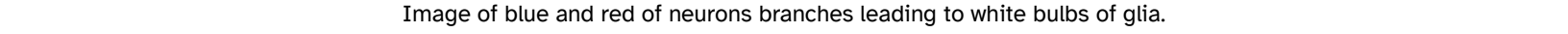


Figure 6. Neural plasticity can be summed up in the phrase: “Neurons that fire together, wire together.” Or in other words, when certain emotions are paired with certain contexts, we learn to associate the two together.

The responses of specific neural regions may be modified by experience. For example, the front shell of the nucleus accumbens is generally involved in appetitive behaviors, such as eating, and the back shell is generally involved in fearful defensive behaviors (Reynolds & Berridge, 2001, 2002). Research using human neuroimaging has also revealed this front–back distinction in the functions of the nucleus accumbens (Seymour et al., 2007). However, when rats are exposed to stressful environments, their fear-generating regions expand toward the front, filling almost 90% of the nucleus accumbens shell. On the other hand, when rats are exposed to preferred home environments, their fear-generating regions shrink, and the appetitive regions expand toward the back, filling approximately 90% of the shell (Reynolds & Berridge, 2008).

Media Attributions

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16.6: Brain Structures have Multiple Functions

Although much affective neuroscience research has emphasized whole structures, such as the amygdala and nucleus accumbens, it is important to note that many of these structures are more accurately referred to as complexes. They include distinct groups of nuclei that perform different tasks. At present, human neuroimaging techniques such as fMRI are unable to examine the activity of individual nuclei in the way that invasive animal neuroscience can. For instance, the amygdala of the nonhuman primate can be divided into 13 nuclei and cortical areas (Freese & Amaral, 2009). These regions of the amygdala perform different functions. The central nucleus sends outputs involving brain stem areas that result in innate emotional expressions and associated physiological responses. The basal nucleus is connected with striatal areas that are involved with actions such as running toward safety. Furthermore, it is not possible to make one-to-one maps of emotions onto brain regions. For example, extensive research has examined the involvement of the amygdala in fear, but research has also shown that the amygdala is active during uncertainty (Whalen, 1998) as well as positive emotions (Anderson et al., 2003; Schulkin, 1990).

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16.7: What Is Stress?

Learning Objectives

By the end of this section, you should be able to

- Define the concept of stress, a stressor, the stress response and describe the valence and nature of the stress response
- Understand how stress research is carried out in both humans and animal models

Although colloquially we have an idea of what stress is, the aim of this section is to define and understand stress from a biomedical perspective. We will distinguish between stress, a stressor, the stress response, and the point at which we are 'stressed out.' We will learn about the different types of stressors and the nature and valence of the response. An interesting point to consider as you read ahead: is stress always bad?

Definition of stress

Most of us will never encounter a mountain lion, but we have all experienced stressful situations or the feeling of being 'stressed out'. Take a moment to think about a stressful situation you have experienced. How did it make you feel (physically, emotionally, cognitively)? (See Figure 12.2.) Because stress is 'personal' (i.e., a subjective experience), it can mean different things to different people. In order to study it from a biological perspective, however, we need a scientifically tractable definition to start from.

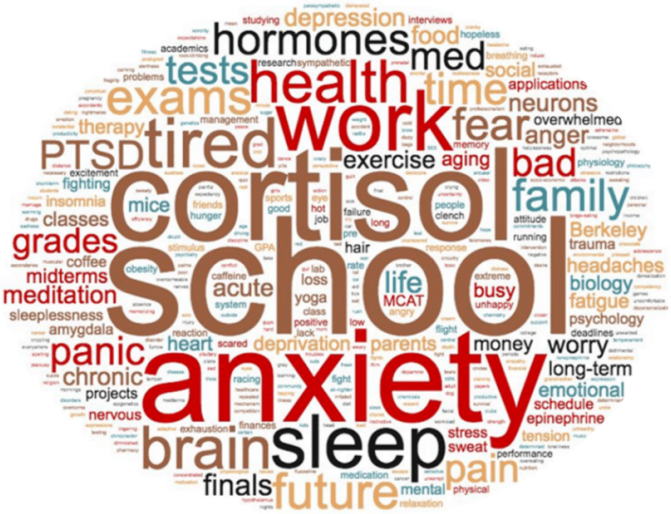


Figure 12.2 Stress associations "What does stress mean to you?" This word cloud shows responses of UC Berkeley students.

Biomedical perspective

Hans Selye—the founder of the field of stress research—defined stress from a physiological viewpoint as "the nonspecific response of the body to any demand made upon it." According to Selye, "anything that speeds up the intensity of life, causes a temporary increase in stress" (Selye, 1974). To fully understand this definition, we need to first define the concept of allostasis. Allostasis means "achieving stability through change." It includes the mechanisms that maintain life-sustaining functions (for example, body temperature, blood sugar levels, fluid balance, etc.) which must be kept within a pre-set range. In addition, allostasis also includes processes that promote adaptation to challenge and expand our survival or coping capabilities. A classic example is fat accumulation in a bear preparing for hibernation. Fat accumulation is an anticipatory change that prepares the bear for survival during winter. Here, allostatic mechanisms accommodate this change, i.e., an expanded physiological state to promote survival.

Based on Selye´s definition, any stimulus that speeds up the intensity of life (be it good or bad, pleasurable or painful, real or implied), and perturbs the physiological and psychological integrity of an organism is defined as a stressor. Interestingly, these can be deviations in variable, and even opposite directions: exposure to extreme heat or cold, starvation or obesity, injury, or threat to one's well-being, like when encountering a predator. Stress is the body's stereotyped physiological response to that stimulus. It is an evolutionarily conserved response and essential for survival. The stress response is orchestrated across all cells and tissues of the body to mobilize energy to support vital functions which are necessary to survive the immediate threat. For example, pumping glucose and oxygen to the heart, skeletal muscles and brain, and away from functions that are not pertinent to the immediate survival (e.g., digestion and reproduction).

Now that we've shifted our focus to the physiological response that occurs after exposure to a stressor, we notice that regardless of the specific stressor that initiated it, the broad physiological response will largely be the same. For example in our mountain lion scenario, both the students (i.e., potential prey), as well as the mountain lion itself, experience a stress reaction during the encounter. It is important to note that a similar physiological cascade of events can be initiated by an internal cue, in the absence of a physical threat. One can be sitting in a room, thinking about a fearful situation, and this may be sufficient to mount a full physiological response. Over decades of research, accumulating data has started to bridge our understanding of the physiological and psychological realms of stress, to create a unified picture. You will soon learn how the psychological appraisal of a situation influences the physiology of the stress response.

Now, most of us have probably experienced the feeling of being 'stressed out', the point at which a stressor becomes too much (i.e., it lasts too long, is too intense, or too much for a certain person to deal with) and leads to detrimental effects on the body. The term 'stressed out' was coined by another of the founders of the field of stress research, Bruce McEwen, to mean only the negative aspects of the response. We will revisit this idea of being 'stressed out'—a concept termed allostatic (over)load or toxic stress—in 12.4 Clinical Implications of Stress.

The stress response (aka the 'fight-or-flight' response)

Our working definition in this chapter for the stress response is: a physiological reaction that occurs in response to an actual or perceived harmful event, attack or threat to survival, which results from the coordinated action of the central and peripheral autonomic nervous systems and endocrine (hormonal) system; to generate physiological, cognitive, cardiovascular and metabolic changes that allow an organism to respond to a perturbance, promoting fitness and survival. We will explain this in detail throughout this chapter.

Generally, an event (stressor, stimulus) occurs, like a mountain lion appearing on our morning run. Or there is the perception that a threatening event might happen. This can be hearing a roar, or the thought that a mountain lion was spotted here last week. This is briefly followed by an appraisal of the threat. This appraisal relies on neural activation in the amygdala (the brain's alarm center), the prefrontal cortex (which regulates decision-making) and other circuits. And finally, there is a response to the threat (fighting, running away or freezing). The appraisal of the threat, the predictability of the stressor (whether you expected it or not) and sense of control over the situation (controllability) are 3 critical factors in mounting the stress response and in regulating its termination. We will discuss this in more depth in 12.3 Interindividual Variability and Resilience in Response to Stress .

Note that the focus of the field for many years has been on the 'fight-or-flight' response but there is also the freezing response. Freezing is a form of behavioral inhibition and functions to decrease the likelihood of detection since the visual cortex of many predators is programmed to detect moving objects. Freezing also reduces the chance that we make inadvertent sounds that other animals might detect. Freezing is not a passive state (i.e., the brain has not 'stopped working'). Rather it allows for perception and preparation of further defensive responses (Roelofs, 2017).

Functions that support the stress response

The stress response orchestrates all body systems so that they are primed and optimized to deal with the emergency situation at hand, many of which are diagrammed in Figure 12.3

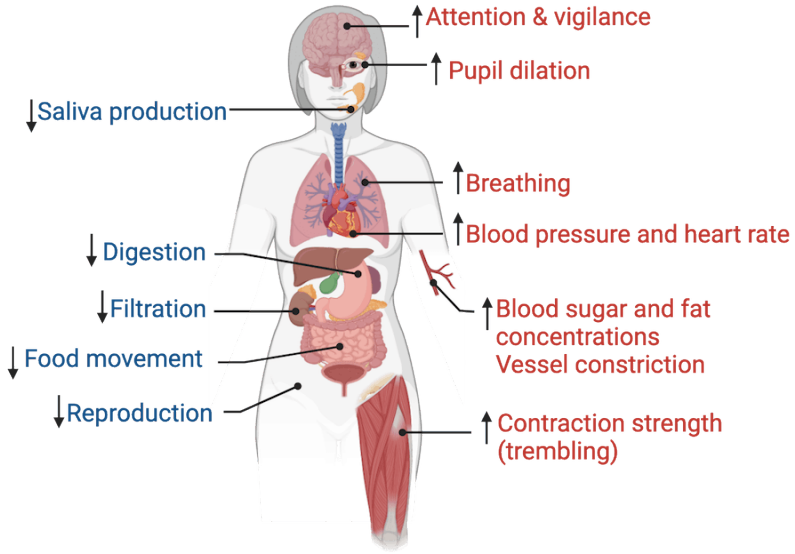


Figure 12.3 Major adaptive body responses to stress

If an individual needs to quickly run away from something, what functions would support this? *Attention* needs to be focused on the situation right now, so there are brain connectivity changes that occur to promote vigilance and sharpen attention. Pupils dilate to better detect even faint stimuli. Quick and deep *breathing* occurs to increase oxygen supply to the heart, skeletal muscles, and brain. Similarly, there are *metabolic changes* that increase the energy supply (increased blood sugar and fat concentrations) in the blood. *Blood pressure* and *heart rate* increase and blood flow is diverted away from other parts of the body and redirected to the muscles. As muscles become more tense, trembling can occur. Blood vessels in the skin constrict since blood flow is being diverted to muscles, resulting in chills or sweating. Everything else, that is, all *non-vital functions* like digestion, kidney filtration, and reproduction are slowed down. Thus, there is a decrease in saliva production (a person's mouth getting dry when they're nervous or anxious) and the output of digestive enzymes decreases. A slowdown of food movement through the bowels also occurs. One caveat, under situations of extreme stress, there might be a dumping of bowel contents. Similarly, because the absorption process through the bowels changes, 'stress diarrhea' can also occur. You may think back to a time when you were about to give a public speech—your mouth went very dry and you had a feeling that you needed to find the closest restroom ASAP. Now you know why.

Classification of stressors

Based on our definition of stress, stressors are anything that take an organism out of homeostatic range and thus can be a host of different stimuli/events. In this section, we will take a look at how stressors are classified and examples of each.

There are 3 main stressor domains:

1. Origin or type describes the modality a stressor comes in. These can be physical, psychological, or social
2. Duration describes how long a stressor lasts. Acute stressors generally range from minutes to hours. Subchronic stressors can last for days and chronic stressors range from weeks to years. Note that the initial stress response to an acute, subchronic or chronic stressor is the same, but differences arise once the stressor becomes a sustained event.
3. Severity describes whether it's a minor, moderate or major life-threatening event. These range on a scale from mild to moderate to severe to traumatic.

These domain divisions are not mutually exclusive, rather a specific type of stressor will range in both duration and severity. Below, we discuss further the 3 types (or origins) of stressors.

Physical stressors

Acute physical stressors include physical exertion or exposure to extreme environmental conditions (e.g., participating in a competitive cycling race, or acute exposure to extreme heat or cold). In the animal world, a classic example is a predator-prey interaction. Another is sustaining an acute injury (e.g., a broken arm). Chronic physical stressors include chronic illness and

obesity/starvation (i.e., moving away from the homeostatic body weight set point). Prolonged exposure to extreme environments is also a form of chronic physical stress. For example, staying at high altitude where the body needs to cope with decreased oxygen availability. Figure 12.4 shows examples of physical stressors, both acute and chronic.



Figure 12.4 Examples of physical stressors (credit: physical exertion: Photograph by David Iliff, distributed under CC Attribution-Share Alike 3.0. (https://commons.wikimedia.org/wiki/F..._July_2012.jpg) acute injury: Photograph by Chrisnorlin, CC Attribution-Share Alike 3.0. (https://commons.wikimedia.org/wiki/F...estle-Xray.jpg) predator-prey interaction: Photograph by s9-4pr, CC Attribution 2.0 Generic. (https://commons.wikimedia.org/wiki/F...337786934).jpg) emergency: Photograph by Sharon Hahn Darlin, CC Attribution 2.0. (https://commons.wikimedia.org/wiki/F..._2021_-_03.jpg) illness: Mohsen Atayi of Fars News Agency, CC Attribution 4.0 International (https://commons.wikimedia.org/wiki/F...age_banner.jpg) starvation:Amousey, public domain. (https://commons.wikimedia.org/wiki/F...rtage_8683.svg) obesity: Ana Felix, CC Attribution 3.0. (https://commons.wikimedia.org/wiki/F...ix_obesity.svg) altitude exposure: Bananakera, CC BY-SA 4.0, commons.wikimedia.org/w/inde...curid=82386984 heat/cold exposure: Levin Holtkamp, CC Attribution-Share Alike 4.0 International. (commons.wikimedia.org/wiki/F...%BCckseite.jpg))

Psychological stressors

Psychological stressors are the most common types of stressors for us modern humans, and what most people think of when asked to give examples of stress. These can also be classified as acute or chronic and range in severity. Figure 12.5 shows examples of psychological stressors. Interestingly, these stressors typically originate from thoughts of a potential perceived threat or worry, yet elicit the same physiological sequela aimed at facilitating the optimal function of the organism as it faces the need to fight, flee or freeze. This stressor category includes mundane events like arguing with a coworker or sitting in traffic, to more notable events like getting divorced, experiencing grief or financial and career worries.



Figure 12.5 Examples of psychological stressors (credit: acute frustration: By Anand V Kaku, CC BY-SA 4.0, commons.wikimedia.org/w/inde...curid=49754281 personal conflict: By Jennifer Pahlka from Oakland, CA, sfo - LOL Just divorced. And no, that's not my car., CC BY-SA 2.0, commons.wikimedia.org/w/inde...curid=10973297 grief and loss: By Let Ideas Compete from Lafayette, Colorado, United States - The Color of Grief, CC BY 2.0, commons.wikimedia.org/w/inde...curid=86277686 care-giving: By Produnis, first published at NursingWiki, CC BY-SA 3.0, commons.wikimedia.org/w/inde...?curid=3472360 school and career: By Alex Proimos from Sydney, Australia - Doing Homework, CC BY 2.0, commons.wikimedia.org/w/inde...curid=25648511 Foreclosure by respres www.flickr.com/photos/respres/2539334956/, CC BY 2.0, commons.wikimedia.org/w/inde...?curid=6694382)

Social stressors

For highly social species, including us humans, social interactions can provide a potent source of stressors, while supportive social bonds can act as an effective buffer of stress responses. Figure 12.6 shows examples of social and societal stressors, both acute and chronic. These can also range in severity. Much of the research on social stress in animal models has focused on social isolation or social hierarchy and its negative effects on wellbeing. In humans, there is also compelling data that demonstrates that social rejection is a potent cue activating the stress response (Dickerson and Kemeny, 2004). Social belonging was critical for survival success in primal societies and hence our brains are particularly sensitive to cues of social exclusion. In fact, the social environment interacts with stress on almost every front: social interactions can be potent stressors, they can buffer the response to an external stressor, and social behavior often changes in response to stressful life experiences. The next frontier in the interaction of the social world and stress is looking at the physiological and psychological effects of virtual social environments, as these take center stage in our daily realities.

Finally, we must consider societal stressors. Societal issues such as poverty, racism and inequality are particularly important to discuss because they have a considerable impact on health and well-being. Growing up in or living in poverty, or experiencing racism or inequality can change the pattern of the stress response throughout life and negatively impact health outcomes and health span. These are critical topics that need to be considered in medical and public health-level discussions.



Figure 12.6 Examples of social and societal stressors (credit: social isolation: "Lunch Guest" by Stephen Kelly/Wikimedia Commons, CC BY 2.0; societal stressors: "Homeless on Paulista Avenue" Wilfredo Rafael Rodriguez Hernandez/Wikimedia Commons, public domain; digital world related stress: Unsplash, public domain)

Valence of the stress response

We now know that the stress response is critical to survival but it has also garnered the reputation of being detrimental to health and wellbeing. This brings up the question of valence: is stress always a bad thing?

Inverted-U nature of the stress response

It turns out that some amount of stress is actually good and can enhance performance in the same domains where too much stress is detrimental (memory and executive function, for example). This type of relationship where increasing amounts of some factor (stress in our case) results first in an increase and then a decrease of a second factor (performance for example) is referred to as an inverted-U relationship (Yerkes-Dodson law). Figure 12.7 shows a typical inverted-U curve with increasing stress (stress/stimulation) on the x-axis and some measure of behavioral performance (e.g., memory function, decision-making, learning, playing an instrument, etc.) on the y-axis.

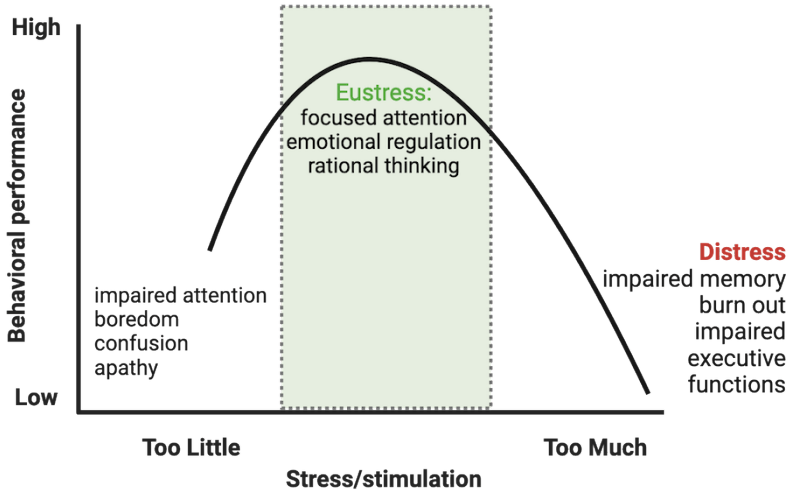


Figure 12.7 Inverted-U nature of the stress response

Notice that there is a point on the curve where performance reaches a peak, where attention gets very focused, rational thinking sharpens and emotional regulation is at its best: an optimal level of stress. This region of positive stress or eustress is defined as stress that is perceived as within an individual's coping abilities, motivates and focuses energy, may feel exciting, improves performance (Lazarus, 1998), and can protect against future stressors (a phenomenon termed 'stress inoculation').

Think about the functions that support the stress response: the sharpening of attention and focus, the increased energy supply in the bloodstream, and something that we didn't discuss but is also important, the mobilization of immune cells ready to protect against damage. This physiological state means that you're prepared and ready to tackle a challenge. For example, an upcoming final exam. You need to be focused, energized and cannot afford to get sick. Interestingly, viewing a challenge, for example, a slew of final exams or a tough new project at school or work as a positive thing can result in eustress. The key is not the stressor itself but how we perceive it. If we see it as an opportunity to learn new skills and showcase our abilities, we will feel energized and motivated to tackle it. On the other hand, if we perceive this as an obstacle or something beyond our coping capacity, we will not feel these positive effects of eustress and instead will likely feel signs of distress. Thus, the mindset with which we approach stress can have a significant impact on the outcome.

Finally, reframing stress-induced physiological reactions like a 'racing' heart as helpful and adaptive versus harmful has been shown to result in improved cognitive and physiological outcomes during/after a stressor (Jamieson et al., 2012). We will learn more about how stress perception, appraisal and reframing of stress-induced arousal can lead to positive outcomes in 12.3 Interindividual Variability and Resilience in Response to Stress.

Detrimental effects of stress exposure

When there is too little or too much stress (negative stress or distress), performance is decreased. With too little stress or stimulation, there might be impaired attention, boredom or even apathy. With too much stress (chronic or traumatic stress exposure), performance declines even further, resulting in impaired memory and executive functions or even burnout. Eventually, this could lead to the development of psychiatric disorders, for example, anxiety, depression, posttraumatic stress disorder (PTSD) or other stress-related pathologies.

An important question, then, is when exactly does stress become detrimental? There is no exact answer because it differs from person to person based on an individual's genetics, epigenetics, life history, capabilities/resources at the moment the stressor occurs, appraisal of the situation and other factors. All of these vary amongst individuals (interindividual variability) and some factors will vary even for the same person at different times (intraindividual variability). You will learn more about this topic in 12.3 Interindividual Variability and Resilience in Response to Stress.

Status and stress in wild baboons

The work of primatologist and neuroscientist Robert Sapolsky examined the effects of stress and social hierarchy on the health and social behavior of a troop of wild baboons in Africa. He found that higher-ranking males had lower levels of stress (lower baseline levels of the stress hormone cortisol) when compared to lower-ranking males, differences that were largely due to better access to resources (food, mates). However, and particularly interesting, was the fact that stress levels were not wholly determined by social rank. For example, an individual´s perception of their social standing and ability to cope with disruptions also had a bearing: higher-ranking baboons could experience stress (significant spikes in cortisol levels) if they were constantly challenged within the troop´s social hierarchy.

Sapolsky also found that chronic exposure to stress had negative effects on the health of the baboons. Lower-ranking baboons exposed to chronic stressors (social subordination, lack of access to resources and constant social threat) had compromised immune function, increased rates of illness and were more vulnerable to cardiovascular disease and diabetes.

His work served to establish the link between social status, stress and health outcomes which has tremendous impact for understanding the role of socioeconomic status and stress-related health outcomes in humans (e.g., the detrimental impact of poverty on health).

Neuroscience across Species: Methods to study stress

To understand the nature, dynamics and outcomes of the stress response, we carry out research in humans and in a variety of

animal models, which we will discuss in this section.

Human research on stress

Research on the effects of stress in humans is largely correlational—that is, an investigator studies the relationship between two variables (for example, exposure to a traumatic stressor and the development of PTSD), as opposed to actually manipulating one of the variables. In these correlational designs, study participants are typically individuals with extreme exposure to stress or trauma (e.g., individuals that were in a severe car accident, experienced sexual abuse, participated in combat, experienced childhood maltreatment). Researchers use a cross-sectional study design, comparing those who experienced the extreme stressor(s) to a control group with similar demographics in order to understand the effects of stress exposure on different outcome variables. When studying stress-related pathologies, like anxiety, depression or PTSD, study participants will be individuals that meet the clinical criteria for diagnosis of those disorders and controls will be age and sex matched people who do not meet diagnostic criteria.

We can also study stress in humans in a laboratory setting where subjects are exposed to a stressful setting, and consequently, a stress response is induced. This design allows for better control over timing. This type of study is not correlational in nature as it involves manipulation of one of the variables, i.e., the stressor. For example, you can induce stress and then measure the dynamics of stress hormone concentration rising, and then resolving to baseline. The most common protocols are tasks that involve public speaking or scenarios that involve unpleasant social interactions. For example, a scenario using a virtual ball game where the study participant is purposely excluded (the ball is not passed to them). A widely used human laboratory stressor which reliably induces a stress response was developed at the University of Trier (Germany). It's called the Trier Social Stress Test (TSST). It combines elements of anticipatory stress, public speaking and performing mental mathematics before a panel of judges (Figure 12.8).



Figure 12.8 Trier social stress test The TSST is a psychosocial human laboratory stressor that reliably elicits a stress response. Image credit: John Coetzee/Wikimedia Commons, CC BY-SA 3.0

The TSST has been used in dozens of studies. It was used to: 1) map the magnitude and duration of neuronal and hormonal aspects of stress responses, 2) identify between-subject variability in the response, and 3) understand resilience and vulnerability to stress upon first exposure and repeated exposure.

Animal models of stress

Animal models enable us to study the molecular, cellular and physiological mechanisms underlying the body's response to stress. The stress response is conserved throughout evolution, and a similar response can be measured across taxa. This similarity across species has enabled the development of a variety of different animal models (monkeys, apes, chinchillas, mice, rats, fruit-flies, zebrafish) to examine stress-related effects through laboratory interventions and field studies. Lab studies take advantage of the fact that variables like timing and severity of the stressor, as well as environmental conditions (nutrition, type of housing, temperature, humidity, light-dark cycle, etc.) can be controlled. Other advantages to using lab-based models is that the responses

to stress can frequently be measured before and after a stressor in the same animal, and genetics and life history of individual animals are controlled for. Most stressors currently in use are social/psychological in nature and reflect the types of stressors most relevant to humans. Rodents are a widely used animal model and the following sections will focus on them. Figure 12.9 diagrams some of the common stress models in rodents that we will discuss below.

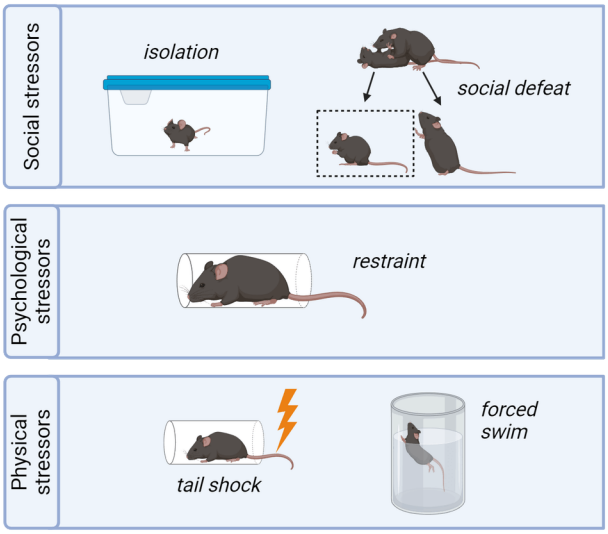


Figure 12.9 Stressor models in rodents

Social stress models

Social isolation: Like humans, rodents are social animals. Thus, social access or social interactions can be manipulated to activate a stress response. Social isolation is a moderate to severe stressor. It can be applied chronically, for example having a mouse live alone in a cage for a certain period of time (months) or grow up in cages where they're isolated from one another during a developmental period like childhood. Social isolation can also be an effective stressor acutely: removing a mouse from their home cage for ~24 hours can induce a stress response. Maternal separation is a specific type of social isolation during the developmental period that aims to model early-life adversity or neglect and how that influences stress responsivity throughout life.

Social defeat: Frequently implemented using a resident-intruder test, social defeat is a severe stressor which uses physical conflict between a smaller mouse (intruder) and an older, aggressive, dominant, male mouse (resident) in order to generate a stress response. After a brief physical confrontation, a plexiglass divider is inserted into the cage. This physically separates the mice but still allows the smaller mouse to see and smell the aggressor mouse, which serves as a further psychological stressor. This interaction repeats for 10-30 days. Social defeat has been used as a model for bullying and depression in humans.

Psychological stress models

Immobilization/restraint: In this widely used laboratory stressor, animals are placed in a restraining tube or bag so that they cannot move. It doesn't physically hurt them but rather serves as a psychological stressor since it prevents any movement or escape. Immobilization can be short (e.g., one 3-hour long session) or longer-term (e.g., 3 hours/day for 28 days) and can thus be used to model both acute and chronic stress. It can also be made more severe/traumatic if it is paired with exposure to predator odor, for example, fox urine or a collar worn by a cat.

Physical stress models

Tail shock: As the name implies, tail shock stress uses an electrical shock administered to the rodent's tail. Tail shock is generally used in studies aiming to investigate stress-induced anxiety/depression.

Forced swim: Rats or mice are made to swim in a tall cylinder without the possibility of escape for a set duration of time. This stressor can be both a source of stress and an assay for stress-induced changes in behavior that may be relevant to features of

depression. During forced swim, an animal will initially try to escape (show a burst of activity) and then become immobile, i.e., make only movements necessary to keep its head above water. Increased immobility is interpreted as a sign of behavioral despair or helplessness.

Validity of animal models for human disease

When establishing or utilizing an animal model for the purpose of developing insight relevant to human physiology, we need to ensure that the animal system is a valid model for the human system. Comparing animal models to humans can be especially challenging when we are interested in things like thoughts and feelings (i.e. more abstract functions of the brain). For example, we can determine that a person is depressed by asking them detailed questions and they can report back how/what they are feeling. This is, of course, impossible in a mouse (or other animal). Thus, we need to consider ways to 'interrogate' the mouse's behavior and figure out what aspects are meaningful or mimic the human disorder.

When modeling diseases in non-human animals, there are three criteria that must be taken into account for validation: 1) face validity (is the observable behavioral outcome similar to human symptoms; the behavior needs to be a good analog of the human behavior, not necessarily the same behavior), 2) construct validity (does the underlying mechanism reflect the cause of the disease in humans), and 3) predictive validity (are the same treatments effective). To learn more about how we assess animal models of stress-induced depression, see the Feature box on "How do we model depression?"

How do we model depression?

To model stress-related pathologies, such as anxiety or depression in rodents, selected stressors are generally either psychological or social. In addition, we need behavioral assays that can capture and allow us to quantify different aspects or symptoms of the disorder. Social defeat stress (SDS) is a relevant social/psychological stressor which reliably elicits depressive-like symptoms in rodents.

What does depression look like when you're a mouse? Figure 12.10 shows several common assays we use for behaviors that we interpret as relevant to core features of depression.

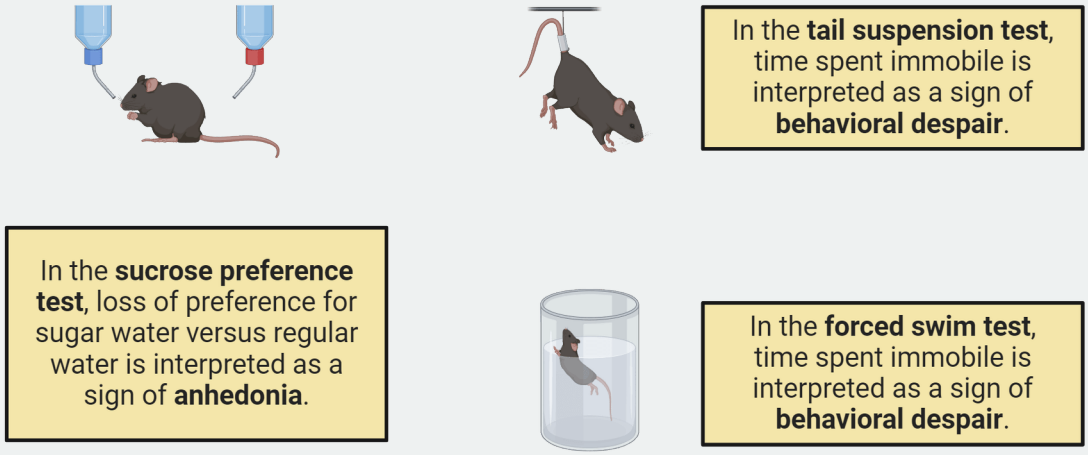


Figure 12.10 Depression assays in rodents

In the sucrose preference test, we measure whether a mouse has lost its preference for sweets (a rewarding treat). Rodents tend to prefer a sweet solution over plain water. Decreased preference for the sucrose solution indicates a loss of interest in pleasurable, rewarding stimuli. This mimics anhedonia—a decreased ability to experience pleasure from activities usually found enjoyable—which is a core symptom of depression in humans.

Two additional assays that measure the core depressive-like symptom of behavioral despair in rodents are the forced swim test (FST) and tail suspension test (TST). These 2 tests were both originally developed as screening tools for antidepressant drugs.

As described above, the FST measures time spent immobile as an indicator of behavioral despair. In the tail suspension test, a rodent is hung from a tube by its tail 10 cm above the cage floor for a brief period of time. After an initial struggle, the rodent will exhibit periods of immobility which are thought to reflect lack of active escape behavior. In both tests, increased immobility is interpreted as a sign of behavioral despair. Antidepressants shorten this immobility period, showing the key criterion of predictive validity. Notice that the FST and TST are stressors themselves. Thus, you can both induce stress and measure the behavioral response which make them convenient tools for quickly screening drugs. The FST in particular has excellent capacity to detect effective treatments. However, to model a disease, a panel of behavioral assays that measure different aspects of the disorder and capture the widest range of human symptoms should always be utilized. Can you think of any potential limitations in using tests like the FST or TST? How else could one interpret 'immobility' in these tests?

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16.8: Neural Mechanisms and Circuitry of the Stress Response

Learning Objectives

By the end of this section, you should be able to

- Describe the fast (millisecond) neural mechanisms that mediate the 'fight-or-flight' response
- Understand the function of the endocrine system and its role in the stress response
- Describe the circuitry of stress in the brain
- Explain how stress modulates the function of stress-responsive regions of the brain
- Identify the connection between the neural circuitry of stress and HPA axis function

Recall that the stress response consists of the following sequence of events. A threat cue arrives; for example, we spot a mountain lion during our morning run. Or we might *perceive* that such an event might occur (we hear a roar or we remember reading in the news that a mountain lion was sighted here last week). The brain's alarm center—the amygdala—is activated with input from other brain regions like the hippocampus which provides situational context information and the prefrontal cortex which regulates decision-making. The amygdala activates: 1) the sympathetic ('fight-or-flight') branch of the autonomic nervous system which mediates a fast (millisecond) neural response culminating in the release of epinephrine (also known as adrenaline) and 2) the hypothalamus, which initiates a slower, hormonal response (hypothalamic-pituitary-adrenal (HPA) axis response) that requires 3-4 minutes to start reaching the body's organ systems via circulating blood. These two systems (nervous and endocrine) are interconnected and work very tightly with one another to facilitate this response. We are now prepared to respond: fight, flee or freeze for further perception and defensive action planning. Termination of the stress response occurs later via engagement of the parasympathetic branch of the autonomic nervous system, which opposes sympathetic activation, and activation of allostatic mechanisms that restore homeostasis.

In this section, we will learn the steps of activation and deactivation in each of these systems and the neural circuitry (major stress-responsive brain regions) that both mediate and are in turn, modulated by stress exposure.

Sympathetic versus parasympathetic nervous system function

Recall from our earlier discussion on Structure and Function of the Nervous System: Cells and Anatomy that the autonomic nervous system (ANS), also known as the involuntary nervous system, regulates housekeeping or vegetative bodily functions. The ANS has two 'branches': the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). Both systems innervate the same organs, but in an opposing manner. While the PNS mediates 'rest-and-digest' functions, the SNS is involved in the quick (millisecond) neural 'fight-or-flight' response as shown in Figure 12.11.

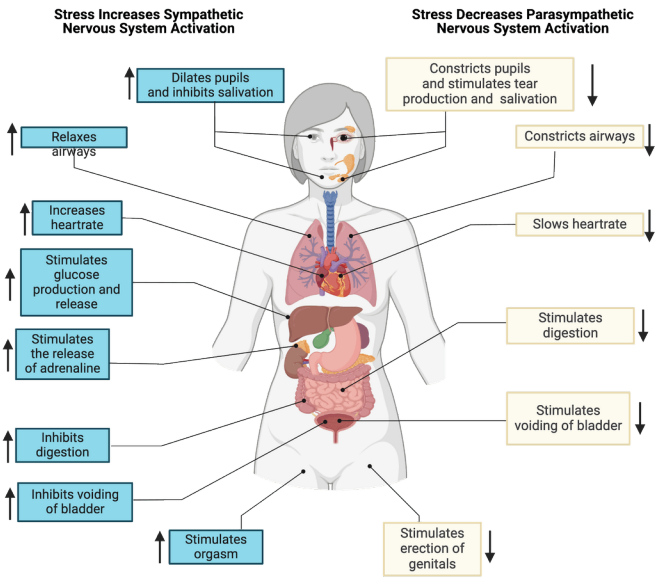


Figure 12.11 Stress and the autonomic nervous system

The SNS mediates this rapid neural response to stress in two ways:

1. Direct innervation of organs/tissues to effect changes through neural signaling (sympatho-neural system). This pathway originates in the hypothalamus and releases norepinephrine (noradrenaline) onto visceral effectors in target organs, e.g. the heart, lungs, stomach, liver, etc.
2. Through innervation of the adrenal gland medulla (sympatho-adrenomedullary system). This pathway synapses directly onto chromaffin cells of the adrenal medulla, triggering the release of epinephrine (adrenaline) into circulation. It mimics the hormonal response we will cover next to some extent because it results in hormonal release, but it is carried out via neuronal innervation of the adrenal medulla (not through a 2-step chain of hormones). The adrenal gland is also unique in that it does not receive PNS innervation like other glands/organs do.

Epinephrine and norepinephrine are very similar in structure and function. Their downstream effects are broadly to increase heartbeat resulting in increased blood pressure, shunt blood away from the skin and viscera to the skeletal muscles, create a rise in blood sugar, and increase metabolic rate, bronchodilation, and pupillary dilation.

HPA axis stress response

Coincident with the SNS activation upon perceiving a stressor, the hypothalamic-pituitary-adrenal axis (HPA axis) is also activated, leading to a chain of events involving multiple glands in order to produce powerful and sometimes long-lasting effects. While the SNS activation takes milliseconds, the sequence of steps in HPA activation take several minutes to be triggered one after the other. Like the SNS, though, the HPA axis is typically tightly regulated by multiple excitatory and inhibitory signaling inputs, ensuring a rapid response to stressful events, and a timely shut down of the response and return to equilibrium.

The HPA axis consists of the tiered release of 3 hormones from the 3 structures/glands that comprise it (the hypothalamus, the pituitary and the adrenal glands). The sequence of steps is diagrammed in Figure 12.12.

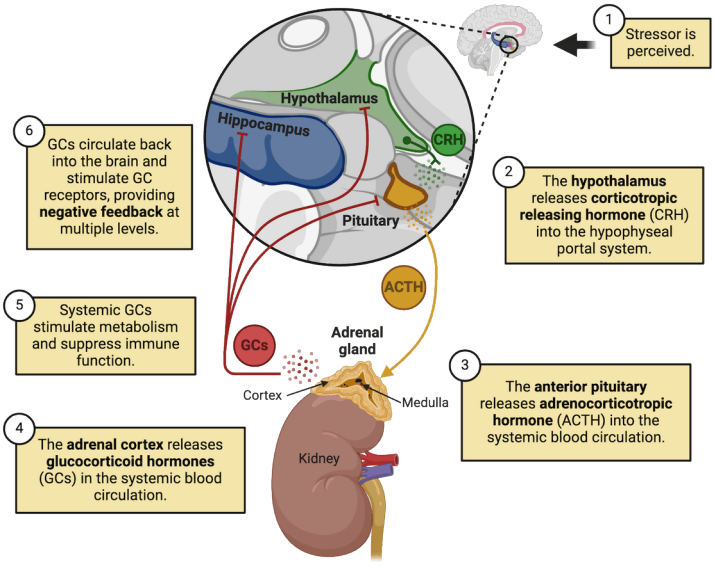


Figure 12.12 HPA axis

A stressor is perceived and corticotropin releasing hormone (CRH) is released from the hypothalamus into the hypophyseal portal system, a small blood network that connects the hypothalamus to the anterior pituitary (step 2 in Figure 12.12). As shown in Figure 12.13, the pituitary gland is comprised of two distinct anatomical parts: the anterior pituitary and posterior pituitary. The anterior pituitary produces and secretes various hormones in response to signals from the hypothalamus. Most relevant to the stress response, CRH from hypothalamic neurons stimulates the anterior pituitary gland to produce and secrete adrenocorticotropic hormone (ACTH) into the systemic bloodstream (step 3 in Figure 12.12).

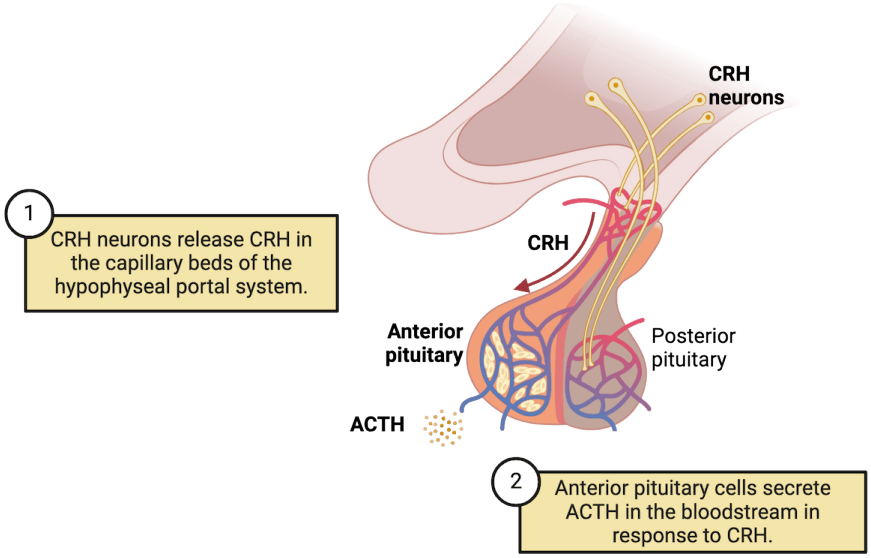


Figure 12.13 Microcircuit of the pituitary gland

ACTH circulates throughout the body, eventually reaching the adrenal glands, which sit on top of the kidneys. ACTH then induces the synthesis and release of the glucocorticoid hormone cortisol (cortisol in most mammals including humans; corticosterone in most laboratory rodents) from the cortex (outer shell) of the adrenal glands (step 4 in Image Figure 12.12). Glucocorticoids have massive and far-reaching effects on the body and brain, including increases in blood pressure, increased glucose circulation, decreased reproductive axis output, complex effects on immune functions and various other effects (step 5 in Figure 12.12). In addition to glucocorticoids, the adrenal gland also produces epinephrine and various other hormones from cells in the adrenal medulla (inner core) in response to the fast neural stress response described above. The adrenals are therefore a convergence location for HPA and neural components of the stress response, albeit via separate parts of the gland.

Feedback mechanisms

Glands of the endocrine system not only secrete hormones, but they respond to them as well. These responses allow for tight regulation of the amount of hormones in the bloodstream. One of the ways it achieves this is through feedback to the original gland. Negative feedback in an endocrine system like the HPA axis occurs when a hormone feeds back to some level of its activating system in order to inhibit further secretion.

There are several classifications of feedback in endocrine systems, diagrammed in Figure 12.14.

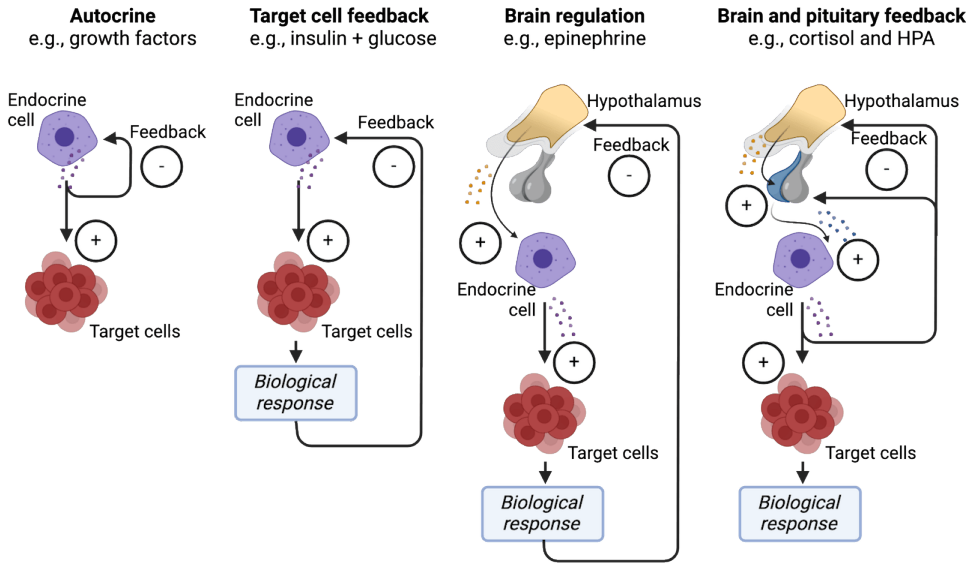


Figure 12.14 Feedback mechanisms

When a hormone binds to receptors on its originating cell to change hormone secretion levels, it is called autocrine feedback. Another mechanism, called target cell feedback, occurs when a hormone binds a target cell and elicits a biological response that feeds back to the original driver and inhibits further secretion. Feedback mechanisms can get complex and involve regions of the brain in addition to glands. Negative feedback involving the brain can look like an endocrine response that feeds back to the brain region that initiated hormone secretion (often the hypothalamus) in order to shut that brain region activity down (brain regulation). Sometimes the pituitary also gets involved, working as an intermediary between the higher brain region and the endocrine cells (brain and pituitary feedback).

HPA axis negative feedback fits the 'brain and pituitary' model, occurring at multiple levels, shown in Figure 12.14. The major negative feedback targets of glucocorticoids released by the adrenals is shown as step 6 in Figure 12.12. Most proximate to the adrenals, the pituitary gland responds directly to glucocorticoids, shutting down production of ACTH in response to high glucocorticoid levels. When pituitary function is impaired, it can impact the homeostasis of the HPA axis and potentially cause other neuropsychiatric symptoms by altering the function of other brain regions. For instance, Cushing's syndrome is a type of pituitary adenoma (benign tumor) that produces too much ACTH, resulting in overflowing glucocorticoids in the body. Patients with Cushing's syndrome not only exhibit impaired body metabolism, but also display comorbidity with various psychiatric conditions, for example personality disorders, psychosis, depression, and anxiety disorders. Although the exact mechanisms underlying the link between Cushing's syndrome and psychiatric disorders are unknown, it is likely that the high glucocorticoid levels may directly impact other brain regions expressing glucocorticoid receptors or indirectly impact overall brain function at a circuit level.

The hypothalamus is also an important regulator of the pituitary and serves as a site for glucocorticoid feedback resulting in inhibition of CRH secretion. Several other brain regions also participate in glucocorticoid negative feedback to the HPA. The hippocampus has direct connections with the hypothalamus, and these inhibit the hypothalamus when the hippocampus is exposed to high levels of glucocorticoids. Receptors for glucocorticoids are also expressed in other areas of the limbic system, such as the prefrontal cortex, amygdala, and thalamus. Negative feedback through these indirect pathways to the hypothalamus shuts down the response elicited by the HPA axis. These areas of the limbic system contribute to control of the HPA axis and create more complex feedback mechanisms. We will learn more about these higher brain regions' roles in the stress response in later sections.

Stress hormone cortisol receptor signaling

Both negative feedback and the effects of glucocorticoids on body organ systems rely on these hormones binding to receptors expressed on target cells. Glucocorticoids, like cortisol, can bind to receptors expressed by cells all over the body. In fact, every cell in our body expresses at least one type of glucocorticoid receptor. While most neurotransmitter receptors we have learned about are present on the cell surface, glucocorticoid receptors are found mainly inside the cell, floating in the cytoplasm. Glucocorticoids like cortisol, the main stress-related glucocorticoid in humans, are steroid hormones, which are lipid-based. Being small fatty molecules, they diffuse freely through the cell membrane to bind intracellular glucocorticoid receptors. When the ligand cortisol binds to a glucocorticoid receptor, there is a conformational change in the receptor itself that leads to dimerization with another activated receptor, and exposure of a nuclear localization signal that directs it to the nucleus. In the nucleus, the dimerized complex acts as a transcription factor, and modulates the transcription of thousands of genes (Figure 12.15). This mechanism of action is global to all cells, but different cell types respond with a unique pattern of gene expression changes, which arises from the specific array of receptor and transcription factors expressed in each cell.

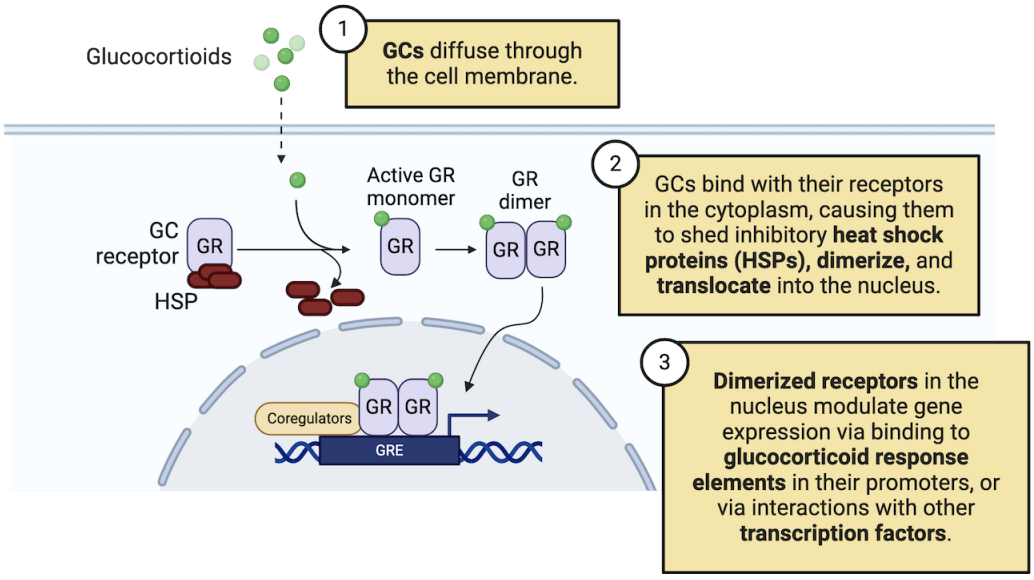


Figure 12.15 Glucocorticoid receptor action

There are two different receptors for glucocorticoids, called glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Cells can have one or both. MRs are expressed in the kidney, colon, heart, adipose tissue, sweat glands, and central nervous system. They bind aldosterone and cortisol with high affinity. In vivo, MRs are 80-100% occupied at normal levels of cortisol. GRs, on the other hand, are expressed everywhere in the body and bind cortisol with lower affinity. GRs range from 10-80% occupancy. At normal cortisol levels, there is lower GR occupancy and at high levels there is higher occupation, making GR the stress-responsive receptor (Figure 12.16).

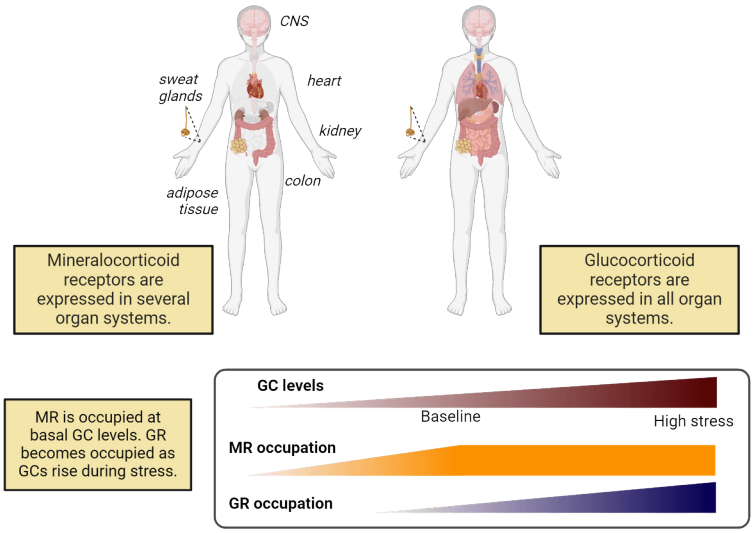


Figure 12.16 Glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) expression and occupancy

SNS and HPA axis effects on the body and restoring balance

Do epinephrine/norepinephrine and cortisol have the same physiological effects? Mostly yes. This is because the rapid neural response and slower HPA endocrine response converge on the same organ systems. At first glance, this seems redundant. This convergence, however, means that there are numerous spots for regulation such that if a particular mechanism fails, there is a backup mechanism that can orchestrate the same alarm response.

We've learned throughout this topic that there are negative feedback loops that can stop the stress response at discrete points, for example, during HPA axis activation. But how is balance restored to the whole organism after this type of massive activation? Clearly, the SNS must be de-activated and the PNS must be activated. One of the ways of engaging PNS function is through deep breathing. This expands the diaphragm which stimulates the vagus nerve. The vagus (cranial nerve X) supplies parasympathetic information to visceral organs of the cardiovascular, respiratory, digestive and urinary systems and vagal stimulation activates the PNS. Termination or the 'end' of the stress response is not a clear-cut event, however. Cortisol, for example, can remain elevated for hours.

How stress affects the brain and behavior

We know that stress affects all organs throughout the body. However, the effects of stress on cells and circuitry of the brain are critical, because the brain regulates both arms of the response—the nervous and endocrine systems. In this section, we will move beyond the HPA axis and learn how connections between individual brain regions shape information and ultimately behavior. The brain regions we will discuss are summarized in Figure 12.17.

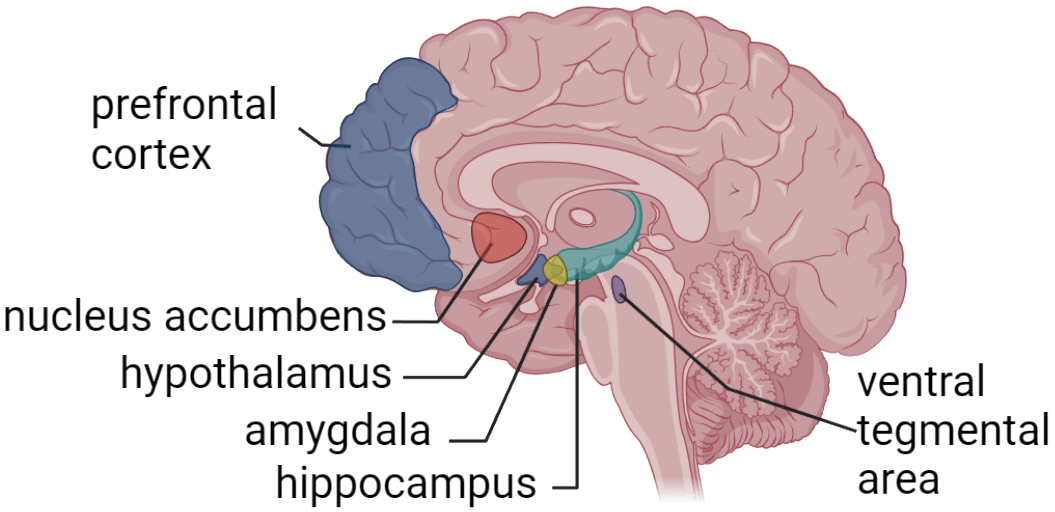


Figure 12.17 Major stress-sensitive brain regions

Amygdala

The amygdala is an almond-shaped cluster of nuclei located in the medial temporal lobe and is comprised of several subregions that are interconnected in a microcircuit. There are 2 amygdalae, one in each cerebral hemisphere. The amygdala as a whole helps coordinate emotional responses such as anxiety and fear to aversive stimuli. It plays a major role in the processing of physiological and behavioral responses to stress and is characterized by high inhibitory tone under resting state conditions. Exposure to stress, through threat-related input from the thalamus or high levels of glucocorticoids, leads to hyperactivity of the amygdala and is accompanied by the removal of this inhibitory control. The prefrontal cortex (PFC; discussed below), which mediates executive function, can balance amygdala activity by providing part of this inhibitory tone. The amygdala, in turn, sends outputs to the paraventricular nucleus of the hypothalamus (where CRH is synthesized), as well as several other brain regions that help coordinate fear and anxiety responses.

As a result of its role in emotion coordination, amygdala activity can potently modulate learning and memory, particularly fear learning induced by stress. For example, disrupting or blocking basolateral and central amygdala GRs attenuates fear conditioning in rodents (Donley et al., 2005, Kolber et al., 2008). Some of the stress-related regulation of learning also appears to rely on the direct actions of CRH, released by hypothalamic neurons directly onto neurons of the central nucleus of the amygdala which express CRH receptors (Haubensak et al., 2010; Gilpin et al., 2015; Tovote et al., 2015). Additionally, inhibition of central amygdala-CRH neurons disrupts the extinction of conditioned fear memories, indicating a potential role for this subpopulation of neurons in stress-associated fear learning (Jo et al., 2020).

The function of the amygdala in response to stress has been well documented in studies that utilized functional magnetic resonance imaging (fMRI) which measures small changes in blood flow as a proxy for brain activity (see Methods: fMRI). It is notable that patients with PTSD exhibit exacerbated amygdalar responses to emotional stress compared to healthy individuals (Morey et al., 2012). Thus, while some stress may enhance fear learning, too much can be detrimental (the inverted U). Stress-reduction interventions such as mindfulness-based training are correlated with decreases in the amygdala structure density (Holzel et al., 2010), underscoring the importance of the amygdala in the stress response and as a target for stress-reduction interventions.

Hippocampus

The hippocampus, located in the medial temporal lobe of each cerebral hemisphere, is an integral brain region for stress responses. It is highly sensitive to stress due to the abundant expression of GR and MR stress hormone receptors (Sapolsky et al., 1984). As we learned earlier in this section, the hippocampus plays a role in negatively regulating HPA axis activity, particularly in the shutdown of the HPA axis following activation. The hippocampus also mediates stress effects on several forms of learning and memory in complex ways. Stress can have both enhancing and impairing effects on hippocampal memory depending on the severity, length, and the stage that is affected (memory formation, consolidation, or retrieval). Generally, emotionally arousing

events are very well remembered, a process mediated via GR signaling and amygdala input. Experiencing moderate or severe levels of stress, for example, may boost memory formation (a traumatic event tends to be very strongly encoded). However, because stress exposure can also modulate other stages like memory consolidation and retrieval, severe stress may also lead to impaired memory function.

The hippocampal response to stress involves several cell types, including neurons and glia, both of which may contribute to stress-related pathology or resilience in the hippocampus (Figure 12.18). Mature neurons in the hippocampus are highly sensitive to steroid stress hormones. Activation of MR/GR-expressing hippocampal neurons is a critical part of the HPA axis negative feedback loop to the hypothalamus. Hippocampal neurons also change how they function in response to stress, particularly if the stressor is chronic. For example, a series of studies revealed that stress-associated neurosteroids can impact long-term potentiation or neurotransmitter release from the presynaptic terminals in hippocampal neurons (Venero and Borrell, 1999; Karst et al., 2005; Groeneweg et al., 2011; Popoli et al., 2011).

One relatively unique (and stress-sensitive) aspect of the hippocampus is that it is one of very few regions in the adult brain that can generate new functional neurons in most mammalian species that have been studied to date. Integration of new neurons to existing neural circuitry has been implicated in spatial and emotional learning and memory functions, and in the regulation of the HPA axis. For example, increased neurogenesis in the ventral region of the dentate gyrus can reduce responses to anxiogenic (stress-inducing) stimuli (Anacker et al., 2018), indicating that neurogenesis may serve as a potential mechanism for resilience to stress. In addition to mediating responses to stress, adult neurogenesis is also regulated by exposure to stress. Chronic or traumatic stress exposure is a strong suppressor of hippocampal neurogenesis (Snyder et al., 2011; Cameron and Glover, 2015; Anacker et al., 2018; Cope and Gould, 2019). Acute moderate stress, in contrast, can promote adult hippocampal neurogenesis and is correlated with increased fear extinction (Kirby et al., 2013). The neurogenic response to stress, therefore, also shows the inverted-U pattern that is common to stress responses.

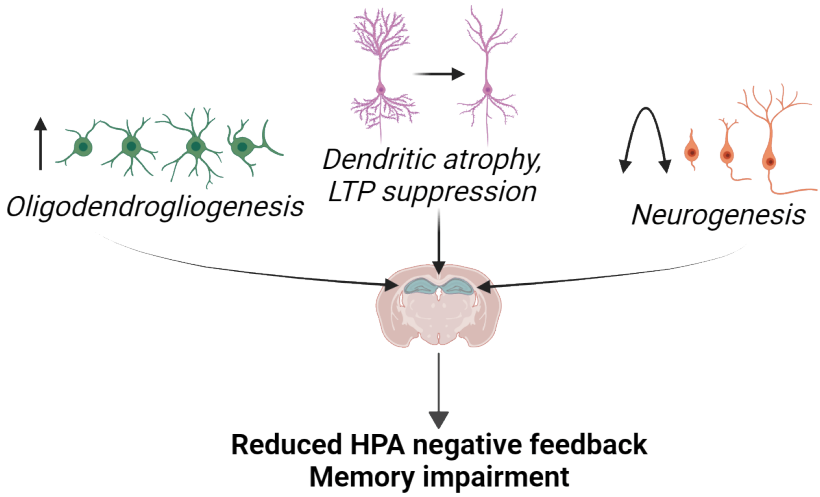


Figure 12.18 Hallmarks of stress in the hippocampus

In addition to neurons, other supporting cells (glial cells) can respond to stress and play a role in stress integration. For example, a series of recent studies have highlighted a role for oligodendrocytes in response to stress. Chronic stress can promote the generation of oligodendrocyte precursor cells via glucocorticoid exposure and susceptibility to acute stress is linked to increases in myelin plasticity in the rat hippocampus (Chetty et al., 2014; Long et al., 2021). These findings indicate a potential role for hippocampal myelin and oligodendrocyte plasticity in stress susceptibility and resilience.

Prefrontal cortex

The cortex is comprised of multiple complex brain structures that play a key role in cognitive and executive functions. In this section, we will learn about a key cortical area, the PFC, and projection areas such as the ventral tegmental area (VTA) and nucleus accumbens (NAc) in HPA axis integration and the stress response.

The PFC is located in the anterior part of the frontal lobe and occupies one third of the frontal lobe in the human cerebral cortex.

Through its interaction with other brain regions, the PFC orchestrates complex cognitive tasks requiring attention, planning, reasoning, and decision-making and exerts top-down or high-order control of other brain regions. Part of that function, which we discussed above, is providing inhibitory input to the amygdala, thereby helping to prevent, reduce or terminate stress responses.

Catecholamines play an important role in stress regulation of PFC function. Dopamine, in particular, modulates PFC function and PFC function modulates dopaminergic function. Figure 12.19 diagrams these two types of pathways (DA to PFC and PFC to DA).

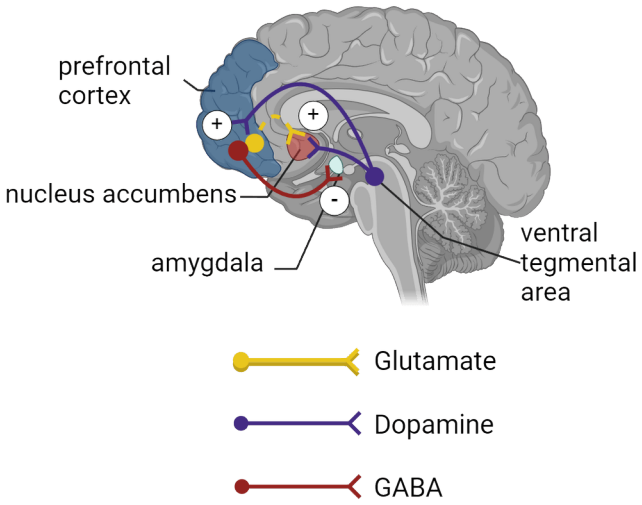


Figure 12.19 PFC dopamine interactions during stress

First, a large group of dopamine neurons in the VTA are known to project their axons to the PFC (Guiard et al., 2008). These dopaminergic neurons fire in response to stressful stimuli. Thus, when exposed to stress, a subset of VTA dopamine neurons is activated (Brischoux et al., 2009), and the activated dopamine neurons in the VTA projecting to the PFC increase dopamine neurotransmitter levels in the PFC (Holly and Miczek, 2016). Small amounts of dopaminergic stimulus in the PFC will acutely increase PFC functions like working memory but if the stressor is more severe, it can flip to causing deficits in working memory (i.e., an inverted-U relationship).

The PFC feeds back onto the dopaminergic system via its projections to the NAc, converging there to modulate dopamine input from the VTA onto the NAc neurons (see Figure 12.19). The NAc is well-known for reward learning behavior, but recent studies point to a role in negative prediction error—predicting negative outcomes based on previous learning experience—as part of a coping mechanism for inescapable stress (Cui et al., 2020). The NAc receives glutamatergic inputs from the medial PFC (mPFC) and stimulation of mPFC has been shown to stimulate dopamine release in the NAc (Quiroz et al., 2016). This signaling supports the negative prediction error coping mechanism.

Neurochemical balance often plays a key role in the high-order control mediated by the PFC. As noted above, some dopaminergic input in the PFC promotes function while too much impairs it. Both acute or chronic stress can lead to neurochemical imbalances in the PFC (for example, increase in catecholamine neurotransmitter release (Finlay et al., 1995)). Long-term or severe shifts in dopamine input (and other neurotransmitters) result in dysregulation of other brain regions while eliciting susceptibility towards various neuropsychiatric disorders including PTSD, mood disorders, and attention deficit and hyperactivity disorders (ADHD).

Hypothalamus

As we saw previously, the HPA axis is critical for maintaining endocrine homeostatic balance, but more recent studies have also provided circuit-based evidence that hypothalamic CRH neurons (which release the first of the HPA axis trio of hormones) serve as a key component for proper behavioral responses to acute stress in rodents. We've previously mentioned how CRH input in the amygdala seems to directly support fear extinction, but CRH has other direct behavioral effects and may be particularly important for stress coping behaviors. Upon exposure to acute foot-shock stress, for example, mice exhibit distinct behaviors such as grooming, walking, and rearing. When hypothalamic CRH neurons are inhibited via optogenetic silencing (see Methods: Optogenetics), these behaviors are not displayed, indicating that hypothalamic CRH neuronal activation is important as part of stress-coping mechanisms (Fuzesi et al., 2016).

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16.9: Interindividual Variability and Resilience in Response to Stress

Learning Objectives

By the end of this section, you should be able to

- Describe the factors that influence interindividual variability in the stress response
- Explain the concept of resilience and describe some of the beneficial effects of stress
- Describe some useful strategies to optimize the stress response

Not surprisingly, individuals vary greatly in their response to stress due to factors like genetics, epigenetics, biological sex, developmental and later life history, and even preconceptional and transgenerational influences. Additionally, factors like how a stressor is perceived, whether it's predictable or controllable and the social milieu can dramatically alter an individual's response. The good news is that not all stress is bad—moderate stressors have beneficial effects. In addition, multiple interventions including physical exercise, breathing exercises, meditation, and mindfulness-based stress reduction are proven techniques that can help not just mitigate but optimize one's response to stress.

Factors that influence interindividual variability in response to stress

So far, we have described the generic response that is activated by stress—a response that is similar between many different manifestations of stress (physical, social or psychological) and evolutionarily conserved across taxa. This response involves the stereotypical neural and endocrine axis activation, but it can vary greatly between individuals. Biological, life history and psychological factors all contribute to this interindividual variability. For example, an individual's genetic and epigenetic makeup, biological sex, and stress exposure during critical periods (e.g., *in utero*, neonatal and early life, adolescence, and exposure during aging later in life) all impact their response to stress. Recent evidence suggests that preconceptional and transgenerational mechanisms are also involved in setting up or shaping this interindividual variability. Finally, factors like an individual's physiological and emotional state (are they hungry, tired), psychological differences in how a person perceives/appraises a stressor, whether the stressor is deemed as predictable or controllable, the availability of social resources, and specific characteristics of the encountered stressor can all lead to a more heterogeneous and fine-tuned response.

Genetic factors

Genetic factors that influence the stress response include polymorphisms in genes involved in glucocorticoid signaling and HPA axis regulation, monoamine neurotransmitter function, and regulation of brain plasticity. For example, the gene encoding FK506-binding protein 51 (FKBP5/FKBP51) is an important modulator of stress responses. FKBP5 acts as a co-chaperone for the glucocorticoid receptor. Specific alleles of the FKBP5 gene (e.g. T allele) are associated with blunted GR-dependent feedback inhibition of the HPA axis, resulting in dysregulated axis function (e.g. prolonged cortisol responses). In other words, people with certain genetic forms of the FKBP5 protein will take longer to turn off the HPA axis (and get their circulating cortisol levels back to normal) after a stressor because of impaired GR function compared to people with more typical forms of FKBP5.

These mutations in FKBP5 (and the chronically impaired shutdown of stress responses) have clinically relevant effects on behavior. For example, the T allele is associated with increased anxiety, attentional bias towards threat, hippocampal activation after fear/threat induction, and changes in amygdala volume which can predispose to development of stress-related pathology. In fact, alleles associated with greater FKBP5 induction and longer cortisol responses are associated with higher risk for Major Depressive Disorder, Posttraumatic Stress Disorder, suicidality, psychosis, aggression and violent behavior (for review see Zannas et al., 2016).

Developmental Perspective: Critical periods for stress exposure

Just like there are critical periods for learning and development, there are critical periods for stress exposure. During periods of

our development, the brain is especially plastic, allowing for changes that can translate to risk or resilience in the face of stress later in life. During these periods, factors in the environment combine with those of our genetics to influence neurodevelopment. These effects can persist into adulthood, influence the trajectory of our lives, and manifest as vulnerabilities to mental health.

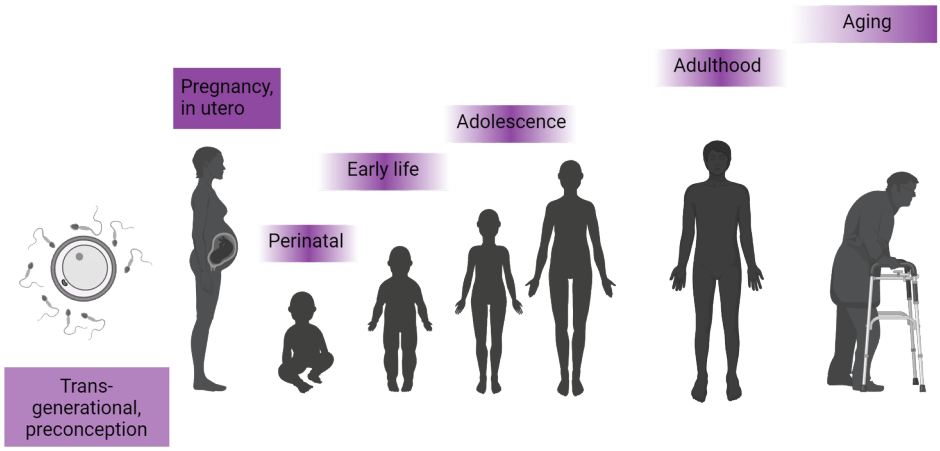


Figure 12.20 Stress-critical periods

In utero

Before birth, our neurodevelopment is already being influenced by the world around us. Many studies of prenatal stress come from retrospective studies where a mother has experienced a disaster, for example war, malnutrition, hardship in personal relationships, or tensions in their everyday environment. Many of these retrospective studies have focused on historical events, for example, a year of extreme food shortage in the Netherlands during World War II, known as the Dutch famine, or more recently the events in New York City on September 11, 2001, also known as the 9/11 attacks, which affected women at different stages of pregnancy.

As we know, stress exposure elicits an HPA axis and neural response. Although the placenta acts as a selective barrier, some stress hormones produced by the mother can cross through the placenta and reach the fetus, triggering release of additional stress hormones (Weinstock, 2005). Evidence suggests that maternal stress exposure is associated with shorter gestational age, increase in preterm births, low birthweight, and small size for gestational age (Class et al., 2011). This exposure to maternal stress and high cortisol levels can also lead to deficits in mental development scores and cognitive ability once a fetus matures into childhood (Brouwers et al., 2001; Bergman et al., 2010). It is also associated with autistic traits and ADHD behaviors (Ronald et al., 2011), emotional problems (O'Connor et al., 2002), and higher cortisol response to a stressor (Davis et al., 2011). Animal models show that maternal stress alters HPA axis function, cortisol, and CRH levels throughout the lifetime of the offspring (Weinstock, 2008). Thus, the effects of maternal stress hormones can alter neurodevelopment in the fetus and contribute to adverse consequences throughout life.

Early life stress

Exposure to stress that occurs in the timeframe from infancy to adolescence, can also have a major impact on the trajectory of development. During this period, stress can come from maltreatment, neglect, or exposure to trauma or stressful life events. Early life stress can increase the risk of developing psychiatric disorders in adulthood (Carr et al., 2013), for example depression and anxiety (Heim and Nemeroff, 2001). It can also increase the likelihood of developing alcohol or drug dependence (Enoch, 2011). In rodents and primates, early life stress can evoke depression-like behaviors and altered HPA axis responsiveness that lasts into adulthood (Pryce et al., 2005).

Epigenetics, the chemical modification of DNA without a change in nucleotide sequence, can account for a major part of the developmental trajectory following stress. To understand this idea of epigenetic modification, we first need to appreciate how DNA is packed into the nucleus. The DNA contained in each cell's nucleus is not lying about like loose spaghetti. It is actually

packed together quite purposefully, folded and wrapped around on itself and around proteins called histones so that the ~3 billion nucleotide base pairs that make up the human genome can fit into the cramped quarters of the nucleus. Epigenetic changes are chemical modifications attached to the DNA itself or to the histones that the DNA wraps around. These modifications change how loosely or tightly the DNA is packed. Genes that are in stretches of DNA that are packed up especially tightly are less readily expressed (transcribed into RNA) while genes in segments of DNA that are packed more loosely are accessible and more easily transcribed.

Early life stress has been shown to induce changes in the epigenome, specifically in genes that regulate the HPA axis, which persist throughout life and can modulate HPA axis and stress reactivity. For example, the quality of maternal care during the neonatal period—modeled in rodents as increased pup licking and grooming by rat mothers—results in epigenetic modifications that enhance feedback sensitivity and efficient HPA axis shutdown following stress. See Feature Box on the persistent effect of maternal care on stress vulnerability and resilience. Similarly, early life stress (duration of maternal separation, for example) has been shown to induce changes in the epigenome that persist throughout life and can confer either vulnerability or resilience to stress. Additionally, recent research is beginning to uncover how transgenerational effects (i.e., events experienced by previous generations) can modulate individual variability in stress responses. See Feature Box on preconceptional, historical and transgenerational effects of stress.

Adolescence

The transition from childhood to adolescence represents another vulnerable period to stress exposure. Internally, dramatic physiological and hormonal changes occur. At the same time, the development of complex behaviors, including a notable dependence on peer relationships, as opposed to parental ones, emerges. These intense changes combined with high brain plasticity makes adolescence a crucial period in development where vulnerability is heightened. Exposure to stress during this period has been shown to increase the risk for depression and is associated with social and educational impairments (Fletcher, 2010).

Aging

In aging populations, changes in the brain and in the endocrine system occur in some, but not all individuals. A particularly vulnerable part of the brain to the aging process is the hippocampus. During aging, a decrease in hippocampal function and reactivity to cortisol leads to a decrease in the efficient shut down of HPA axis activation. This is seen in some aged individuals as hyper-reactivity to stress, resulting in higher levels of baseline and stress-related cortisol, and a deficient shutdown of activation. This is a vicious cycle for the aging hippocampus, as the increased levels of cortisol lead to increased neurodegeneration, cellular vulnerability and memory decline, which contributes to greater effects from stressors and could be at least partially responsible for aging the hippocampus (Miller and O'callaghan, 2005).

People behind the science: The persistent effect of maternal care on stress vulnerability and resilience

How a mother cares for their child can vary widely. There are variations in social, emotional, and socio-economic contexts. If these variations result in neglect or abuse towards a child, they can lead to persistent negative effects on stress reactivity (vulnerability to stress). Drs. Darlene Francis, Frances Champagne, Michael Meany, and Moshe Szyf have made significant contributions to our understanding of the long- term effects of maternal care on stress reactivity. Through their work with rodents, initiated primarily at McGill University and subsequently pursued at other institutions, they showed that early experiences can translate into later life behaviors via epigenetic mechanisms. They studied this phenomenon using rats as a model. Rats, it turns out, can be very caring mothers and one of the main ways they care for their pups is by regularly licking and grooming them. Through observations of rat maternal behaviors like pup licking, grooming, and nursing, this team of researchers found that a greater frequency of these behaviors resulted in increased numbers of hippocampal GRs, enhanced glucocorticoid feedback sensitivity and more modest HPA axis responses to stress in the adult offspring of high maternal care mothers. Furthermore, their work showed that GR gene expression is controlled by epigenetic modifications (altered chromatin structure and DNA methylation of a promoter region for the GR gene) which can persist into adulthood (Liu et al., 1997; Weaver et al., 2004). Ultimately, their work provided valuable insight into the epigenetic processes behind transmission of individual variabilities in stress reactivity.

Preconceptional, historical and transgenerational effects of stress

Stress has obvious effects on one's own body and offspring, but there can be detrimental effects on subsequent generations as well. Ancestral environments and behaviors can create lasting beneficial or detrimental effects. One way in which the effects of stress can be transferred to a future generation is through biological inheritance. For example, when a mother conceives a female embryo, that offspring creates all the eggs she will have throughout her lifetime before she even leaves the womb. Any experiences of the grandmother then could have some effect on the granddaughter. Another mechanism of transmission is social inheritance. Maternal care is an excellent example of this: here a mother's care for their child can affect emotional outcomes later in life. Lastly, ecological inheritance or the shared experience of trauma at a community level can also be a mechanism of transmission. Survivors of the Holocaust and Native American experiences of genocide and oppression provide evidence that effects of trauma and stress can extend beyond the generation directly exposed and contribute to the development of depression, anxiety and PTSD in offspring that themselves were not exposed. These transgenerational effects most likely also rely on epigenetic modification of DNA. Evidence suggesting this ecological inheritance is seen in the offspring of trauma survivors, where low cortisol levels are associated with parental PTSD (Yehuda & Bierer., 2007; Perroud et al., 2014). Epigenetic modifications in the FKBP5 gene, a co-chaperone for the glucocorticoid receptor (discussed above under genetic factors affecting interindividual variability), have also been observed in both Holocaust survivors (mothers) and their offspring (Yehuda et al., 2016).

Transgenerational transmission is not only seen in humans, it applies to other species as well. *Caenorhabditis elegans* (nematode worms), for example, show altered gene expression in response to temperature changes for at least 14 generations (Klosin et al., 2017). They also show changes in small RNAs (regulators of gene expression) if ancestors were starved for extended periods (Rechavi et al., 2014). *Drosophila melanogaster* (fruit flies) also show an obesity phenotype for two generations if an ancestor was placed on a high-calorie diet (Buescher et al., 2013). In rodents, work by Dr. Brian Dias is revealing the epigenetic mechanisms involved in transgenerational inheritance of fear learning. You can learn more about Dr. Dias' innovative work and his path in research in the talk "Great Scientists, Great Failures".

Biological sex differences

Sex differences in stress responses have garnered significant attention within the field of neuroscience and psychology. Numerous studies have demonstrated that males and females exhibit distinct patterns of physiological and behavioral responses when faced with stressful situations. These differences extend to both acute and chronic stressors, with variations in stress hormone secretion, neural activation, and coping strategies. For example, rodent studies have shown that females exhibit unique patterns in the number, distribution, membrane trafficking, and signaling of CRH receptors (Bangasser and Wiersielis, 2018) - patterns which are affected by estrogen. Similarly, female rats are known to release higher levels of glucocorticoids after acute restraint stress (Goel et al., 2014). These differences point to nuanced, sex-specific HPA axis function in response to stress.

At the behavioral level, studies have shown, for example, that female rodents generalize fear responses more than males. Fear generalization occurs when conditioned fear responses 'spread' (or generalize) to new stimuli. This effect is dependent upon estrous cycle phase and thus has been linked to sex hormone, specifically estrogen signaling. Although stress is thought to affect fear learning-related brain regions similarly in males and females, distinct molecular and gene expression profiles at the synaptic level are sex-specific. Understanding these types of differences will allow us to develop more tailored and effective interventions. Women, for example, have higher prevalence of PTSD which involves aberrant fear conditioning, fear generalization and a lack of proper fear-extinction. For review, see Fleischer and Frick, 2023.

A main challenge in the field is the difficulty of setting up experimental designs that represent true sex differences using animal models. For example, some rodent models like social defeat stress are based on behaviors mainly exhibited by males. Thus, it has been challenging to examine stress responses using the same set of stressors and behavioral assays in animals of different sexes.

Stress perception, appraisal, and reappraisal

Appraisal of a stressor, whether a person perceives it as harmful or a positive, challenging experience, can dramatically change the stress response. Interestingly, an individual's response to stress seems to have a strong inherent or innate component. In humans, for example, an individual's genetic and environmental/epigenetic makeup affects their processing and perception of stress (i.e., positive or negative valence attributed to a stressor) such that individuals respond differently to the same stressor.

A study by Forkosh et al., 2019 identified four stable 'personality types' in mice (termed identity domains) based on unbiased behavioral tracking which persisted through time, developmental stages and stressful changes in their social environment. These 'personality types' corresponded to specific patterns of gene expression in the insular cortex, mPFC and amygdala.

Numerous studies have found that individuals who perceive stress as having a negative impact on their health suffer more serious health problems, including premature death (Keller et al., 2012; Nabi et al., 2013). Not surprisingly, abnormal patterns of appraisal are seen in various stress-related psychopathologies. The good news is that the stress response can be changed by reframing it as helpful. A study by Jamieson et al. (Jamieson et al., 2012) tested whether reappraisal of stress-induced arousal (for example, a 'racing' heart) as helpful and adaptive, as opposed to harmful, could improve physiological and cognitive outcomes. The results showed that participants in the reappraisal group displayed a more adaptive physiological response (improved cardiovascular functioning), reported higher levels of perceived resources and showed decreased attentional bias for emotionally negative information. That is, they dealt much better with the stressful situation even when the reappraisal training consisted of brief instructional materials. Notice that the reappraisal intervention did not change the actual increased physiological arousal caused by the stressor; it is not an intervention aimed at decreasing or dampening arousal. What changed was the 'rethinking' of what that arousal means (whether it's positive versus negative) and that is what ultimately influenced the measured outcomes. Neuroimaging studies have shown that reappraisal is associated with activation of frontal cortical areas (i.e., regions regulating executive functions) like the dorsal anterior cingulate cortex and medial PFC (Kalisch, 2009).

Stress predictability and controllability in animal models

To understand the molecular mechanisms underlying appraisal, we must turn to animal models. However, animals cannot report if they are 'reappraising' a stressful situation, thus, we must examine whether things like predictability or controllability over the stressor can change their response. Experiments have shown that rodents exposed to stressors that were not predictable had significantly higher and longer glucocorticoid responses than those presented with a regularly scheduled stressor. Similarly, the work of Steven Maier's group at the University of Colorado Boulder has shown that controllability (a rat controls the cessation of a presented stressor by turning a wheel, for example) alters the neural and behavioral response, but doesn't change the HPA axis output. Animals receiving the exact same stressor (i.e., amount, intensity, and duration of an electrical shock) but who differed on whether they could terminate the shock or not, displayed similar HPA axis activation but dramatically different behavioral responses. Animals that could not stop the shock (uncontrollable stress) later failed to learn to escape in a different context, were afraid of new things, were less dominant, showed less social interactions, and had exaggerated responses to drugs of abuse (see Figure 12.21).

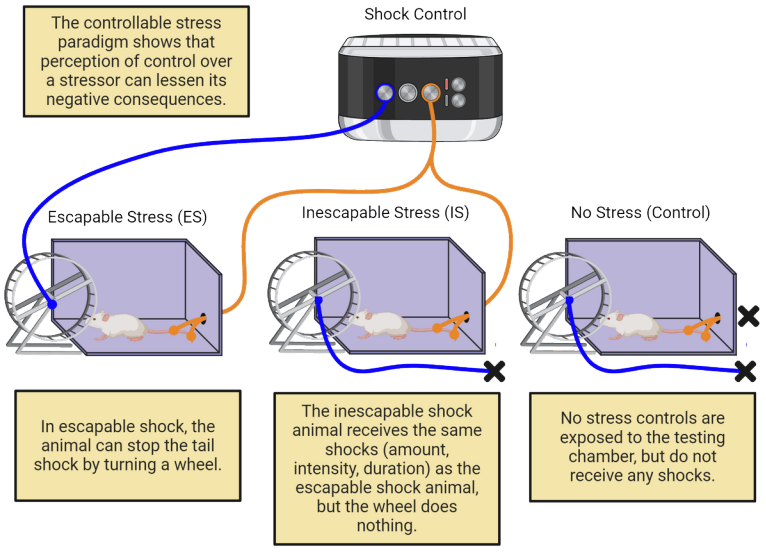


Figure 12.21 Controllable stress in rodents

A large amount of work has gone into understanding the neural circuitry of this behavioral difference. Studies have found that uncontrollable stress produces robust activity in the dorsal raphe nucleus which increases release of serotonin, amygdala activation, and development of learned helplessness. Exposure to controllable stress, however, activates the medial PFC which inhibits dorsal raphe nucleus activation and blocks the negative behavioral outcomes (Amat et al., 2005; Amat et al., 2006).

Social support and buffering of the stress response

Many social animals display an interesting characteristic: when together with a conspecific they show dampened stress responses and better recovery from stressful experiences. This phenomenon is called social buffering and it has been observed in numerous species including rodents, felines, birds, nonhuman primates and humans.

Candidate molecular mediators of social buffering

Not much is known about the molecular mechanisms or neural pathways mediating the effects of social buffering. A candidate molecular mediator is the neuropeptide oxytocin—which is known for its role in social affiliative behaviors in many mammalian species.

Although no direct mechanism has been established, evidence suggests that oxytocin is released in response to stress, is associated with social/affiliative interactions after stress and can decrease HPA axis activation (via inhibition of CRH activation and ACTH and corticosteroid release), as well as SNS responses (Taylor, 2002). Additional mediators involved in stimulating and regulating the effects of social support include norepinephrine/noradrenaline, prolactin, vasopressin, serotonin and endogenous opioids.

Brain regions involved in social buffering

In humans, a study by Eisenberger et al., (Eisenberger et al., 2007) found that greater social support and decreased cortisol responses to a social stressor were associated with decreased activity in the dorsal anterior cingulate cortex (dACC) and prefrontal cortex (PFC)—brain regions that have been linked to social distress. A recent study in adolescent mice also points to a role for the PFC. In this study, social support (the presence of a mouse attempting to free a restrained mouse) blocked the negative effects of restraint stress on working memory, memory consolidation and retrieval. These stress-alleviating effects were dependent upon inhibition of stress-induced signaling cascades and normalization of stress-induced gene expression changes in the PFC (Kim et al., 2018).

Stress drives social affiliation

Social buffering is encouraged by the fact that, in many social species, stress directly promotes behaviors that will increase social interaction. Thus, stress and social buffering can form a loop, where stress drives affiliative behaviors, which in turn reduce the experience of stress (see Figure 12.22). For example, moderate stress is associated with increased affiliative behaviors in rats. A study by Muroy et al (Muroy et al., 2016) found that moderate stress exposure increased affiliative behaviors (huddling/affiliative contact, better sharing of a water resource, improved homecage stability (dominance rank) and oxytocin signaling). When the stress was made more severe by addition of predator odor, however, oxytocin signaling was reduced and the positive social effects were eliminated. These findings suggest that even the drive for affiliation by stress may follow an inverted-U pattern.

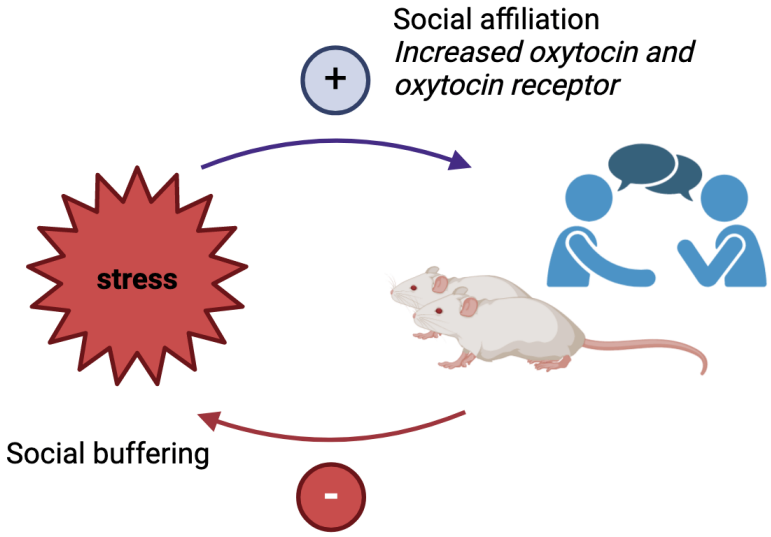


Figure 12.22 Stress-social behavior interaction Stress stimulates social affiliative behaviors, which lead to social buffering to reduce the impact of the stressor.

In humans, acute stress has also been shown to increase affiliative interactions and prosocial behavior. For example, increased time interacting and higher group cohesion were observed in study participants awaiting an electrical shock versus groups awaiting a mildly embarrassing or ambiguous stimulus (Morris et al., 1976). In terms of prosocial behavior, participants exposed to a socioevaluative stressor (the TSST) showed greater trust and sharing in interactive games with monetary stakes (von Dawans et al., 2012). Importantly, affiliative social interactions, for example, contact with a friend or other supportive person during times of stress can decrease sympathetic reactivity and cortisol levels, facilitating recovery. This, in turn, can positively influence health and life expectancy (for review see House et al., 1988; Taylor, 2011). Lack of social connection (e.g. social isolation), on the other hand, can increase HPA axis and SNS activity and is a major risk factor for stress-related psychiatric conditions like depression and anxiety.

Summary of factors affecting interindividual variability in the stress response

Figure 12.23 shows a summary of the factors discussed in this section. Factors and their associated brain regions are displayed at the top. Some brain regions are attuned to various factors. For example, the reward system is sensitive to predictability (i.e., novelty), controllability and duration of a stressor. The frontal cortex is similarly attuned to duration, controllability and stressor predictability, and additionally mediates stressor appraisal; the stress dampening effects of social support are integrated here as well. Brainstem regions, the circumventricular organs and the limbic system are attuned to stressor type and the physiological state of the organism (metabolic, inflammatory state, for example), which can influence an individual's perception of stress.

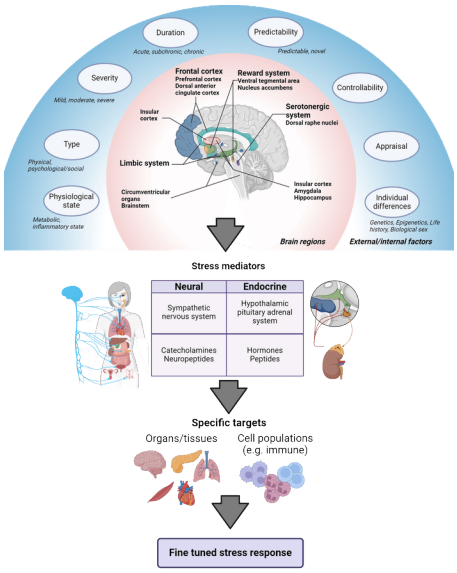


Figure 12.23 Summary of factors affecting interindividual variability in the stress response

The brain assimilates both external and internal inputs and constructs a 'grid' of brain activity specific for each stressor. This pattern of brain activity varies 1) between individuals (due to individual differences based on genetics, epigenetics, life history events, biological sex, emotional and physiological state, etc.) and 2) between different stressors. The response is then integrated at the level of the hypothalamus and specific brainstem nuclei to produce fine-tuned neural and endocrine outputs that are designed to deal with the specific challenge. For example, stressors that exert metabolic pressure (hypoglycemia) induce secretion of growth hormone from the pituitary gland (Jezova et al., 2007) while stressors that elicit pain activate pain relief pathways. The severity of the painful stressor further fine-tunes which type of pain relief pathway is activated: opioid versus non-opioid. Exposure to heat or cold stress requires activation of brown fat to restore internal body temperature, while encountering a mountain lion requires priming of the immune system in case of injury. For the latter two examples, specificity is mediated by differential activation of sympathetic fibers in adipose tissue and the spleen (an immune organ) respectively, in response to different types of physical stressors (Iriki and Simon, 2012). SNS peripheral nerve terminals can also co-secrete various neuropeptides that further fine tune the generic stress response.

Thus, the type of neural activation (e.g., which SNS fibers), variety of secreted factors, their concentration and different combinations diversify the stereotypical neural and endocrine stress response. Moreover, even secretion of the canonical stress hormones ACTH and corticosterone depend on the stressor context. For example, lactating female rats caring for a litter generally show blunted ACTH and glucocorticoid responses to common laboratory stressors. However, if the stressor involves danger to the pups (inclusion of predator odor or a male intruder in the home cage), then plasma levels of ACTH and glucocorticoids rise significantly (Deschamps et al., 2003). In this example, the organism's physiological state is also an important factor. For in depth review, see Haykin and Rolls, 2021.

Resilience

Resilience is the capacity to adapt following adversity. It is not a fixed trait—it can change throughout life and is multidimensional: for example, a person can be resilient to injury but not to psychological stress. The inverted-U curve can be used to understand how stress responsivity (vulnerability or resilience) varies between individuals (Sapolsky, 2015). For example, the curve can be right- or left-shifted along the x-axis (see the blue and orange curves in Figure 12.24).

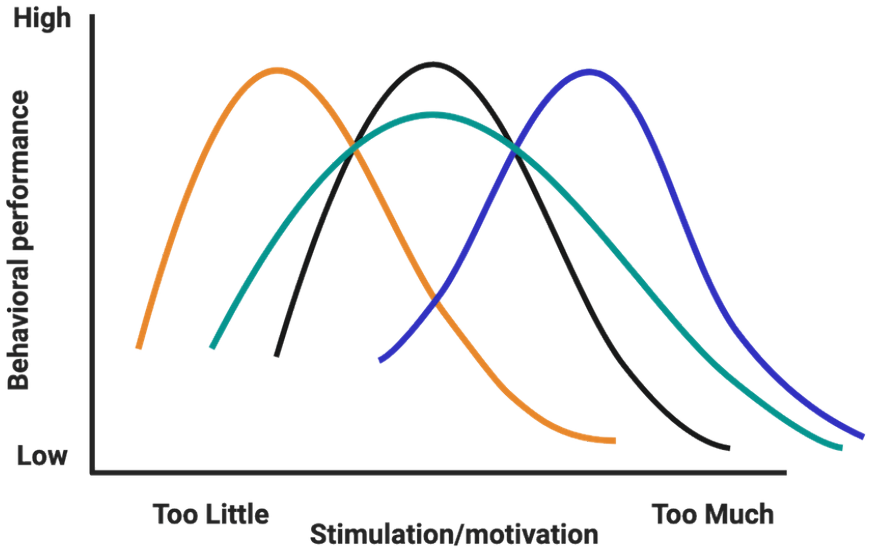


Figure 12.24 Interindividual variability in the stress response Different individuals can show different inverted-U curves of reponse to stressors.

The 'right' amount of stress (eustress) that yields optimum function for the person with the blue curve is much higher than that for the person with the orange curve. This optimal level will also vary in different domains for the same person and for the same person at different points in time (intraindividual variability). Curves could also be flattened (wider; see green curve). The individual with the green curve would require really low or really high HPA axis activation for it to be detrimental to their function.

Little is known about the mechanisms that shift inverted-U curves to the right, that is, towards resilience. Most resilience studies have been done at the group level and few have focused on individuals, i.e., those who respond (are vulnerable) versus those that don't respond (are resilient) to stress. Additionally, does resilience mean that there was no change or a lack of molecular response? Or was there a protective response that helped resilient individuals bounce back? The answer seems to point to the latter, but the mechanisms are yet mostly unknown.

How to optimize the stress response

How can we optimize our response to stress? That is, modulate it towards eustress versus distress? As mentioned before, reappraisal of a (mild-moderate) stressor as an adaptive challenge can improve physiological and cognitive stress outcomes. We can also engage in *exercise*—a physical stressor—which can enhance our adaptive capacity and has been shown to have numerous beneficial effects on stress responses. Exercise produces in the short-term feelings of calmness and reduced anxiety and can lead to long-lasting adaptations in neuroendocrine/HPA axis function after chronic training. It has reported antidepressant effects and has been shown to increase overall resilience, well-being and healthspan. Acute vigorous exercise increases levels of endogenous cannabinoids in the bloodstream. These neurotransmitters are similar to compounds found in cannabis (marijuana) and may mediate post-exercise feelings of calm, reduced anxiety and sometimes euphoria, colloquially referred to as a 'runner's high' (Raichlen et al., 2013; Volkow et al., 2017). Training over several weeks attenuates resting/basal levels of stress hormones (Hackney, 2006). Furthermore, the stress-attenuating effects of chronic exercise training seem to carry over into reduced stress responses to other life stressors (Traustadóttir et al., 2005).

Meditation is an Eastern spiritual-associated practice that has been adapted for stress reduction and is currently a very active area of study. Research into meditation seems to point to enhanced executive control of attention (Tang et al., 2007), reduced cortisol levels (Tang et al., 2007; Fan et al., 2014) and improvements in mood (Basso et al., 2019). Note that research is limited to human subjects and correlational studies. Please see the demonstration video for an example of a short, guided meditation. To learn more about meditation research, see the work of Richard Davidson (University of Wisconsin-Madison; current leader in the field) and the Mind & Life Institute.

Finally, there are interventions like Mindfulness-based stress reduction (MBSR) (Kabat-Zinn, 2013) - an evidence-based program that combines mindfulness meditation, body awareness and examination of patterns of thought, emotion, behavior/action as tools for effectively coping with stress. MBSR has been shown to enhance attention skills, increase emotional regulation and significantly reduce rumination and worry. It has been very successfully utilized as an intervention for ameliorating anxiety, depression, and pain.

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16.10: Clinical Implications of Stress

Learning Objectives

By the end of this section, you should be able to

- Define allostatic (over)load and explain its consequences
- Describe the pathological effects of stress exposure and some of its clinical implications
- Describe the role of microglia in stress-related mood and neurodegenerative disorders

The cumulative 'wear and tear' from prolonged or severe stress exposure can tax our adaptive systems predisposing us to pathology and stress-related disorders. In this section, we will learn more about the concept of allostatic (over)load, which describes what can happen when stress becomes 'too much'. We will also discuss common stress-related nervous system disorders and the role of microglia, the brain's resident immune cells.

Allostasis vs. allostatic (over)load

We now know that the stress response is a necessary, survival-promoting response that allows us to adapt to challenges. What happens, however, if this response is activated for too long or too often, as a result of repeated exposure to stressors, or lack of proper shut down?

Well, it's very much the continuation of the beneficial, life-saving aspects of stress that become detrimental when they are prolonged or chronic (inverted-U nature of the response). Think about the acute effects of stress. For example, you are confronted with a stressor and your blood pressure increases because that is what's needed in order to run away from the threat. But, if your blood pressure is increased constantly, that becomes your new set point and now you have hypertension. Hypertension is a disease that affects most organ systems in the body. In the long-term, it increases wear and tear on many systems and accelerates the aging process. Other bodily systems are similarly affected. The immune and reproductive systems are turned down leading to immune suppression and reproductive distress/dysfunction. In the digestive tract, you can develop ulcers and decreased nutrient absorption. If the excessive stress exposure came early on in life, it can result in stunted growth. In terms of metabolism, glucose thrown into the bloodstream helps the muscles in the short run (escaping the threat) but can lead to diabetes if chronic. Similarly, in the brain, prolonged or severe stress exposure can lead to regional changes in brain structure (dendritic hypo/hypertrophy, remodeling, circuit plasticity) that can alter brain function and lead to pathologies such as anxiety, depression, and PTSD.

Recall that allostasis refers to the processes that restore homeostasis and also allow us to adapt through change. Our body's activation of the nervous, endocrine (and immune) systems during a stress response, for example, are allostatic mechanisms that allow us to adjust and increase our resilience in the face of stress. Allostatic (over)load, on the other hand, is the physiological cost of that adaptation to our body, i.e., the 'wear and tear' that accumulates after repeated or chronic stress exposure (see Figure 12.25).

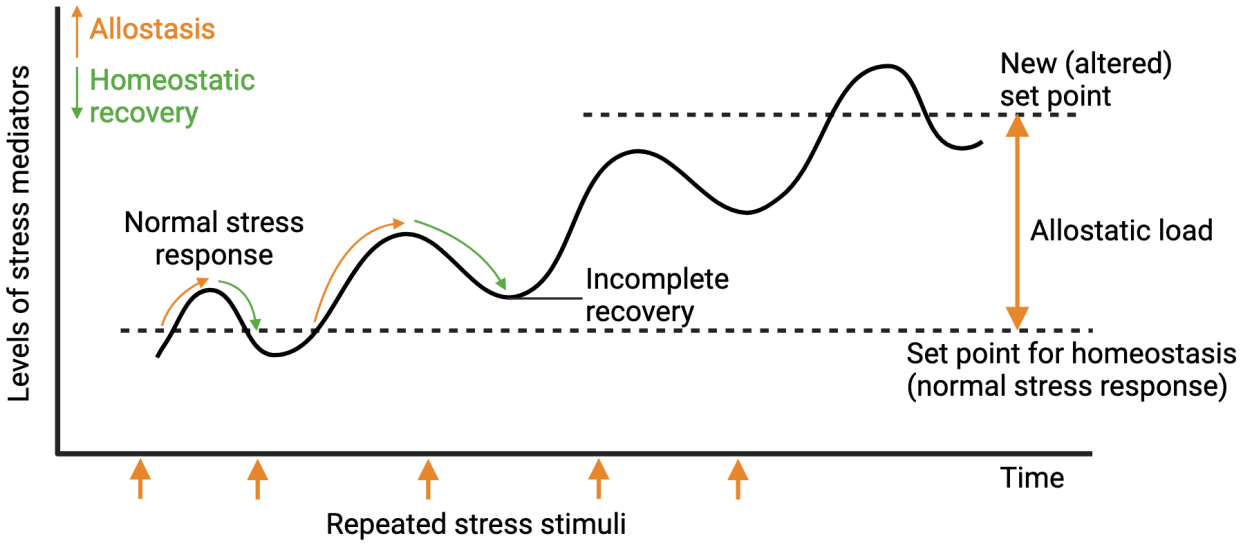


Figure 12.25 Allostatic overload Allostatic load is the difference between new and old set points that arises due to a cumulative burden of adaptation to stress.

Types of allostatic (over)load include:

1. Frequent activation of allostatic systems: e.g., repeated hits from multiple stressors resulting in overexposure to stress hormones.
2. Lack of adaptation to a repeated stressor: e.g., not getting used to public speaking.
3. Failure to shut off stress response activation after the stressor has passed: i.e., the inability to efficiently shutoff the stress response resulting in overexposure to stress hormones.
4. Failure to adequately activate the stress response: e.g., an inability to mount the proper HPA activation.

These aren't mutually exclusive. There can be combinations of these occurring at the same time.

Ultimately, continual or chronic stress exposure results in allostatic (over)load. Allostatic (over)load serves no useful function and can predispose individuals to stress-related disorders and pathology. Some of the clinical consequences are discussed below.

Mood disorders

Mood disorders are often accompanied by a distorted or inconsistent emotional state that persistently interferes with the ability to function. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) categorizes several disorders as part of mood disorders including major depressive disorder (MDD), bipolar disorder, and others. Many studies have implicated that both acute and chronic stress are related to the onset of MDD (McEwen, 2004). One potential mechanism connecting stress and mood disorders is dysregulation of the neurotransmitter serotonin. Serotonin is a crucial neurotransmitter for mood regulation in the brain. Chronic stress is known to modulate neurotransmitters linked to mood disorders and their receptors. For instance, chronic stress reduces 5-HT1A autoreceptor sensitivity in the dorsal raphe nucleus—the brainstem nucleus where serotonergic cell bodies are located (Chaouloff et al., 1999). Although 5-HT1A receptors are not actively engaged in anti-depressant drug effects, the receptors are well-known for regulating the entire serotonergic system. Furthermore, an increase in stress hormones due to hyperactivity of the HPA axis has been shown to elevate expression of the gene encoding the serotonin reuptake transporter—a main target of major anti-depressant drugs, which inhibit the transporter's ability to reuptake/remove serotonin from synapses (Tafet et al., 2001). It is notable that dysregulation of serotonin homeostasis during critical periods (in utero, childhood, adolescence) and adulthood via exposure to chronic stress and dysregulated HPA axis function may produce long-lasting changes in the brain and ultimately impact the development of (and affect treatments for) mood disorders including MDD.

Anxiety disorders

Anxiety disorders are often characterized by intense and excessive symptoms of anxiety and worry that last persistently.

According to the DSM-5, there are multiple types of anxiety disorders, diagnosed based on potential causes and symptoms such as generalized anxiety disorders, social anxiety disorders, phobias, and panic disorders. One of the risk factors for anxiety disorders includes exposure to chronic stress. Chronic stress is well known to enhance amygdala-mediated fear. For example, a study by Rosekranz et al. revealed that chronic stress can activate neural excitability in the lateral amygdala circuitry (Rosenkranz et al., 2010). The amygdala circuitry is particularly important in the regulation of emotion, anxiety, and fear. Thus, heightened amygdala activation mediated by stress plays a role in the development of anxiety disorders.

Repeated and chronic exposure to stress may also result in hyperactivity of the HPA axis, which can contribute to anxiety. A subgroup of patients with anxiety disorders often displays hyperactivity of the HPA axis (Tafet and Nemeroff, 2020). Furthermore, anti-anxiety drugs, such as benzodiazepines, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs), all modulate components of the HPA axis. For instance, some types of benzodiazepines have been shown to alleviate anxiety symptoms and reduce the activity of CRH neurons in the hypothalamus, indicating the potential impact of anti-anxiety drugs on HPA axis regulation.

Posttraumatic stress disorder (PTSD)

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can develop in a subset of individuals exposed to a traumatic event (e.g., severe car accident, combat, sexual assault, natural disaster). It is characterized by persistent reexperiencing of the trauma (e.g., intrusive memories and flashbacks), avoidance of stimuli associated with the trauma and numbing of general responsiveness (similar to symptoms of depression) (see Figure 12.26).

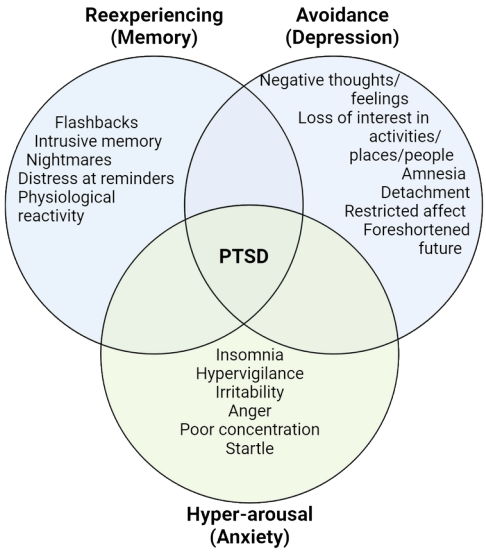


Figure 12.26 Core symptoms of PTSD

Women are twice as likely to have PTSD than men (Kessler, 1995). Immediately following exposure to severe trauma, most individuals will present with a collection of these symptoms (i.e., will display an acute stress response). Yet, in most people, these symptoms will resolve within months. Only 15-25% of individuals will continue to show persistent symptoms a year after the traumatic event and meet the diagnostic criteria for PTSD (Yehuda et al., 1998). Thus, PTSD represents a physiological failure to recover from an acute stress response that is almost universal.

Not surprisingly, patients with PTSD display HPA axis dysregulation, but paradoxically, they show lower overall cortisol levels, especially in the hours immediately after the trauma (Mason et al., 1986; Yehuda, 2002). Additionally, they have an abnormally high noradrenaline/cortisol ratio which suggests a loss of coordinated activity between HPA axis and ANS function. Cortisol administration shortly after trauma (in ER patients exhibiting low cortisol levels) has been successful as a preventative intervention for PTSD (Zohar et al., 2011). Non-pharmacological interventions in the form of cognitive behavioral therapy, sometimes coupled with virtual reality scenarios, have also proven successful in treating the symptoms of PTSD.

Cognitive and memory disorders

Stress can affect multiple aspects of cognition including attention, learning, and memory. Some major cognitive/memory disorders in humans are Alzheimer's disease (AD), attention deficit disorder, and dementia. Each of these is affected by stress exposure. Stress exacerbates AD (Machado et al., 2014; Justice, 2018), there's a high comorbidity rate of PTSD with attention deficit disorder (Cuffe et al., 1994; Adler et al., 2004), and chronic stress is associated with dementia (Peavy et al., 2012) and increased risk for dementia later in life (Johansson et al., 2010). Stress-sensitive brain regions like the hippocampus and PFC likely contribute to these phenotypes.

Interestingly, PTSD can be viewed as a memory disorder, and it is easy to understand many of the symptoms via this lens. In addition to the strong recall of the traumatic event, PTSD patients report problems with declarative memory (remembering facts), fragmentation of memory and dissociative amnesia (not being able to recall important personal information). A salient feature of PTSD is an aberrant consolidation of the traumatic memory event (aberrant fear learning). It may manifest as a lack of fear extinction (new safety cues are not associated with the old memory) or a generalization of the fear response. For example, if the event was the experiencing of a bomb blast, then the result could be a sensitivity to other loud noises (Parsons and Ressler, 2013; Shalev et al., 2017; Fenster et al., 2018).

Addiction, compulsive and impulse disorders

Addiction is a compulsive behavior or use of a substance characterized by an inability to control consumption and withdrawal symptoms when unable to access it. Gambling and shopping are examples of behaviors that can lead to a non-substance addiction. Substance abuse is highly studied and provides the basis for what we know about stress and addiction. Stress is a prominent risk factor for developing a substance use disorder or relapsing (Schmid et al., 2009; Enoch, 2011; Duffing et al., 2014; Tschetter et al., 2022). Stress and substance use both activate the HPA axis and connected amygdala, while down-regulating activation of the hippocampus and the PFC, leading to impaired decision making and impulsivity. These similarities suggest that stress may influence and further aggravate the effects of many drugs of abuse and contribute to addiction. Therefore, reducing stress could aid in efforts to treat addictions or prevent susceptibility.

Stress and (neuro)immune function

We all know that exposure to pathogens leads to characteristic changes in physiology and behavior. When we're sick, we feel tired and sleepy, lose motivation, withdraw socially, don't feel as hungry or thirsty, might have a fever and our brains might feel foggy. Sometimes we might also feel more sensitive to pain or more anxious and depressed. This constellation of symptoms is called the sickness response, and it is remarkably similar to endophenotypes that characterize stress-related mood disorders like MDD, anxiety and PTSD. This intriguing observation hinted at the idea that neuropsychiatric conditions like mood disorders had an immune component. That is, the immune system might be involved in regulating an organism's motivational state. This idea led to intense interest in the role of the immune system in brain function and how it relates to stress.

As we know, stress can affect every cell and tissue in the body, hence it is no surprise that it has profound effects on immune system function. In general, following the inverted-U pattern, acute stress seems to enhance immune responses while chronic stress has a suppressive effect. However, both acute and chronic stress can generate anti-inflammatory and proinflammatory responses, leading to a more complex picture. In recent years, inflammation has garnered a negative reputation, but it is in fact a necessary and beneficial immune response after an acute stressor like an injury/infection: here the immune system attacks the invaders, clears the threat and helps to promote healing. Inflammation is deleterious, however, if it becomes prolonged. Studies have shown, for example, that chronic socio-environmental stressors (poverty, bereavement) are associated with increased expression of genes involved in inflammation and decreased expression of antiviral responses—the conserved transcriptional response to adversity. This transcriptional program is thought to promote a state of chronic, low-grade inflammation which can result in development of inflammation-related diseases.

Stress and microglia—the brain's resident immune cells

The brain, largely isolated from cells of the immune system due to the presence of the blood-brain-barrier, was long thought to be an immune-privileged organ; however, it contains its own tissue-resident immune cells: microglia. In recent years, there has been intense interest in understanding the crucial role of microglia in brain development and function.

As the resident phagocytes, microglia actively scan their environment for disruptions in homeostasis. They are first responders

to threat (e.g., infection with a virus, tissue damage), play a critical role in neurodevelopment and perform numerous functions in the maintenance of the healthy adult brain. For example, they use their phagocytic activity to remove debris, dead/dying neurons and other cells. They also lend trophic (growth) support to neurons, modify synaptic connections and plasticity, and modulate neuronal activity. Additionally, because they are immunocompetent cells, microglia produce and release anti- and proinflammatory mediators (cytokines and chemokines), some of which have roles in synaptic plasticity and memory function. Figure 12.27 diagrams some of these cellular functions which impact brain function and development.

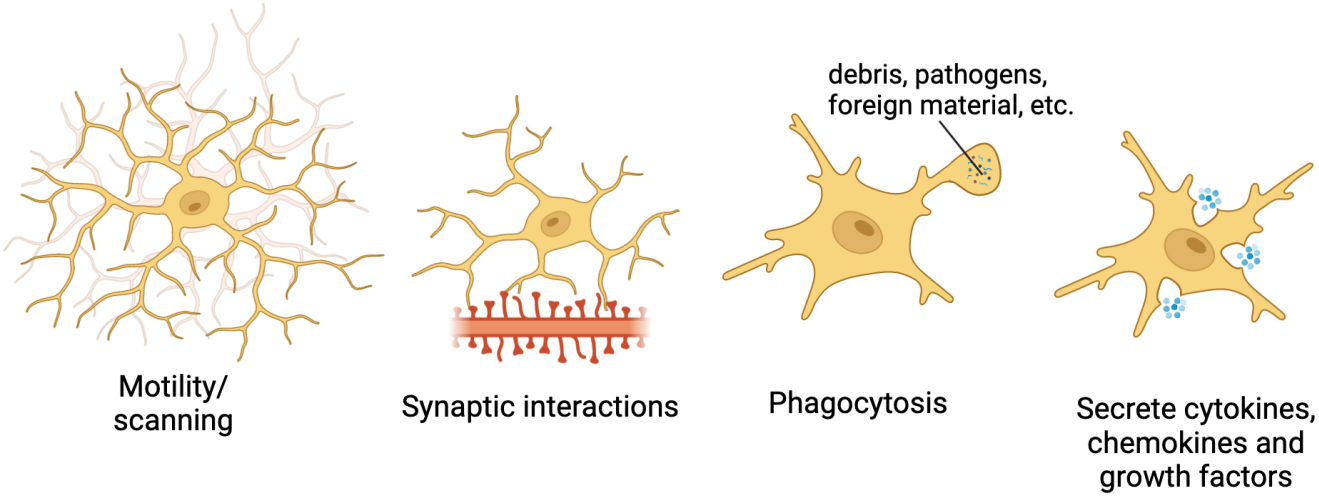


Figure 12.27 Microglial functions Through several cellular functions, microglia regulate injury/illness response, healthy brain function and neurodevelopment.

Homeostatic or surveilling microglia exhibit a highly branched morphology with a small cell body and unique transcriptional signature. This phenotype is suppressed when disruptions to CNS homeostasis occur (for example, during infection or aging). At the same time, microglia undergo changes in morphology, transcription and proinflammatory mediator profile (a spectrum of different functional states grouped under the umbrella term 'activation') which at the extreme becomes a phenotype characteristic of neurodegeneration. One of these activation states, termed 'primed', is seen in microglia under neuroinflammatory conditions like stress and aging. Microglia can also proliferate, increasing their numbers in response to homeostatic disruptions. Below, we will discuss more specifically the role of microglia in stress-related pathology with a focus on mood and cognitive dysfunction/ neurodegenerative disorders.

Inflammatory priming and mood disorders

Microglia can respond directly to key stress mediators, including glucocorticoids and the catecholamines epinephrine and norepinephrine. Although glucocorticoids are widely known for their immunosuppressive effects, they can also have a more permissive role. A number of studies have implicated glucocorticoids in stress-induced inflammatory priming—that is, a sensitization or heightened immune response in microglia to subsequent inflammatory stimuli—in stress-related brain regions like the hippocampus. In other words, glucocorticoid exposure can make microglia more susceptible to a second inflammatory stimulus, and this can then trigger an exaggerated or prolonged inflammatory response that can damage nearby neurons or other cells and negatively affect brain function.

Experiments have tested the causal role of glucocorticoids in this phenomenon. For example, exposure to tailshock stress in rats where glucocorticoids signaling was blocked (via application of GR antagonists or adrenalectomy, removal of the adrenal glands) blocked this type of exaggerated inflammatory response in hippocampal microglia when subsequently stimulated with a bacterial product. Other experiments using β-adrenergic receptor agonists or antagonists and repeated social defeat stress have shown that catecholamines are also implicated in stress-induced microglial priming in regions of the brain related to threat-appraisal. Additionally, they play a critical role in the mobilization and redistribution of specific types of inflammatory peripheral immune cells to the CNS (for review see Frank et al., 2019). This type of infiltration of peripheral immune cells into the brain, along with a greater overall local inflammatory microenvironment, lead to a full-blown state of neuroinflammation.

Inflammatory priming is thought to contribute to the development of a number of mood disorders and their related symptoms. For example, microglia that have been primed by repeated stress exposure release several molecules that can directly impact

emotion-related behaviors. IL-1β is one such molecule. It is a cytokine released by microglia that both contributes directly to further HPA axis activation and also drives sickness behaviors, like decreases in motivation to obtain a reward. Loss of motivation for previously rewarding stimuli is a core symptom of depressive disorders. Another protein released by stress-primed microglia, PGE2, stimulates increases in social avoidance and greater anxiety responses to stress (for review see Wolf et al., 2017). How this vicious cycle of stress and microglia function contributes to mood disorders is an active field of research which may yield new ways to treat depression and anxiety in the future.

Stress, microglia and neurodegeneration

Neurodegeneration is the age-related, progressive damage to neuronal structures and function in the CNS. It can result in disruptions to cognitive performance and is seen in disorders like Alzheimer's disease (AD) and other dementias. Notably, a life-long history of stress exposure is a risk factor for developing cognitive deficits, brain atrophy and AD (Gracia-Garcı a et al., 2015, Alkadhi, 2012) and psychosocial stress, in particular, is a risk factor for late-onset AD (LOAD). Chronic stress has also been shown to worsen neurodegeneration and cognitive impairments in rodent models of AD (Carroll et al., 2011; Srivareerat et al., 2009). As discussed previously, chronic stress can lead to neuroinflammation, one of the hallmarks of many neurodegenerative disorders including AD.

Microglia play a key role in the establishment and progression of neurodegenerative disorders. Microglial dysfunction is prominent in AD, for example, and several genetic risk factors associated with the disease are specifically or highly expressed by microglia (APOE and TREM2). It is worth noting that during normal aging, microglia lose some of their surveillance/homeostatic capacity and are thought to become more proinflammatory or reactive in general. Additionally, their phagocytic function is impacted.

During neurodegeneration, microglia react to age-related, accumulated debris/protein aggregates through their dedicated pathogen and damage-sensing receptors. They also adopt an 'extreme' activated, primed phenotype termed MGnD (neurodegenerative microglia) or DAM (disease-associated microglia) characterized by induction of genes associated with cellular damage and degeneration. This phenotype also includes higher expression of immune modulators that induce astrocyte activation and aid in recruitment of inflammatory and other specialized immune cells that further contribute to neuronal damage. Thus, chronic stress can exacerbate neurodegeneration by compromising microglial homeostatic support for neurons/synaptic function and sensitizing microglia towards a primed state which leads to neuroinflammation and neuronal dysfunction and death. Interestingly, regions like the frontal cortex and hippocampus which are particularly sensitive to the effects of stress are also amongst the first brain areas affected in AD.

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17: PSYCHIATRIC DISORDERS

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17.1: Biopsychology of Psychological Disorders Overview

Most psychological researchers and clinicians agree that mental health is best understood through a "biopsychosocial" perspective that considers how biological, psychological, and sociocultural factors contribute to **psychopathology**. This biopsychology textbook focuses on the biological underpinnings of psychological disorders, emphasizing brain function and genetics. While treatment approaches are introduced, more comprehensive coverage is found in clinical and abnormal psychology courses.

Psychological disorders emerge from complex interactions among biological, social, and environmental factors. The precise nature of these interactions in shaping disorders for individuals remains a challenging question. Interacting factors and varied symptom profiles (within and across individuals) complicate diagnosis. To promote consensus in diagnoses, researchers and clinicians have developed classification systems that traditionally focus on observable symptoms. Although biological factors influence psychological functioning (Wyatt & Midkiff, 2006), biological evidence was rarely used to inform diagnosis. Historically, technological limitations (e.g., in neuroimaging and genetic testing) hampered scientists from adequately examining the biological bases of psychological disorders. Now, given technological advances, scientists have begun exploring how biological factors, such as brain structure, brain function, brain chemistry, and genetics contribute to psychological disorders and may eventually inform diagnosis.

What are Psychological Disorders?

Perhaps the simplest approach to conceptualizing psychopathology is to label behaviors, thoughts, and inner experiences that are atypical, distressful, dysfunctional, and sometimes even dangerous, as signs of a psychological disorder. For example, if you ask a classmate for a date and you are rejected, you probably would feel a little dejected. Such feelings would be normal. If you felt extremely depressed—so much so that you lost interest in activities, had difficulty eating or sleeping, felt utterly worthless, or contemplated suicide—your feelings would be atypical, would deviate from the norm, and could signify the presence of a psychological disorder. However, just because something is atypical, does not necessarily mean it is disordered.[1]

The American Psychiatric Association (APA) Definition of a Psychological Disorder

A formal definition developed by the American Psychiatric Association (APA, 2022) characterizes a psychological disorder as a condition that consists of the following:

- **Significant disturbances in thoughts, feelings, and behaviors**. A person must experience inner states (e.g., thoughts and/or feelings) and exhibit behaviors that are clearly disturbed—that is, unusual, but in a negative, self-defeating way. Often, such disturbances are troubling to those around the individual. For example, if an individual is uncontrollably preoccupied with germs and bathes for hours each day, their inner experiences and behaviors would be considered atypical and negative (disturbed) and would likely trouble family members.
- **The disturbances reflect some kind of biological, psychological, or developmental dysfunction**. Disturbed patterns of inner experiences and behaviors should reflect some flaw (dysfunction) in the internal biological, psychological, and developmental mechanisms that lead to normal, healthy psychological functioning. For example, the hallucinations observed in schizophrenia could be a sign of brain abnormalities.
- **The disturbances lead to significant distress or disability in one's life**. A person's inner experiences and behaviors reflect a psychological disorder if they cause the person considerable distress, or greatly impair their ability to function as a normal individual. As an illustration, a person's fear of social situations might be so distressing that they avoid all social situations (e.g., preventing that person from being able to attend class or apply for a job).
- **The disturbances do not reflect expected or culturally approved responses to certain events**. Disturbances in thoughts, feelings, and behaviors must be socially unacceptable responses to certain events that often happen in life. For example, it is perfectly natural (and expected) that a person would experience great sadness and might wish to be left alone following the death of a close family member. Because such reactions are culturally expected, they wouldn't signify a mental disorder.[2]

Understanding the Classification Systems of Psychological Disorders

Studying psychological disorders begins with systematically discerning significant signs and symptoms. Identifying and labeling a set of symptoms is crucial for a proper diagnosis. This process enables professionals to use a common language and communicate about the disorder with the patient, colleagues, and the public. For these reasons, classification systems that systematically organize psychological disorders are necessary. The current main classification system is the **Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)** published by the American Psychiatric Association (2022). Another classification system used for mental and behavioral disorders is the **International Classification of Diseases (ICD-11)** and is primarily used by the World Health Organization to support the global comparison of morbidity statistics. While the ICD-11 is also used in medical settings around the globe, the DSM-5 remains the main instrument for diagnosis. Despite its dominance in the field, using the DSM-5 for clinical diagnosis has some limitations. For example, individuals displaying very different symptoms may be diagnosed with the same psychological disorder, or conversely, individuals displaying very similar symptoms may be diagnosed with different disorders. Given this variation in symptom display and the DSM-5's focus on mapping symptoms onto psychological disorders, it makes sense that scientists are examining how biological factors may inform understanding and diagnosing psychological disorders.

In the rest of this chapter, we give an overview of some common psychological disorders and their underlying biological factors. Overall, there are hundreds of psychological disorders (characterized by the DSM-5 in over 1000 pages). Here we cover a few that are interesting to students: schizophrenia, mood disorders including depression and bipolar disorder, anxiety, obsessive-compulsive disorder, and post-traumatic stress disorder.[3]

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1. This section contains material adapted from: Spielman, R. M., Jenkins, W. J., & Lovett, M. D. (2020). 15.1 What Are Psychological Disorders?. In Psychology 2e. OpenStax. Access for free at https://openstax.org/books/psychology-2e/pages/15-1-what-are-psychological-disorders License: CC BY 4.0 DEED. 12.01: Biopsychology of Psychological Disorders Overview#return-footnote-312-1
2. This section contains material adapted from: Spielman, R. M., Jenkins, W. J., & Lovett, M. D. (2020). 15.1 What Are Psychological Disorders?. In Psychology 2e. OpenStax. Access for free at https://openstax.org/books/psychology-2e/pages/15-1-what-are-psychological-disorders License: CC BY 4.0 DEED. 12.01: Biopsychology of Psychological Disorders Overview#return-footnote-312-2
3. This section contains material adapted from: Spielman, R. M., Jenkins, W. J., & Lovett, M. D. (2020). 15.2 Diagnosing and Classifying Psychological Disorders. In Psychology 2e. OpenStax. Access for free at https://openstax.org/books/psychology-2e/pages/15-2-diagnosing-and-classifying-psychological-disorders License: CC BY 4.0 DEED. 12.01: Biopsychology of Psychological Disorders Overview#return-footnote-312-3

definition

The scientific study of mental illness or disorders.

×Close definition

The current classification system used to diagnose psychological disorders by mental health professionals. Editions of the DSM are typically updated every 5-7 years

×Close definition

A classification system for mental and behavioral disorders used primarily by the World Health Organization to support the global comparison of mortality and morbidity statistics.

×Close definition

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17.2: Schizophrenia

Schizophrenia is a psychological disorder that is characterized by major disturbances in thought, perception, emotion, and behavior. About 0.3-0.7% of the population experiences schizophrenia, and the disorder is usually first diagnosed during early adulthood (late teens to mid-20s). Many people with schizophrenia report significant difficulties in some day-to-day activities, such as holding a job, paying bills, caring for oneself, and maintaining relationships with others. Symptoms of schizophrenia fall into three categories: 1) positive symptoms (symptoms that are "added"), which include hallucinations and delusions; 2) negative symptoms (symptoms that are "subtracted" or taken away), which include flat affect and social withdrawal; and 3) disorganized symptoms, which include disorganized speech and behavior (APA, 2022).

A **hallucination** is a perceptual experience that occurs in the absence of external stimulation. Auditory hallucinations (e.g., hearing voices) are most common, occurring in roughly two-thirds of patients with schizophrenia (Andreasen, 1987).

Delusions are beliefs that are contrary to reality and are firmly held despite contradictory evidence. **Paranoid delusions** refer to the (false) belief that other people are plotting to harm them (e.g., that their mother is plotting with the FBI to poison their coffee). **Grandiose delusions** refer to beliefs that one holds special power, unique knowledge, or is extremely important (e.g., claiming to be Jesus Christ or be a great philosopher). **Somatic delusions** refer to the belief that something highly abnormal is happening to one's body (e.g., that one's kidneys are being eaten by cockroaches).

Negative symptoms refer to a reduction or absence of normal behaviors related to motivation, interest, or expression (Correll & Schooler, 2020). Negative symptoms of schizophrenia include withdrawal from social relationships, reduced speaking, blunted emotion, and reduced experience of pleasure.

Disorganized thinking refers to disjointed and incoherent thought processes—usually detected by what a person says. The person might ramble, exhibit loose associations, jump from topic to topic, or talk so incomprehensibly that it seems they are randomly combining words.

Disorganized or abnormal motor behavior refers to unusual behaviors and movements: becoming unusually active, exhibiting silly child-like behaviors (giggling and self-absorbed smiling), engaging in repeated and purposeless movements, or displaying odd facial expressions and gestures. In some cases, the person exhibits **catatonic behaviors**, showing decreased reactivity to the environment or maintaining a rigid, bizarre postures for extended periods.[1]

Neural Mechanisms Underlying Schizophrenia

Scientists have identified several neural and biological signatures of schizophrenia. A highly consistent abnormality in brain structure in schizophrenia is enlarged ventricles (the cerebrospinal fluid-filled spaces in the brain). The ventricles in individuals with schizophrenia average around 30% larger than in controls (**Figure 1**) (Horga et al., 2011). Individuals with schizophrenia typically have smaller hippocampi, amygdalae, and thalami (van Erp et al., 2016) and thinner cortex in frontal and temporal lobe regions (van Erp et al., 2018). Functional neuroimaging studies have shown that patients with schizophrenia display hyperactivity in the hippocampus, a neural structure involved in learning and memory (Kraguljac et al., 2021). This hippocampal hyperactivity is thought to dysregulate the dopamine circuit, which may contribute to distorted interpretations of salience in individuals with schizophrenia. Dopamine dysregulation is one of the most prominent neural mechanisms underlying schizophrenia, and as a result, the most common schizophrenia medications target dopaminergic circuitry.

3D render of a non-Schizophrenic versus a Schizophrenic brain.

Figure 1. Image showing enlarged ventricles that are often observed in individuals with schizophrenia. Ventricles are cavities in the brain that are filled with cerebro-spinal fluid.

One early influential biological account of schizophrenia is the "**dopamine hypothesis of schizophrenia**," which suggests that excessive **dopamine** activity is related to schizophrenia (Meltzer & Stahl, 1976). This account was inspired by work showing that drugs that decrease dopamine activity may reduce symptoms related to schizophrenia, and drugs that enhance dopamine activity may increase symptoms (Carlsson & Lindqvist, 1963).

Newer iterations of the dopamine hypothesis have proposed region-specific dopamine imbalances, with reduced dopaminergic activity in the frontal cortex linked to negative symptoms (e.g., social and emotional withdrawal) and hyperactive dopaminergic

activity in the striatum associated with positive symptoms (e.g., delusions and hallucinations) (Davis et al., 1991; Pycock et al., 1980). Excess dopamine in the striatum (a subcortical structure involved in processing salience) might cause delusions and hallucinations by making neutral items seem overly important or "aberrantly salient" (Figure 2) (Kapur et al., 2003).

The dopamine hypothesis is an influential but by no means complete explanation for schizophrenia, as newer research has established the important role of other neurotransmitter systems including serotonin and glutamate (Stahl, 2018).

Diagram of the dopamine release pathway

Figure 2. Visualizing striatal dopamine dysregulation's influence on psychosis: excessive dopamine in the striatum could lead to "aberrant salience" (i.e., ascribing too much importance to a stimulus), and ultimately, psychosis. Current antipsychotic medication acts downstream of the primary dopaminergic dysregulation. [Image: Adapted from Howes, O. D., & Kapur, S. (2009)].

Another influential account is the **neural diathesis-stress model of schizophrenia**, which proposes that schizophrenia may result from an interaction between preexisting vulnerabilities ("diathesis" means vulnerability or predisposition) and stress caused by life experiences. As discussed in the Genetics Chapter, schizophrenia is highly heritable and has a strong genetic component. People with a close genetic relative with schizophrenia, like a parent, sibling, or twin, are more likely to develop schizophrenia. However, genetically predisposed individuals are far more likely to develop schizophrenia if they experience significant life stress—the stressful events can trigger or catalyze the development of the disorder.

Schizophrenia is highly comorbid with substance abuse disorder and some evidence suggests that the use of various substances (particularly marijuana) may increase an individual's risk of developing schizophrenia if the genetic predisposition is also present (McCutcheon et al., 2020; Patel et al., 2020). Finally, psychedelics, like LSD and psilocybin, may also increase the risk of psychotic episodes (Simonsson et al., 2023). While psychedelics research shows promise for treating some psychiatric conditions, studies typically exclude individuals with or at risk for schizophrenia or psychotic disorders.

Stress worsens symptoms of schizophrenia and the diathesis (predisposition) is marked by a heightened stress response (Walker & Diforio, 1997). The hypothalamic-pituitary-adrenal gland (HPA) axis releases the hormone cortisol in response to stress. HPA-axis dysfunction, possibly linked to hippocampal abnormalities in schizophrenia, may amplify dopamine neurotransmission and stress sensitivity. Hippocampal, HPA axis, and dopamine dysfunction likely combine to heighten stress responses and schizophrenia vulnerability. To combat the effects of stress, researchers highlight resilience or protective factors, including social support, self-esteem, coping skills, and antipsychotic medication (Pruessner et al., 2017).

While we focus here on the diathesis-stress model for schizophrenia, diathesis-stress models (i.e., the important interaction between predisposition and stressful life events) also apply to other disorders such as depression and anxiety (Arnau-Soler et al., 2019).

Treatments of Schizophrenia

While schizophrenia symptoms are most effectively managed with a combination of psychopharmacological, psychological, and family interventions (where family members are taught about treatment and support options), rarely do these treatments restore a patient to premorbid levels of functioning (Kurtz, 2015). Despite recent advances in treating schizophrenia, it is still viewed as requiring lifelong treatment and care.

Psychopharmacological treatments. Among the first antipsychotic medications used for the treatment of schizophrenia was Thorazine, which is thought to primarily work by blocking postsynaptic D2 dopamine receptors (thereby decreasing dopamine activity in certain parts of the brain). Thorazine decreases positive symptoms, calms severely agitated patients, and allows for the organization of thoughts. Despite their effectiveness in managing psychotic symptoms, conventional antipsychotics such as Thorazine also produced significant side effects including muscle tremors, involuntary movements, and muscle rigidity.

Due to the side effects of conventional antipsychotic drugs, newer, arguably more effective second-generation or atypical antipsychotic drugs have been developed (e.g., clozapine, risperidone, aripiprazole). Atypical antipsychotics affect both dopamine and serotonin receptors, unlike conventional antipsychotics that target only dopamine receptors. This broader action makes atypical antipsychotics more effective in treating both positive and negative symptoms, leading to their use as the typical first-line treatment of schizophrenia (Barnes & Marder, 2011).

Over half of schizophrenic patients discontinue antipsychotic medications due to side effects and other factors like homelessness, substance use disorders, and lack of health insurance (Leucht et al., 2011). Therefore, it is important to incorporate psychological interventions, such as cognitive behavioral therapy (CBT) and family therapy, along with psychopharmacological

treatment to both address medication adherence, and provide additional support for managing symptoms (Bridely & Daffin, 2024).[2]

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2. This section contains material adapted from: Bridley, A., & Daffin, L. W., Jr., (2024). Fundamentals of Psychological Disorders. Washington State University. https://opentext.wsu.edu/abnormal-psych/ License: CC BY-NC-SA 4.0 12.02: Schizophrenia#return-footnote-316-2

definition

Schizophrenia is a psychological disorder characterized by major disturbances in thought, perception, emotion, and behavior. Major symptoms include hallucinations, delusions, disorganized thinking, abnormal motor behavior, and negative symptoms.

×Close definition

Perceptual experience that emerges in the absence of external stimulation. Extends across different sensory sources (i.e., visual, auditory, tactile, etc.)

×Close definition

False beliefs that are contrary to external reality and are firmly held despite contrary evidence

×Close definition

Characterized by intense irrational thoughts and fears centered on perceived victimization or belief that one is being persecuted

×Close definition

Characterized by intense irrational thoughts and fears centered on perceived victimization or belief that one is being persecuted

×Close definition

Characterized by false beliefs that a person's internal or external bodily functions are abnormal

×Close definition

Refer to an absence or reduction of normal behaviors related to motivation and interest, such as social withdrawal, diminished affective response, lack of interest.

×Close definition

Prominent feature of Schizophrenia; characterized by a pattern of incoherent and illogical thought processes

×Close definition

Prominent feature of Schizophrenia; characterized by extremely disjointed and atypical motor behavior that can cause problems in everyday life, ranging from childlike silliness to unpredictable agitation

×Close definition

Subtype of disorganized or abnormal motor behavior; involves significant reductions in voluntary movement and reduced reactivity to environmental stimulation

×Close definition

An enduring account that suggests a dysregulated dopamine system contributes to symptomatology of schizophrenia; has undergone many iterations

×Close definition

Neurotransmitter involved in learning, motivation, and reward. Implicated in schizophrenia

×Close definition

Stress, through its effects on cortisol, acts upon a pre-existing vulnerability to trigger or worsen schizophrenia symptoms.

×Close definition

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17.3: Depression and Bipolar Disorder

Mood disorders are characterized by severe disturbances in mood and emotions—most often depression, but also mania and elation (Rothschild, 1999). All of us experience fluctuations in our moods and emotions, and often these fluctuations are caused by events in our lives. We become elated if our favorite sports team wins the big game and dejected if a romantic relationship ends or if we lose our job. At times, we feel fantastic or miserable for no clear reason. People with mood disorders also experience mood fluctuations, but their fluctuations are extreme, may last longer, distort their outlook on life, and impair their ability to function.

The DSM-5 includes two general categories of mood disorders: depressive disorders and bipolar disorders. **Depressive disorders** are a group of disorders in which depression is the main feature. Depression is a vague term that, in everyday language, refers to an intense and persistent sadness. People with depressive disorders often feel sad, discouraged, and hopeless. They may lose interest in activities once enjoyed, experience a decrease in drives such as hunger and sex, and/or doubt personal worth. Depressive disorders vary by degree, but this chapter highlights the most well-known: major depressive disorder (sometimes called unipolar depression).

The criteria for diagnosing major depressive disorder (MDD) are detailed in the DSM-5 (APA, 2022). Briefly, to meet criteria for major depressive disorder, an individual must experience symptoms regarded as severe, including either depressed mood or loss of interest in activities most of the day, almost every day for at least two weeks. The symptoms must impair functioning or cause significant distress.

Major depressive disorder is experienced each year by about 7% of the population in the United States (APA, 2022; Bridley & Daffin, 2024). Young adults (18 to 29 year-olds) report higher rates of MDD than any other age group. Rates of MDD in women are about twice as high as in men. The estimated lifetime prevalence of major depressive disorder in women is 21.3% compared to 12.7% in men (Nolen-Hoeksema, 2001; Bridley & Daffin, 2024).

Bipolar disorder and related disorders are a group of disorders in which mania is the defining feature. **Mania** is a state of extreme elation and agitation. When people experience mania, they may become extremely talkative, behave recklessly, or take on many tasks simultaneously.[1]

Bipolar disorders are diagnosed based on the presence of manic or hypomanic episodes (APA, 2022; Bridley & Daffin, 2024). Bipolar I requires at least one manic episode, characterized by abnormal, persistent mood elevation or irritability lasting nearly all day, every day, for at least a week. Bipolar II is diagnosed when only less severe *hypomanic* episodes occur for at least 4 days. A manic episode might be preceded and/or followed by a major depressive episode. Bipolar I disorder afflicts 1.5% and bipolar II disorder afflicts 0.8% of the U.S. population.

Neural Mechanisms Underlying Depression

Brain Activity. Depression involves an overall reduction in brain activity, and some parts of the brain are more affected than others. In brain-imaging studies using PET scans, people with depression display abnormally low activity in the **prefrontal cortex**, a brain region involved in cognitive control, decision-making, planning, and emotion regulation.

Abnormal activity in the prefrontal cortex, especially in its lateral, orbitofrontal, and ventromedial regions, often correlates with the severity of the depression. The **lateral prefrontal cortex** is involved in cognitive control—directing attention, inhibition, and working memory to perform a task. The **orbitofrontal cortex** is involved in decision-making and reward valuation, crucial for delaying gratifications to obtain long-term benefits. The **ventromedial prefrontal cortex** is involved in several social and emotional processes such as regulating negative emotions and processing of self-relevant information. Disruption of these brain regions contributes to hallmark characteristics of mood disorders, including impaired concentration, poor decision-making, increased self-focus and negative affect.

Some research shows that *left* prefrontal activity is associated with positive feelings. The left prefrontal cortex is thought to inhibit negative emotions generated by limbic structures like the **amygdala**, which are overly active in people with depression. Patients who respond to antidepressants show reduced amygdala overactivity; whereas continuing amygdala overactivity despite treatment often predicts depression relapse.

Genetics. Genetics contributes to depressive disorders. Heritability for depressive disorders is about 40% and the risk of developing depression when a family member has had depression is 1.5-3 times higher than the general population (Fan et al., 2020; Kendler et al., 2009). Nevertheless, depressive disorders are still thought to arise from complex gene-environment interactions.[2]

Brain Chemistry. Mood disorders are associated with abnormal levels of certain neurotransmitters, particularly serotonin and norepinephrine (Thase, 2009). These neurotransmitters regulate bodily functions often disrupted in mood disorders, including appetite, sex drive, sleep, arousal, and mood. Low activity levels of serotonin and norepinephrine have long been documented as contributing factors to developing depressive disorders. This relationship was discovered accidentally in the 1950s when monoamine oxidase inhibitors (MAOIs) (which increase available serotonin and norepinephrine) were given to tuberculosis patients, and miraculously, their depressive moods also improved (Bridley & Daffin, 2024). While these neurotransmitters are involved in depression and can be targeted to reduce symptoms, the exact mechanisms are still under investigation.

Treatments for Depressive Disorders

Pharmacology. Major Depressive Disorder is among the most frequent and debilitating psychiatric disorders, so research on treatments is extensive. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are often the most common first-line attempt at treatment for MDD. As their name indicates, SSRIs block the reuptake of serotonin into the presynaptic cell. This action maintains higher levels of serotonin in the synapse, potentially reducing depressive symptoms (Figure 3). However, while serotonin levels can rise within an hour after taking an SSRI, it typically takes several weeks for SSRIs to actually improve symptoms.[3] Although their exact mechanism of action is unclear, SSRIs are commonly prescribed due to their effectiveness and relatively mild side effects. However, other drug classes, including tricyclics and MAOIs, can also be effective in treating depression.

Figure 3. Many medications designed to treat mood disorders work by altering neurotransmitter activity in the neural synapse. Selective serotonin reuptake inhibitors (SSRIs), for example, inhibit the reuptake of serotonin back into the presynaptic cell, which preserves high levels of serotonin in the synapse.

Tricyclic antidepressants are like SSRIs in that they work by altering the number of neurotransmitters available for neurons. More specifically, they block the absorption or reuptake of serotonin and norepinephrine, thus increasing their availability for postsynaptic neurons.

Monoamine oxidase inhibitors (MAOIs) also work by increasing the available neurotransmitters. In basic terms, monoamine oxidase is released in the brain to remove excess norepinephrine, serotonin, and dopamine. MAO *inhibitors* essentially block the monoamine oxidase from removing these neurotransmitters, thus resulting in an increase in these brain chemicals, which are all involved with depressive symptoms (Shulman, Herman & Walker, 2013).

Psychotherapy—Cognitive Behavior Therapy (CBT). While we focus more on biomedical-related approaches in this biopsychology book, psychotherapy approaches, such as CBT are common and effective treatments for MDD. Cognitive Behavioral Therapy (CBT) focuses on the interconnected cognitive triangle of cognitions (thoughts), behaviors, and emotions. CBT aims to improve mood by modifying maladaptive thoughts and behaviors through various cognitive and behavioral interventions. CBT generally follows four phases of treatment:

- Phase 1: Increasing pleasurable activities.
- Phase 2: Challenging automatic, negative thoughts that can maintain depressive symptoms.
- Phase 3: Identifying negative thoughts as they arise. This helps the patient see how their thoughts contribute to their disorder.
- Phase 4: Changing thoughts. The final stage involves challenging the negative thoughts and replacing them with positive thoughts.

Brain Stimulation. For some people with depression, medications and psychotherapy don't work. In cases of "treatment-resistant depression" (defined as at least two unsuccessful trials with antidepressant pharmacotherapy), several other treatment options can be effective. **Electroconvulsive therapy (ECT)** involves electrically stimulating the brain of an anesthetized patient in a hospital setting. Electrodes placed on the head pass electrical currents through the brain to induce a seizure (Figure 4). ECT is very effective in treating depression—one meta-analysis showed major decreases in depression symptoms with remission rates around 50% (Dierckx et al., 2012) and ECT may be more effective than drug therapy (UK ECT Review Group, 2003). ECT's mechanisms of action are not well understood, but ECT alters neurotransmitter levels (e.g., increased excitatory glutamate) and

its effects could stem from disrupting and rewiring neural circuits (Ousdal et al., 2022). Electroconvulsive therapy does have some side effects, such as short-term memory impairments, but is generally safe and well-tolerated (Semkovska & McLoughlin, 2010). Finally, ECT is considered one of the safer treatment options for severely depressed pregnant women in terms of fetal impact (Pompili et al., 2014).

Figure 4. An illustration depicting electroconvulsive therapy, showing an anesthetized patient with electrodes attached to his head.

More invasive than ECT, **Deep Brain Stimulation (DBS)** uses electrodes implanted in the brain to disrupt limbic-cortical circuits and can effectively treat depression (Mayberg et al., 2005). Less invasively, **repetitive transcranial magnetic stimulation (rTMS)** uses repetitive pulses of magnetic stimulation over the scalp to depolarize underlying neurons in the prefrontal cortex. This modulates neural circuitry involved in emotion regulation and depressive symptoms, and has been shown to be a safe and effective way to treat depression in an outpatient setting (McClintock et al., 2017).

Psychedelic-assisted therapy. Another promising approach for treatment-resistant depression is psychedelic-assisted therapy, which combines psychotherapy with the use of psychedelic substances like LSD or psilocybin. This method aims to induce altered states of consciousness to facilitate therapeutic breakthroughs. In treating depression, these substances may help patients gain new perspectives on their lives, break negative thought patterns, increase emotional responsiveness, and induce neuroplasticity. Sessions are conducted in controlled settings with a trained professional, and typically involve preparation, the psychedelic experience itself, and integration therapy afterward. Studies show promising results for treatment-resistant depression, with many patients showing significant and lasting improvements after a single psychedelic session (This contrasts with typical antidepressant treatments, which often involve years of continuous use). (Carhart-Harris et al., 2021; Goodwin et al., 2022; Nutt & Carhart-Harris, 2020; Voineskos et al., 2020).

In sum. Major depressive disorder has a variety of effective treatment options. Research has shown that psychopharmacological interventions are more effective in rapidly reducing symptoms, while psychotherapy, or combined pharmacological and therapy approach, is more effective in establishing long-term relief of symptoms. For cases of treatment-resistant depression, other treatment options, including brain stimulation and psychedelic-assisted therapy can be effective.[4]

Neural Mechanisms Underlying Bipolar Disorders

Research on the cause, course, and treatment of **bipolar disorders** (BD) have made major advances, but the mechanisms underlying episode onset and relapse remain poorly understood. BD has biological causes and is highly heritable (McGuffin et al., 2003). High heritability may suggest that BD is fundamentally a biological phenomenon. However, the course of BD varies greatly both within a person over time and across people (Johnson, 2005). For those with genetic vulnerability, psychosocial factors can trigger episodes (Johnson et al., 2008; Malkoff-Schwartz et al., 1998). Recent findings suggest bipolar disorders and schizophrenia have similar brain and genetic profiles, potentially aligning bipolar more closely with psychotic disorders than depression (Birur et al., 2017; Lichtenstein et al., 2009).

Biological explanations of bipolar disorder have centered on brain function. Many fMRI studies of BD focus on emotional processing, reflecting the view that BD is primarily an emotional disorder (APA, 2000). Findings show that regions of the brain involved in emotional processing are activated differently in people with BD relative to healthy controls (Altshuler et al., 2008; Hassel et al., 2008; Lennox et al., 2004). However, emotional brain-response studies in BD patients yield inconsistent results. The variability stems from testing participants in different illness phases (manic, depressed, inter-episode), small sample sizes, and lab stimuli that may not elicit a sufficiently strong brain response.

In terms of psychosocial factors in bipolar, research has focused on the environmental contributors. Environmental stressors, particularly severe stressors (e.g., loss of a significant relationship), can adversely impact the course of BD. Following a severe life stressor, people with BD have increased risk of relapse (Ellicott et al., 1990) and suffer more depressive symptoms (Johnson et al., 1999). Interestingly, positive life events can also adversely impact the course of BD. After attaining a desired goal, people with BD can suffer more manic symptoms (Johnson et al., 2008). Such findings suggest that people with BD may have a hypersensitivity to rewards.

Due to the close relationship between depression and bipolar disorder, researchers initially believed that bipolar disorder involved low levels of norepinephrine and serotonin. However, it is now believed that low levels of serotonin and *high levels* of norepinephrine may explain mania episodes (Soreff & McInnes, 2014).

Treatment of Bipolar Disorder

Treatment for bipolar disorder is debated. One approach uses mood stabilizers like Lithium or Depakote. These mood stabilizers are less potent at treating depressive symptoms, so are sometimes combined with antidepressants if necessary. The alternative is using newer antidepressants early without mood stabilizers, but this lacks strong research support and risks triggering manic episodes in bipolar patients. Consequently, mood stabilizers, especially Lithium, remain the primary treatment for bipolar disorder (Bridley & Daffin, 2024). Lithium affects neuronal activity by decreasing excitatory (dopamine and glutamate) neurotransmission while increasing inhibitory (GABA) neurotransmission, along with other compensatory neurotransmitter changes to achieve homeostasis (Malhi et al., 2013).

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2. This section contains material adapted from: Duboc, B. (2002). The Brain from Top to Bottom. Mental Disorders: Depression and Manic Depression: Parts of the Brain That Slow Down or Speed Up in Depression. Access for free at https://thebrain.mcgill.ca/ License: CC (Copyleft). 12.03: Depression and Bipolar Disorder#return-footnote-319-2
3. This section contains material adapted from: Gershon, A. & Thompson, R. (2024). Mood disorders. In R. Biswas-Diener & E. Diener (Eds.), Noba textbook series: Psychology. Champaign, IL: DEF publishers. Retrieved from http://noba.to/aqy9rsxe License: CC BY-NC-SA 4.0 DEED 12.03: Depression and Bipolar Disorder#return-footnote-319-3
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definition

A class of psychological disorders marked by severe disturbances to emotions and mood

×Close definition

A class of mood disorders; marked by a persistent feeling of sadness and loss of interest that causes significant impairments in daily life

×Close definition

A type of obsessive-compulsive disorder. Characterized by persistent, intense focus and anxiety over perceived body defects and flaws in appearance

×Close definition

Prominent feature of bipolar disorder and related disorders; a state of abnormally and persistently excessive enthusiasm and irritable mood

×Close definition

Covers the front part of the frontal lobe of the cerebral cortex. Supports executive functions such as goal-directed behavior, cognitive flexibility, habit formation. Implicated in many psychological disorders

×Close definition

Part of the prefrontal cortex that supports higher-order functions such as working memory, selective attention, and planning. It is implicated in mood disorders.

×Close definition

A region of the frontal lobes of the brain above the eye sockets.

×Close definition

Part of the prefrontal cortex that is involved in value computation, decision-making, and emotion regulation. Implicated in mood disorders

×Close definition

Almond-shaped neural structure that is primarily responsible for regulating emotional responses, especially fear.

×Close definition

Psychiatric procedure that involves passing electrical currents through the brain to trigger a brief seizure. Effective in treating depression.

×Close definition

implanting electrodes within areas of the brain. The electrodes produce electrical impulses that affect brain activity to treat certain medical conditions.

×Close definition

A neuroscience technique whereby a brief magnetic pulse is applied to the head that temporarily activates or inhibits ongoing neuronal activity.

×Close definition

Characterized by extreme mood swings from depressive lows to manic highs

×Close definition

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17.4: Anxiety

What is **anxiety**? Most of us feel some anxiety almost every day of our lives. Maybe you have an important upcoming test, presentation, big game, or date. Anxiety can be defined as a negative mood state that is accompanied by bodily symptoms such as increased heart rate, muscle tension, a sense of unease, and apprehension about the future (APA, 2013; Barlow, 2002) (**Figure 5**).

Figure 5. Common physical symptoms of anxiety are feeling dizzy, unsteady, and lightheaded; shortness of breath; chest pain, palpitations and/or accelerated heart rate; and nausea or abdominal distress. People may also experience sweating, trembling, feelings of faintness, or a fear of losing control, among other symptoms.

Anxiety disorders are characterized by excessive and persistent fear and anxiety, and by related disturbances in behavior (APA, 2013). While anxiety is universally experienced, anxiety disorders cause considerable distress. Anxiety disorders are common: approximately 25–30% of the U.S. population meets the criteria for at least one anxiety disorder during their lifetime (Kessler et al., 2005). Anxiety disorders affect more women than men; within a 12-month period, about 23% of women and 14% of men will experience an anxiety disorder (National Comorbidity Survey, 2007). Anxiety disorders are the most frequently occurring class of mental disorders and are often comorbid with each other and with other mental disorders (Kessler et al., 2009).[1]

While all anxiety disorders are characterized by excessive fear, anxiety, or avoidance behavior, they differ from one another in the types of objects or situations that provoke these responses (Bridley & Daffin, 2024). Some common anxiety disorders are:

- Generalized anxiety disorder (GAD)—an underlying excessive worry related to a wide range of events or activities and an inability to control that worry.
- Specific phobia—fear or anxiety specific to an object or a situation (e.g., animals, heights, water, needles, airplanes, elevators).
- Agoraphobia—intense fear of public situations or places where escape seems difficult
- Social anxiety disorder—fear or anxiety related to social situations, especially when evaluation by others is possible
- Panic disorder—series of unexpected panic attacks coupled with the fear of future panic attacks

Neural Mechanisms Underlying Anxiety Disorders

Anxiety disorders are associated with genetic factors and abnormalities in brain circuits that regulate and process emotion. Family and twin studies indicate that anxiety disorders have a moderate genetic heritability (~30-40%; making it less heritable than schizophrenia or bipolar disorder) (Hettema et al., 2001). Over 200 genes link to anxiety disorders, with distinct gene clusters for subtypes like generalized anxiety disorder, social anxiety disorder, and panic disorder. The identified genes are expressed in brain regions linked to anxiety and emotion processing, such as the basal ganglia, hippocampus, and amygdala (Karunakaran & Amemori, 2023).

The brain circuits underlying anxiety involve bottom-up signals from the amygdala that indicate the presence of potentially threatening stimuli, and top-down control mechanisms from the prefrontal cortex that signal the emotional salience of stimuli (Nuss, 2015). The amygdala is involved in triggering panic attacks through its **central nucleus**, which connects with brain structures (e.g. in the brainstem), that control autonomic functions such as respiration and heart rate. Animal studies have shown that electrically or pharmacologically stimulating the amygdala's central nucleus produces behaviors associated with panic (Herdade et al., 2006). People with an anxiety disorder show hyperactive amygdala response to stimuli (Etkin & Wager, 2007). These bottom-up signals from the amygdala might be over-indicating the presence of potentially threatening stimuli. "Top-down" control originating from prefrontal areas can inhibit the amygdala to regulate emotion. However, people with anxiety disorders show reduced prefrontal activation (Etkin, 2010), and they require more prefrontal activation to successfully reduce negative emotions (Nuss, 2015).

Treatments of Anxiety Disorders

Research examining the role of neurotransmitters in anxiety-related circuits has focused largely on GABA, the primary inhibitory neurotransmitter in the brain that reduces neuronal excitability. Insufficient GABAergic inhibition of neurons might drive the amygdala hyperactivity seen in anxiety disorders. Therefore GABA receptors are a primary target for anti-anxiety medication. In animal studies, injecting GABA agonists (activators) into the amygdala (thereby activating the inhibitory neurons) decreased

measures of fear and anxiety (Sanders & Shekhar, 1995). GABA receptors are modulated by drugs called benzodiazepines, such as well-known brand names like Valium, Xanax, and Ativan. Benzodiazepines bind to the $GABA_A$ receptors, which causes an influx of chloride (Cl^-) ions. The increase of negative chloride ions hyperpolarizes the neuron's membrane potential, thereby inhibiting it and making it less likely to fire. Through enhanced neuronal inhibition, benzodiazepines reduce amygdala reactivity to aversive stimuli and anxiety (Del-Ben et al., 2012).

Benzodiazepines were the primary anxiety treatment for decades. However, due to addiction risk and limited long-term efficacy, they're now recommended only for short-term use (2-4 weeks). While GABA is an important target for modulating anxiety response in the amygdala, other neurotransmitters such as serotonin, endocannabinoids, and oxytocin, are also important. Current treatment guidelines for anxiety disorders now recommend antidepressants, including serotonin reuptake inhibitors (SSRIs) or serotonin–noradrenaline reuptake inhibitors (SNRIs) (Nuss, 2015).

Cognitive behavioral therapy (CBT) is a well-established non-pharmacological treatment for anxiety disorders and can reduce amygdala hyperactivation (Straube et al., 2006). Finally, even placebos have been shown to decrease anxiety; when individuals thought they received an anti-anxiety drug, some showed a lower anxiety response to emotional pictures. Their placebo response was associated with decreased amygdala activation, as well as increased activation in a modulatory system including the anterior cingulate and the prefrontal cortex (Petrovic et al., 2005). In sum, irrespective of the technique, reducing activity in the amygdala or increasing activity in emotion-regulating circuits can decrease anxiety. Ongoing research seeks to optimize how these networks can be targeted to manage anxiety.

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definition

Intense, excessive, and persistent worry and fear about everyday situations. Linked to heightened physical sensations, such as fast heart rate, rapid breathing, sweating, and fatigue

×Close definition

A group of disorders that are characterized by excessive and persistent feelings of intense worry, fear, and dread, as well as physical sensations like increased blood pressure and fast heart rate

×Close definition

Spherical cell group located in the amygdala that is primarily responsible for the bodily reactions associated with fear

×Close definition

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17.5: Obsessive-Compulsive and Related Disorders

Obsessive-compulsive and related disorders are a group of overlapping disorders that generally involve intrusive, unpleasant thoughts or repetitive behaviors. Many of us experience unwanted thoughts from time to time (e.g., craving double cheeseburgers when dieting), and many of us engage in repetitive behaviors on occasion (e.g., pacing when nervous). However, obsessive-compulsive and related disorders are characterized by intrusive thoughts and repetitive behaviors that are so intense they significantly disrupt daily life. Included in this category are obsessive-compulsive disorder (OCD), body dysmorphic disorder, and hoarding disorder.[1]

OCD involves time-consuming (>1 hour daily) obsessions, compulsions, or both, unrelated to substance use, a medical condition, or another mental disorder (APA, 2013). Obsessions are more severe than fleeting unwanted thoughts or routine worries. Obsessions are persistent, unintentional, and unwanted thoughts and urges that are highly intrusive, unpleasant, and distressing (APA, 2013). Common obsessions include concerns about germs and contamination, doubts ("Did I turn the water off?"), order and symmetry ("I need all the spoons in the tray to be arranged a certain way"), and aggressive or lustful urges. The individual typically recognizes that these thoughts and urges are irrational and attempts to suppress or ignore them, but finds it extremely difficult to do so. Obsessive symptoms can overlap, such as combined contamination and aggressive obsessions (Abramowitz & Siqueland, 2013).

Figure 6. (a) Repetitive hand washing and (b) checking (e.g., that a door is locked) are common compulsions among those with obsessive-compulsive disorder.

Compulsions are repetitive and ritualistic acts performed mainly to reduce distress caused by obsessions or prevent feared events (APA, 2013). Compulsions often include such behaviors as extensive hand washing, cleaning, checking (e.g., that a door is locked), and ordering (e.g., lining up all the pencils in a particular way), and they also include such mental acts as counting or reciting something to oneself (**Figure 6**). Compulsions in OCD aren't pleasurable or realistically connected to the source of distress or feared event. A cycle of obsessive thoughts, anxiety, compulsions, and temporary relief deeply affects individuals with OCD (**Figure 7**). Approximately 2.3% of the U.S. population will experience OCD in their lifetime (Ruscio et al., 2010) and, if left untreated, OCD tends to be a chronic condition creating lifelong interpersonal and psychological problems (Norberg et al., 2008).[2]

Figure 7. Visualizing the typical cycle of obsessive-compulsive disorder. [Image adapted from: https://psychcentral.com/ocd/ocd-cycle].

Body Dysmorphic Disorder. Similar to OCD, **body dysmorphic disorder** involves an obsession with a *perceived* flaw in physical appearance that is nonexistent or barely noticeable to other people (APA, 2013). Individuals believe they are unattractive or deformed, and typically focus on skin, face, or hair. This preoccupation with imagined physical flaws leads to repetitive behaviors and thoughts like excessive mirror-checking, hiding the perceived flaw, comparing with others, and sometimes seeking cosmetic surgery (Phillips, 2005). About 2.4% of U.S. adults meet the criteria for body dysmorphic disorder, with slightly higher rates in women than in men (APA, 2013).[3]

Hoarding Disorder. Once considered a symptom of OCD, hoarding is now recognized as a distinct disorder (Mataix-Cols et al., 2010). People with **hoarding disorder** compulsively keep possessions, regardless of value, cluttering living spaces to dysfunctional levels. Excessive clutter often prevents people from using their kitchen or sleeping in their bed. People with this disorder struggle to discard items, believing the items might be useful later or due to sentimental attachment (APA, 2013). A diagnosis of hoarding disorder requires that hoarding isn't caused by another medical condition or disorder (e.g., schizophrenia). (APA, 2013).[4]

Neural and Genetic Mechanisms Underlying Obsessive-Compulsive and Related Disorders

Genetics. The results of family and twin studies suggest that OCD has a moderate genetic component. The disorder is five times more frequent in first-degree relatives of people with OCD (Nestadt et al., 2000). Additionally, the concordance rate of OCD is 57% for identical twins and 22% for fraternal twins (Bolton et al., 2007). Studies have implicated about two dozen potential genes involved in OCD; these genes regulate the function of three neurotransmitters: serotonin, dopamine, and glutamate (Pauls, 2010).

Brain regions involved in OCD. A key brain region implicated in OCD is the orbitofrontal cortex (Kopell & Greenberg, 2008) (**Figure 8**). In individuals with OCD, the orbitofrontal cortex becomes hyperactive when exposed to triggering stimuli, such as images of unclean toilets or asymmetrically hung pictures (Simon et al., 2010). The orbitofrontal cortex is a region in the "OCD circuit" that, collectively, influences the perceived emotional value of stimuli and the selection of behavioral and cognitive responses (Graybiel & Rauch, 2000). As with the orbitofrontal cortex, other regions of the OCD circuit (e.g., dorsolateral prefrontal cortex, precuneus, and left superior temporal gyrus) show heightened activity during symptom provocation (Rotge et al., 2008). These findings suggest that abnormalities in these regions may contribute to OCD symptoms (Saxena et al., 2001). Consistent with this network explanation, people with OCD show substantially higher connectivity of the orbitofrontal cortex with other regions of the OCD circuit (Beucke et al., 2013).

Figure 8. Different regions of the brain are associated with obsessive-compulsive disorder and related disorders. For example, the anterior cingulate cortex for hoarding disorder; the prefrontal cortex for body dysmorphic disorder; and the orbitofrontal cortex for obsessive-compulsive disorder.

Neuroimaging studies have also highlighted the role of the prefrontal cortex in OCD and body dysmorphic disorder. Individuals with body dysmorphic disorder often abnormally perceive body areas. An fMRI study showed that when people with body dysmorphia viewed faces, they had abnormal prefrontal cortex activity, which may be associated with the perceptual distortions seen in body dysmorphic disorder (Feusner et al., 2007).

These neuroimaging findings highlight the importance of brain dysfunction in OCD and body dysmorphic disorder. However, neuroimaging approaches are limited by their inability to explain differences in obsessions and compulsions, and correlations between brain abnormalities and OCD symptoms are not evidence of causality (Abramowitz & Siqueland, 2013).

Treatments of OCD

Several approaches are commonly used to treat OCD. One effective treatment is a form of Cognitive Behavioral Therapy called exposure and response prevention. In therapy sessions, individuals with OCD are gradually exposed to situations or objects designed to mildly provoke their obsessions in a safe environment. They are instructed to avoid their compulsive responses. Eventually, the high anxiety situations become less anxiety-provoking and more manageable. Exposure and response is also very effective with panic disorder (which is an anxiety disorder). Cognitive Behavioral Therapy is often used in conjunction with pharmacological treatments for OCD. Selective serotonin reuptake inhibitors (SSRIs) are used to treat OCD, but often at higher doses than are used to treat depression. Finally, OCD can be treated effectively with brain stimulation, including both non-invasive techniques like transcranial magnetic stimulation that uses magnetic pulses to stimulate the prefrontal cortex (Trevizol et al., 2016), and invasive techniques like deep brain stimulation that requires surgically implanting a device deep in the brain that can modulate activity in the OCD brain circuit (Alonso et al., 2015).[5]

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definition

A group of disorders that center on a cycle of intrusive thoughts, feelings of anxiety, repetitive behaviors, and short-term reliefs.

×Close definition

A class of psychological disorders; characterized by mania as the defining feature

×Close definition

A type of obsessive-compulsive disorder. Characterized by persistent difficulty in parting with possessions due to a perceived need to save the items

×Close definition

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17.6: Post-Traumatic Stress Disorder

Experiencing extremely stressful or traumatic events, such as combat, crimes, and natural disasters, increases the risk of developing psychological disorders such as **post-traumatic stress disorder (PTSD)**. A diagnosis of PTSD requires that the individual must be exposed to actual or threatened death, serious injury, or sexual violence. This strict diagnostic criterion differs from a common misperception that PTSD could stem from lesser stressors, like an upsetting but non-violent romantic breakup. PTSD symptoms include intrusive memories and flashbacks, avoidance of trauma-related stimuli, persistent negative emotions (e.g., fear, anger, guilt, shame), detachment, irritability, outbursts, and an exaggerated startle response (jumpiness). For PTSD to be diagnosed, these symptoms must occur for at least one month.

Roughly 6% of adults in the United States experience PTSD in their lifetime, with rates about twice as high in women than in men (Goldstein et al., 2016; Olff, 2017). Higher rates occur among people exposed to mass trauma and whose jobs involve duty-related trauma exposure (e.g., police officers, firefighters, and emergency medical personnel) (APA, 2013). Nearly 21% of residents of areas affected by Hurricane Katrina had PTSD one year following the hurricane (Kessler et al., 2008), and 12.6% of Manhattan residents were observed as having PTSD 2–3 years after the 9/11 terrorist attacks (DiGrande et al., 2008).

Neural Mechanisms Underlying Post-Traumatic Stress Disorder

Both the hippocampus and amygdala are involved in emotional processing and are linked to PTSD (**Figure 9**). Individuals with PTSD show reduced volume of several parts of the **hippocampus**, which may result from decreased levels of neurogenesis and dendritic branching (the generation of new neurons and the generation of new dendrites in existing neurons, respectively) (Wang et al., 2010). After effective pharmacological treatment or cognitive-behavioral therapy for PTSD, hippocampus size increases (Bremner & Vermetten, 2004; Levy-Gigi et al., 2013).

Recent work highlights how threat reactivity, the hippocampus, and arousal-related **norepinephrine** (NE) release may interact to shape PTSD severity. Prior work highlights how threat reactivity (i.e., how someone responds to threat-related stressors) is heightened in PTSD. Research in both animals and humans indicates that norepinephrine, a hormone released in response to stress, is associated with abnormal threat reactivity in PTSD (Naegeli et al., 2018; Southwick et al. 1999). Critically, threat alters hippocampal functioning, and a reliable neural signature of PTSD is reduced hippocampal activity during states of threat (Eichenbaum, 2001; Hayes et al., 2011). To clarify how threat may disrupt hippocampal functioning, a recent review proposed that threat-induced arousal increases norepinephrine release, which redirects information processing away from the hippocampus to emotional memory structures like the amygdala (Clewett & Murty, 2019).

The Advanced Understanding of RecOvery afteR traumA (AURORA) study is a multi-site study tracking brain and cognitive development in trauma patients for one year after an emergency department visit (McClean et al., 2020). This landmark effort will generate a comprehensive collection of brain, biospecimen, and behavioral measures to characterize trauma-related disorders, such as PTSD.

One AURORA study (Tanriverdi et al., 2022) examined the relationship between threat reactivity, hippocampus function, norepinephrine systems, and PTSD symptoms. Participants with more severe PTSD symptoms showed weaker hippocampal responses to threat; that link was especially strong in those with greater fear-based startle responses (a marker of arousal-related norepinephrine release). This suggests excessive threat-induced arousal may divert processing from the hippocampus. These findings highlight the interplay between threat reactivity, arousal, and hippocampal function in how PTSD may or may not emerge after exposure to trauma. Finally, whether or not PTSD emerges after trauma is also influenced by genetics, as genes play an important role in the fear and stress circuitry (Banerjee et al., 2017).

Figure 9. Brain regions typically associated with post-traumatic stress disorder include the prefrontal cortex, hippocampus, cingulate cortex, and amygdala.

PTSD Treatments

Several treatment approaches are available to alleviate the symptoms of PTSD (Bridley & Daffin, 2024). Treatment usually starts with a psychotherapeutic intervention, such as:

- Psychological debriefing, wherein individuals who experienced a traumatic event discuss or process their thoughts within 72 hours of the event.
- Cognitive Behavioral Therapy (CBT) works by identifying and challenging the negative cognitions (thoughts) surrounding the traumatic event and replacing them with positive, more adaptive cognitions.
- Exposure Therapy involves a therapist exposing the individual to cues or situations associated with their traumatic memory, then having them use positive coping strategies such as relaxation techniques to reduce their feelings of distress. Exposure therapy, originally developed for anxiety disorders, has proven effective in treating PTSD by helping patients extinguish fears associated with traumatic events. The main types of exposure techniques are *imaginal* (mentally recreating the trauma), *in vivo* (using tangible reminders, such as videos or images), and *flooding* (immediate exposure to most distressing elements). While *imaginal* and *in vivo* exposures follow a gradual approach, *flooding* presents the most distressing memories upfront, potentially risking higher dropout rates. Some research indicates that combining exposure therapy with propranolol drug administration during memory retrieval can weaken the emotional aspects of traumatic memories ("reconsolidation interference" as discussed in the memory chapter) (Brunet et al., 2008; Beckers & Kindt, 2017).
- Eye Movement Desensitization and Reprocessing (EMDR) combines components of CBT and exposure therapy with lateral eye movements following a therapist's finger movements. The eye movements are thought to accelerate information processing and the adaptive resolution of traumatic memories (Shapiro & Maxfield, 2002).

When psychotherapy does not produce relief from symptoms, psychopharmacology interventions are an effective second line of treatment and may include SSRIs, MAOIs, and tricyclic antidepressants.[1] Finally, recent research on psychedelic-assisted therapy, including treatments using MDMA (aka "ecstasy" or "molly"), psilocybin, and ketamine, has shown promise in effectively treating PTSD. In light of promising research, the U.S. Food and Drug Administration awarded MDMA "breakthrough therapy status" to fast-track studies on MDMA treatments of PTSD (Krediet et al., 2020; Mitchell et al., 2023).

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Spielman, R. M., Jenkins, W. J., & Lovett, M. D. (2020). 10.4 Emotion. In Psychology 2e. OpenStax. Access for free at https://openstax.org/books/psychology-2e/pages/10-4-emotion License: CC BY 4.0 DEED.

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definition

A psychological disorder that develops in some individuals who have experienced a traumatic event. It is characterized by intense, vivid memories of the traumatic event or related events and intense emotional and physical reactions.

×Close definition

(plural form, hippocampi)
A nucleus inside (medial) the temporal lobe implicated in learning and memory.

×Close definition

A neurotransmitter and hormone. Plays an important role in arousal and the "fight-or-flight" response. It is housed primarily in the locus coeruleus.

×Close definition

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17.7: Integrating Biological and Psychosocial Approaches

The biological perspective links psychological disorders to biological factors, such as genetics, chemical imbalances, and brain abnormalities (Spielman et al., 2020). Widespread evidence indicates that most psychological disorders have a genetic component. Researchers search for specific genes, genetic mutations, and epigenetic markers that contribute to mental disorders; these may be targeted in future genetic-based therapies (Davidson et al., 2022). Neuroimaging has revealed that abnormalities in brain structure and function are directly involved in many disorders. Progress in neuroimaging technology will continue to improve our understanding of psychological disorders. Advances in understanding neurotransmitters and hormones have yielded insights into their role in psychological disorders, and guide pharmacological treatment approaches.

Over the past decades, biological-based research has made incredible strides in understanding psychological disorders and informing treatment. However, biological markers are generally not reliable enough yet to be useful for clinicians in diagnosing disorders (Abi-Dargham et al., 2023).

In this chapter, we largely focused on pharmacological treatments, but many treatment approaches are effective. In addition to psychotherapy in its various forms, other effective treatment approaches include deep brain stimulation to treat depression, as well as yoga, music therapy, and exercise, as interventions to alleviate symptoms of anxiety. As biological, psychological, and sociocultural factors all contribute to psychopathology, it only makes sense that effective treatment approaches take various forms.

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Spielman, R. M., Jenkins, W. J., & Lovett, M. D. (2020). 15.3 Perspectives on Psychological Disorders. In Psychology 2e. OpenStax. Access for free at https://openstax.org/books/psychology-2e/pages/15-3-perspectives-on-psychological-disorders License: CC BY 4.0 DEED.

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