PSYC 312: BIOLOGICAL PSYCHOLOGY



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PSYC 312: Biological Psychology

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CHAPTER OVERVIEW

1: Biopsychology as a Course of Study

1.1: What is Biopsychology?
1.2: History of Biopsychology
1.3: The Case of Phineas Gage- Connecting Brain to Behavior
1.4: What are the Divisions of Biopsychology?

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1.1: What is Biopsychology?

Learning Objectives

1. Describe the field of biopsychology, its areas of focus, and other names for the field.
2. Discuss a common myth about the brain and why it is false.
3. Discuss materialism (physicalism) and determinism as assumptions underlying biopsychology.
4. Describe the principle of brain organization referred to as "the localization of function."

1.1.1 Overview

Biopsychology is the study of biological mechanisms of behavior and mental processes. It examines the role of the nervous system, particularly the brain, in explaining behavior and the mind. This section defines biopsychology, critically examines a common myth about the brain, and briefly surveys some of the primary areas of research interest in biopsychology.

1.1.2 Biopsychology - The Interaction of Biology and Psychology

Psychology is the scientific study of behavior and mental processes in animals and humans. Modern psychology attempts to explain behavior and the mind from a wide range of perspectives. One branch of this discipline is **Biopsychology** which is specifically interested in the biological causes of behavior and mental processes. Biopsychology is also referred to as biological psychology, behavioral neuroscience, physiological psychology, neuropsychology, and psychobiology. The focus of biopsychology is on the application of the principles of biology to the study of **physiological, genetic, evolutionary, and developmental** mechanisms of behavior in humans and other animals. It is a branch of psychology that concentrates on the role of biological factors, such as the central and peripheral nervous systems, neurotransmitters, hormones, genes, and evolution on behavior and mental processes.

Biological psychologists are interested in measuring biological, physiological, or genetic variables in an attempt to relate them to psychological or behavioral variables. Because most biological psychologists assume that all behavior is controlled by the central nervous system (brain and spinal cord), they seek to understand how the brain functions in order to understand behavior and mental activities. Key areas of focus within the field include sensation and perception; motivated behavior (such as hunger, thirst, and sex); control of movement; learning and memory; sleep and biological rhythms; and emotion. With advances in research methods, more complex topics such as language, reasoning, decision making, intelligence, and consciousness are now being studied intensely by biological psychologists.

1.1.3 Localization of Function: Do humans use only 10% of their brains?

The frequently repeated claim that humans use only 10% of their brains is false. The exact origin of this myth is unknown, but misinterpretations of brain research are likely to blame. In experiments with animal brains during the 1800's through the early 1900's, Marie-Jean-Pierre Flourens and Karl Lashley destroyed and/or removed as much as 90% of the brain tissue of their animal subjects. Nevertheless, these animals could still perform basic behavioral and physiological functions. Some who read these results made the incorrect assumption that this meant that animals were using only 10% of their brains. Subsequently, this interpretation was generalized to humans (Elias and Saucer, 2006). Furthermore, prominent psychologists and researchers, such as Albert Einstein, Margaret Mead, and William James, were also quoted as saying that humans are using only a small portion of their brain (Elias and Saucer, 2006), fueling the 10% myth.

Due to advances in biopsychology and other related fields, we now have a greater understanding of the complexity of the brain. We may not be using our brains as efficiently as possible at all times, but we are using the entirety of our brain as each part contributes to our daily functioning. Studies of humans with brain damage have revealed that the effects of brain damage are correlated with where the damage is and how extensive it is. In other words, where damage occurs determines what functions are impacted and more damage has more of an effect. This reflects a key organizational principle of the brain: the **localization of function**. This principle means that specific psychological and behavioral processes are localized to specific regions and networks of the brain. For example, we now know that damage to a small area less than the size of a quarter at the very base of your brain results in disruption of feeding and regulation of body weight. Damage to another area of the brain located near your temples disrupts your ability to form new memories for facts and events, while leaving your ability to learn new motor tasks (such as skating or riding a bike) completely unaffected. Damage to another brain area causes face blindness, or prosopagnosia, a disorder in which the

afflicted individual can still see normally except that they cannot recognize familiar faces, even the faces of close family members or their own face in a photograph.

1.1.4 The Brain

The most important organ controlling our behavior and mental processes is the brain. Therefore, Biopsychologists are especially interested in studying the brain, its neurochemical makeup, and how it produces behavior and mental processes (Wickens, 2021).

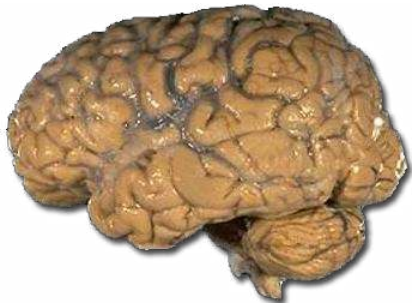


Figure 1.1.1: Photo of the left side of a human brain. Front is at the left. The massive folds of tissue of the brain are known as the cerebral cortex, which hides many additional subcortical structures beneath it. It is interesting to note that the folding of the cerebral cortex increases in mammal species with increasing complexity of the brain of the species and is thought to originate from the "cramming" of more cortical tissue into the skull over evolutionary time. (Image from Wikimedia Commons; Public domain.)

Modern technology through neuroimaging techniques has given us the ability to look at living human brain structure and functioning in real time. Neuroimaging tools, such as functional magnetic resonance imaging (fMRI) scans, are often used to observe which areas of the brain are active during particular tasks in order to help psychologists understand the link between brain and behavior.

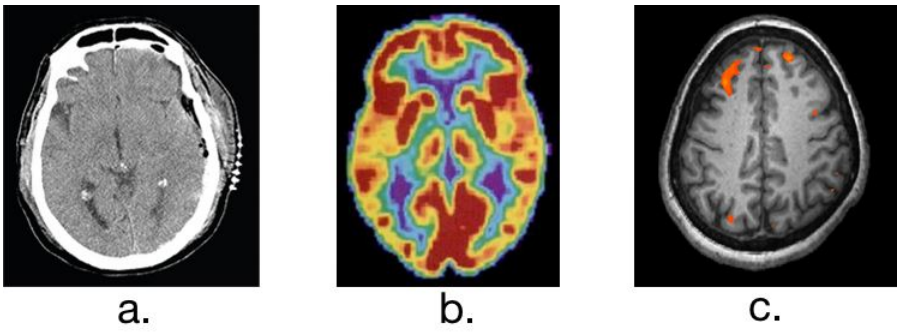


Figure 1.1.2: Images of brain using different instruments. a. CT scan; b. PET; c. fMRI (Wikimedia Commons, CC BY 3.0)

File:Scans_depicting_CT_PET_and_fMRI_brain_scans.jpgMagnetic resonance imaging (MRI) scans of the head are often used to help psychologists understand the links between brain and behavior. As will be discussed later in more detail, different tools provide different types of information. A functional MRI, for example, provides information regarding brain activity while an MRI provides only information about structure.

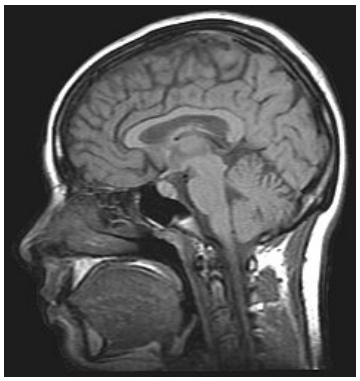


Figure 1.1.3: MRI of Human Brain (Wikimedia Commons, Public Domain)

1.1.5 A Scientific Model of the Universe: Two Basic Assumptions

The modern scientific view of the world assumes that there are at least two fundamental properties of the universe. The first assumption common to most scientists is that the entire universe is material or physical, composed exclusively of matter and energy (including electromagnetic energies, such as light, heat, ultraviolet and various other physical energies, such as electrical, gravitational, and nuclear). According to this view, the entire universe is governed by physical laws. This view of the universe is called **materialism or physicalism**. Materialism is one form of an overarching philosophical perspective known as **Monism**, which suggests a single force is responsible for all actions.

If everything in the universe is physical, then this means that the mental processes and subjective mental experiences of our mind must also be entirely physical processes taking place in an entirely material brain. Using this fundamental assumption of the modern scientific view of the universe, this means that the mind is entirely material, dependent upon the physical activities of an entirely material organ, the brain. On this view, the mind is what the brain does, and the brain and its processes are completely physical, material, just matter and energy in highly specific and organized form. This does not mean that all matter is conscious, nor does it mean that the mind is just energy. The key idea is that the matter and energy must be organized in a particular way. That is, a mind, consciousness, can only emerge from matter, energy, and physical processes if they are organized in a very specific and complex form--that form that we know as a brain and its physical operations.

Although this is the view among most biological psychologists, there are others who believe that the brain, along with the rest of life, was created by a non-material source or divine being and that therefore the mind has divine origins. Typically, this belief is accompanied by the assumption that the mind is not physical, but that it is akin to the non-material. Belief that the mind is non-material and therefore independent of the physical brain and its physical processes is known as **dualism** (or **mind-body dualism, mind-brain dualism**).

The origin of dualism is often attributed to the 17th century French philosopher and mathematician, Rene Descartes. If this view were true, then we would expect that brain damage would have no effect on the mind. However, brain damage does affect the mind and the specific location of the damage produces more or less specific, fairly predictable, effects on the mind, modifying the mind and behavior in various ways. Examples of this are coma due to head injury; the effects of Parkinson's disease on movement after the disease damages areas of the brain known as the basal ganglia; changes in personality and emotion due to injury to the front of the brain, specifically the frontal lobes; memory loss in Alzheimer's Disease; and so on. Though you don't have to accept the assumption of physicalism when studying the brain if your religious beliefs are contrary to the idea, nevertheless it is important that you be aware of the assumption of physicalism/materialism that most biological psychologists accept, at least as a working hypothesis, if not a philosophical position, as they do their brain research.

The second major assumption among most scientists is **determinism**--the belief that all events in the universe have prior causes and that these causes are external to the human will. This implies that humans do not have free will. Instead human behavior is caused by events external to us such as our upbringing, our social and cultural environment, by our brain structure and functioning, and by our genes and our evolution as a species. In some versions of this viewpoint, since we do not have control over many of the factors in our environment, our genes, and our evolution as a species, our brain function and thus our behavior is actually controlled by causes outside of our control. On this view, free will is an illusion that arises from our awareness of our mental processes as we make choices based on our selection of various behavioral options that we see open to us, but what we often fail to realize is that those choices are determined by many factors beyond our awareness and control (Koenigshofer, 2010, 2016). Free will vs. determinism is an issue that is far from being resolved and remains controversial even among scientists, including biological psychologists. Investigation by biological psychologists of the brain processes involved in choice and decision-making is ongoing and may eventually shed light on this difficult issue. Again, it is not necessary for you to be a determinist to study the brain, but it is important for you to be aware of the doctrine of determinism as you consider the implications of brain research as you progress through this textbook and your course in biological psychology.

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1.1.7 Attributions

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1.2: 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.

1.2.1 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.

1.2.2 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.

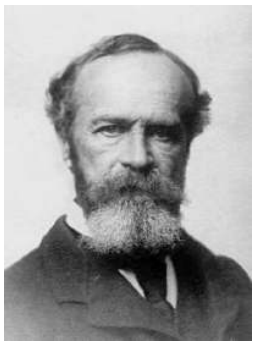


Figure 1.2.1: William James. (Public Domain; via Wikimedia Commons)

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.

1.2.3 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.

1.2.3.1 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.

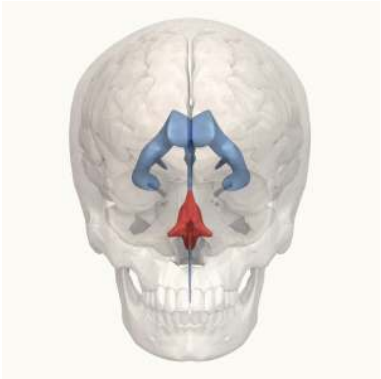


Figure 1.2.2: Human Ventricles (CC BY-SA 2.1; BodyParts3D by DBCLS via Wikimedia Commons)

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) and that the spinal cord was an extension of the brain.

1.2.3.2 Middle Ages



Figure 1.2.3: 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. He also discussed phenomena such as insomnia, mania, hallucinations, nightmares, dementia, epilepsy, stroke, paralysis, vertigo, melancholia, and tremors (Mohamed, 2008). He was the first person to associate mental deficits with deficits in the brain's middle ventricle or frontal lobe (Mohamed, 2008).

1.2.3.3 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 1.2.4: Descartes Drawing - Reflexive role of pain in contracting muscle. (Public Domain; via Wikimedia Commons)

1.2.4 Discoveries of the 19th Century

1.2.4.1 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). It should be noted that this "cranial" theory of brain abilities is not supported today.

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. The prefrontal cortex is an area in the frontal portion of the brain.

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 (see above) 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.

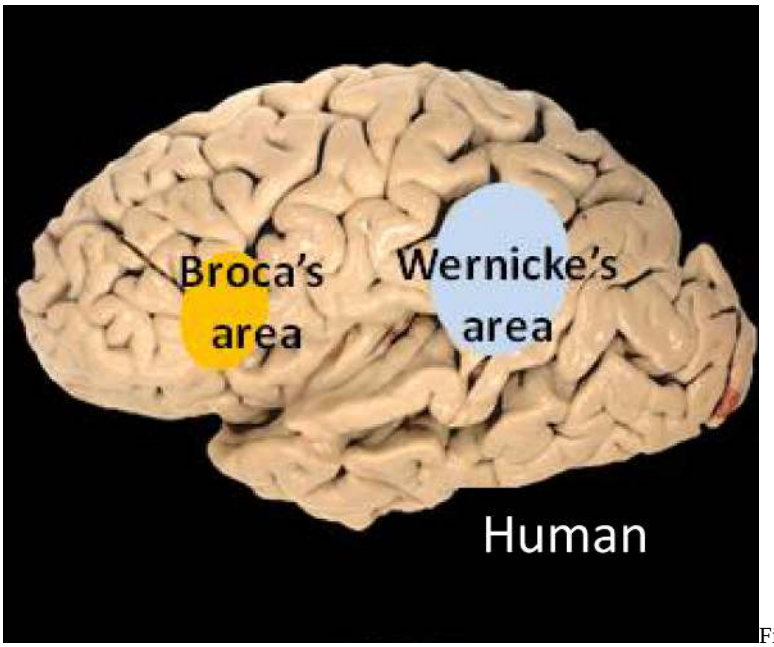


Figure 1.2.5: The two language areas of the brain. (Public Domain; via Wiki media Commons)

1.2.4.2 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).

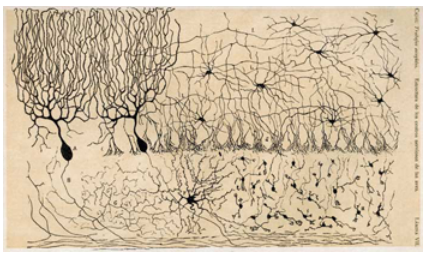


Figure 1.2.6: Ramon y Cajal's Drawing of A Neuron. (Public Domain; via Wikimedia Commons)

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).

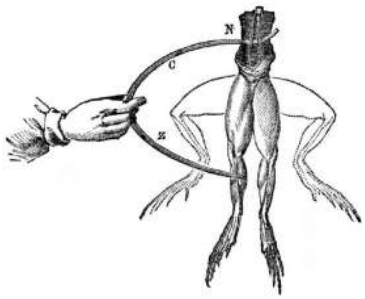


Figure 1.2.7: Drawing showing Galvani's Frog Leg Electricity Experiment. (Public Domain; via Wikimedia Commons)

1.2.5 Discoveries of the 20th Century

1.2.5.1 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).

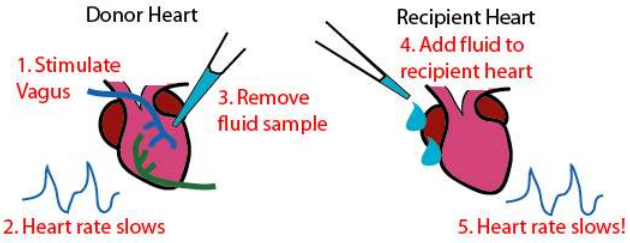


Figure 1.2.8: Loewi's experiment, describing the existence of Vagusstoff. (CC BY-SA 3.0; via Wikimedia Common)

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**.

1.2.5.2 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.

1.2.5.3 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.

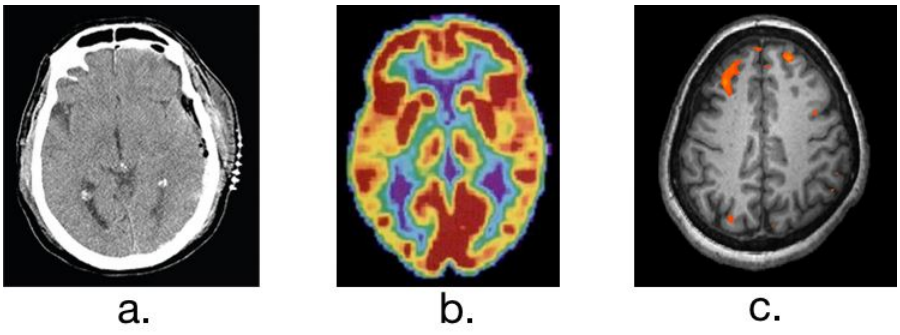


Figure 1.2.9: Images of brain using different instruments. a. CT scan; b. PET; c. fMRI (CC BY 3.0; via Wikimedia Commons)

1.2.6 Today

Several major research efforts and governmental initiatives continue to be developed in order to uncover some of the major questions and practical issues relating to the role of the brain in the human condition. On a global scale starting in 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 (FDA) and the Defense Advanced Research Projects Agency (DARPA), have joined in this effort.

In recent years several new clinical and research innovations in psychobiology have been developed or expanded in their use. One new technique being used more frequently to understand brain function may turn out to be extremely effective in the study and treatment of a variety of clinical issues. **Transcranial magnetic stimulation** (TMS) is a procedure in which magnetic pulses are applied to the brain of a living person with the goal of temporarily and safely deactivating a small brain region. The primary advantage of TMS is that it allows the researcher to draw causal conclusions about the influence of brain structures on thoughts, feelings, and behaviours. Current research has used TMS to study the brain areas responsible for emotion and cognition and their roles in how people perceive intention and approach moral reasoning (Kalbe et al., 2010; Van den Eynde et al., 2010; Young, Camprodon, Hauser, Pascual-Leone, & Saxe, 2010). TMS is also used as a treatment for a variety of psychological conditions, including migraine, Parkinson's disease, and major depressive disorder.

TMS is just one example of the explosion of recent technological and theoretical advancements in the field of psycholobiology. Many more will be illustrated throughout the topics presented in this text.

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1.3: The Case of Phineas Gage- Connecting Brain to Behavior

Learning Objectives

1. Discuss the Case of Phineas Gage and its contribution to biological psychology.

1.3.1 Overview

While experiments are necessary to establish cause and effect relationships, in-depth studies of unique individuals or groups of people who share an experience can be used to inform our understanding of things that we can not study experimentally. Surgical errors, extreme mistreatment, and tragic accidents are impactful events that can alter individuals significantly, providing unique opportunities to study the effects of experiences which can not be ethically studied experimentally. There have been a number of these case studies which have revealed the role of different parts of the brain on our thinking and behavior. One such case is Phineas Gage. Gage lived 12 years after a rod pierced his skull, damaging his left frontal lobe. Researchers were able to gather information about his functioning before and observe his cognitive ability and personality after the accident. His case enabled the field to understand the role of frontal lobe in personality and mental processes.

1.3.2 The Tale of Phineas Gage



Figure 1.3.1: Phineas Gage Portrait After His Accident. (Public Domain; via Wikipedia Common)

The case of Phineas Gage is worthy of expanded coverage as his tragic accident establishes a clear connection between the brain and who we are. Gage, a 25-year-old man, was employed in railroad construction at the time of the accident. As the company's most capable employee, with a well-balanced mind and a sense of leadership, he was directing a rock-splitting workgroup while preparing the bed of the Rutland and Burlington Railroad south of Cavendish, Vermont, USA. At 4:30 PM on September 13, 1848, he and his group were blasting a rock, and Gage was assigned to put gunpowder in a deep hole inside it.

The moment he pressed the gunpowder into the hole with a bar, the friction caused sparks, and the powder exploded. The resulting blast projected the meter-long bar, which was 1.25 inches in diameter and weighed about 13.2 pounds, through his skull at high speed. The bar entered his left cheek, destroyed his eye, passed through the left front of his brain, and left his head at the top of the skull on the right side. Gage was thrown on his back and had some brief convulsions, but he woke up and spoke in a few minutes, walked with a little help, and sat in an ox cart for the 0.7-mile trip to where he was living.



Figure 1.3.2: The injury of Phineas Gage With Frontal Lobe shown in Red. (Public Domain; via Wikimedia Common)

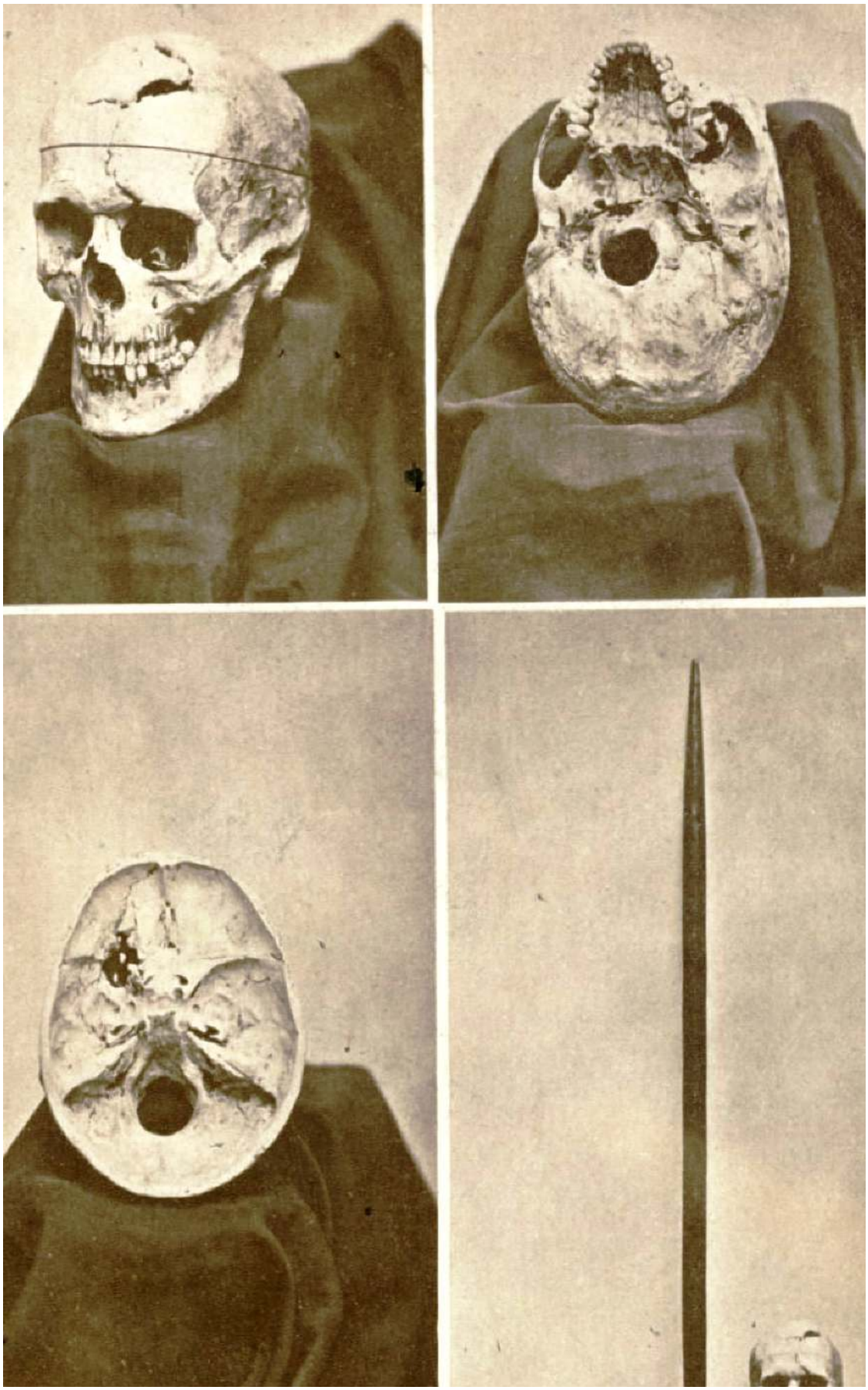
About 30 minutes after the accident, a doctor arrived to provide medical care. Gage had lost a lot of blood, and the next days that followed were quite difficult. The wound became infected, and Phineas was anemic and remained semi-comatose for more than two weeks. He also developed a fungal infection in the exposed brain that needed to be surgically removed. His condition slowly improved after doses of calomel and beaver oil. By mid-November he was already walking around the city.

1.3.2.1 The Consequences

For three weeks after the accident, the wound was treated by doctors. During this time, he was assisted by Dr. John Harlow, who covered the head wound and then reported the case in the Boston Medical Surgery Journal. In November 1849, invited by the professor of surgery at Harvard Medical School, Henry Jacob Bigelow, Harlow took Gage to Boston and introduced him to a meeting of the Boston Society for Medical Improvement .

In his reports, Harlow described that the physical injury profoundly altered Gage's personality. Although his memory, cognition, and strength had not been altered, his once gentle personality slowly degraded. He became a man of bad and rude ways, disrespectful to colleagues, and unable to accept advice. His plans for the future were abandoned, and he acted without thinking about the consequences. And here was the main point of this curious story: Gage became irritable, irreverent, rude and profane, aspects that were not part of his way of being. His mind had changed radically. His transformation was so great that everyone said that “Gage is no longer himself.”

As a result of this personality change, he was fired and could no longer hold a steady job. He became a circus attraction and even tried life in Chile, later returning to the United States. However, there is something still little known about Gage: his personality changes lasted for about four years, slowly reverting later. As a proof of this, he worked as a long-haul driver in Chile, a job that required considerable planning and focus skills. He died on May 21, 1861, 12 years after the accident, from an epileptic seizure that was almost certainly related to his brain injury.



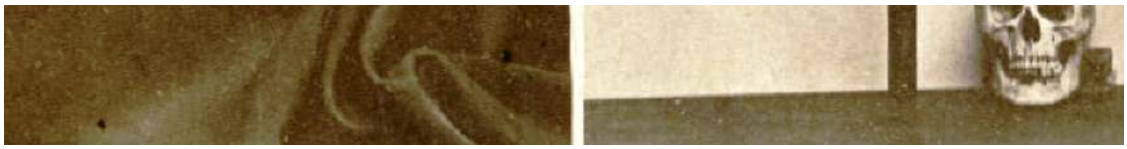


Figure 1.3.3: Frontispiece, showing multiple views of the exhumed skull, and tamping iron, of brain injury survivor Phineas Gage (Public Domain; via Wikimedia Commons

After his body was removed from its grave, Gage's mother donated his skull to Dr. Harlow who in turn donated it to Harvard University.

1.3.2.2 The Legacy

Gage's case is considered to be one of the first examples of scientific evidence indicating that damage to the frontal lobes may alter personality, emotions, and social interaction. Prior to this case, the frontal lobes were considered silent structures, without function and unrelated to human behavior. Scottish neurologist, David Ferrier, was motivated by this fact to investigate the role of frontal lobes in brain function. Ferrier removed the frontal lobes in monkeys and noted that there were no major physiological changes, but the character and behavior of the animals were altered. In other words, he confirmed the role of the frontal lobes that was suggested by Gage's accident in an experiment with a non-human animal.

Knowledge that the frontal lobe was involved with emotions continued to be studied. The surgeon Burkhardt in 1894 performed a series of surgeries in which he selectively destroyed the frontal lobes of several patients in whom he sought to control psychotic symptoms, being the modern prototype of what was later known through Antonio Egas Moniz as psychosurgery. Today, it is well understood that the prefrontal cortex of the brain controls the organization of behavior, including emotions and inhibitions.

Folkloric as it may be, but nonetheless remarkable, the contribution of Phineas Gage's case should not be overlooked, as it provided scientists the baseline for the promotion of studies in neuropsychiatry, and a source of inspiration for world medicine. In 2012, a team of neuroscientists used computer tomography of Gage's skull with typical brain MRI scans to simulate how extensive Gage's brain damage was. They confirmed that most of the damaged area was the left frontal lobe. However, surrounding areas and their neural network were also extensively severed. And it is not just the researchers who keep coming back to Gage. Medical and psychology students still learn about Gage from their history lessons. Neurosurgeons and neurologists still sometimes use Gage as a reference when evaluating certain cases. The final chapter of his life also offers us a thought-provoking discovery about cases of massive brain damage, indicating that rehabilitation may be possible.

1.3.3 Summary

Phineas Gage made a huge contribution to our understanding of the frontal lobe damage and its subsequent change in personality. Furthermore, his case expanded knowledge in neurology in several areas, including the study of brain topography in behavioral disorders, the development of psychosurgery, and finally the study of brain rehabilitation. Also, Gage's case had a tremendous influence on early neuropsychiatry. The specific changes observed in his behavior pointed to theories about the localization of brain function and correlated with cognitive and behavioral sequelae, thereby acquainting us with the role of the frontal cortex in higher-order actions such as reasoning, behavior and social cognition. In those years, while neuropsychiatry was in its infancy, Gage's extraordinary story served as one of the first pillars of evidence that the frontal lobe is involved in personality, which helped solidify his remarkable legacy in world medical history.

1.3.3.1 Attributions

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1.4: What are the Divisions of Biopsychology?

Learning Objectives

1. Discuss the different divisions of biopsychology.

1.4.1 Overview

Neuroscientists study how the nervous system develops, its structure, and what it does. Biopsychology is an integrative discipline that draws knowledge from the other neuroscience disciplines. It then applies that knowledge to the study of behavior and mental processes. In this section, we will examine a few of the disciplines of neuroscience that are of particular interest to biopsychology.

1.4.2 Biopsychology - An Integrative Discipline

Neuroscience is the scientific study of the nervous system. The more neuroscientific research progresses, the more clearly it is established that human behavior and mental processes—the key interests for psychological study—are intimately intertwined with activity in the brain. It encompasses the branch of biology that deals with the anatomy, biochemistry, molecular biology, and physiology of neurons and neural circuits. It also encompasses cognition (thinking) and human behavior.

Our focus, biopsychology is a subset of neuroscience that focuses on behavior and mental processes. Consequently, one of the many names for biopsychology is "**Behavioral Neuroscience**". Biopsychology aims to understand the biological basis of human behavior and mental processes. It is an integrative discipline that draws knowledge from different divisions of neuroscience. These divisions include but are not limited to:

- **Neurophysiology** - the study of the function of the nervous system, focusing on neurons (nerve cells) and their communication.
- **Neuroanatomy** - the study of the anatomy or structure of nervous tissue and neural structures of the nervous system.
- **Neuropharmacology** - the study of how drugs affect cellular function in the nervous system.
- **Developmental neuroscience** - aims to describe the cellular basis of brain development and to address the underlying mechanisms. The field draws on both neuroscience and developmental biology to provide insight into the cellular and molecular mechanisms by which complex nervous systems develop.
- **Cognitive neuroscience** - concerned with the scientific study of biological structures and processes underlying cognition, with a focus on the neural elements of mental processes.
- **Computational neuroscience** - includes both the study of the information processing functions of the nervous system, and the use of digital computers to study the nervous system. It is an interdisciplinary science that links the diverse fields of neuroscience, cognitive science and psychology, electrical engineering, computer science, physics and mathematics.
- **Neurology** - the medical specialty dealing with disorders of the nervous system. It deals with the diagnosis and treatment of all categories of disease involving the central, peripheral, and autonomic nervous systems.
- **Social neuroscience** uses the brain and body to understand how we think and act, with a focus on how we think about and act toward other people. It is an interdisciplinary field that uses a range of neuroscience measures to understand how other people influence our thoughts, feelings, and behavior. (We will examine this branch more in depth in Cognition and Intelligence Chapter)
- **Educational neuroscience or neuroeducation**, seeks to link an understanding of genetics and brain processes with how people learn, for the purpose of informing classroom instruction and experiences.

1.4.3 Summary

In these sections, you have learned about the disciplines who have contributed to biopsychology in its aim to understand the biological aspect of behavior and mental processes. Biopsychology does not stand on its own. Disciplines such as neuroanatomy contribute to our understanding of the different structures of the nervous system, including the brain. Neuroanatomy has helped with our understanding of how some of the major parts of the brain control and contribute to different behaviors. As each of these disciplines expand, biopsychology is able to draw information from each and develop.

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CHAPTER OVERVIEW

2: Research Methods and Ethical Considerations of Biological Psychology and Neuroscience

2.1: Introduction to Research in Biological Psychology
2.2: Non-Invasive Techniques- Structural Imaging
2.3: Non-Invasive Techniques- Direct Functional Imaging Techniques
2.4: Non-Invasive Techniques- Indirect Functional Imaging Techniques
2.5: Invasive Techniques
2.6: Ethical Considerations

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2.1: Introduction to Research in Biological Psychology

Learning Objectives

1. Differentiate between the purpose of structural and functional imaging.
2. Describe the differences between spatial resolution and temporal resolution.

2.1.1 Overview

This chapter will describe the various ways that biological psychologists study the brain. There are many ways to categorize the techniques that are used when studying the brain. We will start by covering the non-invasive techniques, where we are able to study the brain without getting direct physical access to the brain (think of fixing a broken pipe in a wall without having to open the wall up). Then we will move into the invasive techniques, where we study the brain by having direct access (an example would be fixing a broken pipe in a wall by tearing a hole in the wall). Then we will discuss various neuropsychological techniques, where we learn about the brain using people with some sort of brain "issue." For example, people with epilepsy have been extensively studied and we can learn a lot about how the brain works from them. Finally, the last section will address ethical considerations of biological psychology research.

In this section, we will start with a discussion of many modern day neuroscience terms that are important for understanding the different techniques in future sections.

2.1.2 The Terminology of Modern Research Techniques

We have come a long way with how we study the brain. Many techniques now allow us to understand how the brain works without waiting for a horrific accident to occur or conducting some sort of surgery. Techniques have been developed that allow us to see what the brain looks like, as a still image (structurally) or in action (functionally).

2.1.2.1 Structural Imaging

Structural imaging techniques are useful in many situations such as locating tumors, sites of physical brain damage, or finding size differences between the structures of the brain between various groups. Magnetic resonance imaging (MRI), for example, is one such technique that is commonly used to study the brain and to diagnosis knee and shoulder injuries. Structural imaging techniques allow us to look inside the brain (or body) without having to go inside. A series of MRI images can be used to create a picture of the brain.

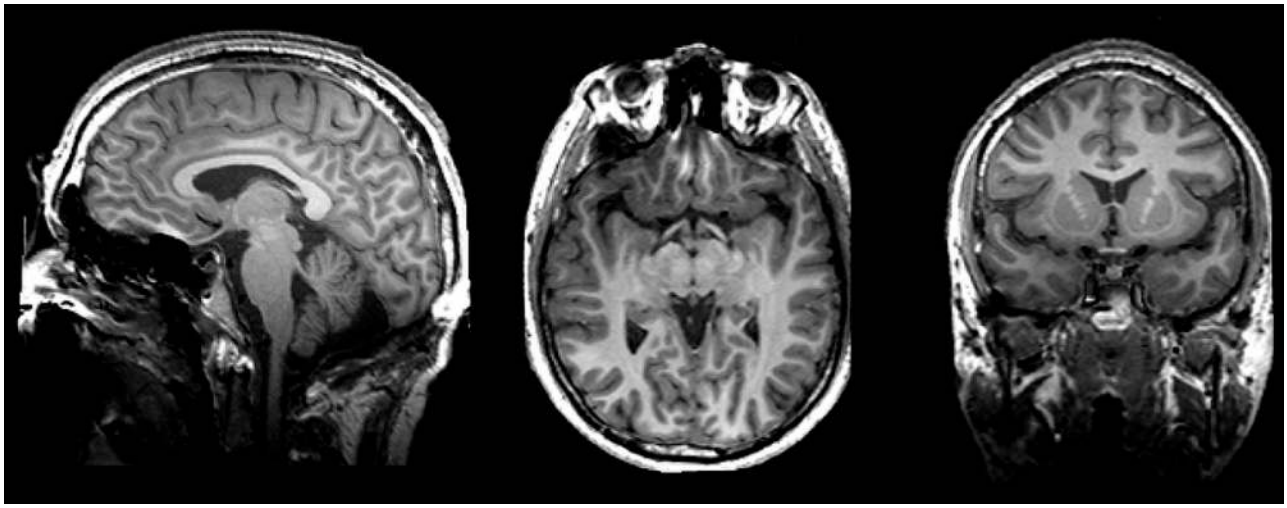


Figure 2.1.1: An MRI (A structural image) of the brain. Note the ability to see specific gyri (bumps) and sulci (grooves). "Deadstar's brain"(opens in new window) by Daniele Oberti(opens in new window) is licensed under CC BY-NC-ND 2.0(opens in new window)

2.1.2.2 Functional Imaging

Many researchers are also interested in how the brain works. Some studies begin with the scientific question of "what does this part do?" Or more commonly, "Where in the brain does this happen?" **Functional imaging** techniques allow researchers to learn about

the brain activity during various tasks by creating images based on the electrical activity or the absorption of various substances that occurs while a subject is engaging in a task. Such techniques can be used, for example, to visualize the parts of the brain that respond when we're exposed to stimuli that upset us or make us happy.

2.1.2.3 Temporal Versus Spatial Resolution

Within functional imaging techniques, researchers are frequently focused on one of two questions. They may ask “When does this activity occur?” Or “Where does this activity occur?” Some techniques are better for answering one of these questions, whereas other techniques are better for answering the other question. We describe how well a technique can determine *when* the activity has occurred as **temporal resolution.** For example, was the brain region activity occurring sometime in the last hour, the last minute, the last second, or within milliseconds? While some techniques are excellent at determining precisely when the activity occurred and other techniques are quite terrible at it. Additionally, we can describe how well a technique can determine *where* the activity has occurred as **spatial resolution.** For example, did the activity occur in the temporal lobe somewhere or can we narrow that down to a specific gyrus (ridge) or sulcus (groove) of the cerebral cortex? If it occurred on a particular gyrus can we narrow it down to a particular portion of that gyrus? As with temporal resolution, some techniques are excellent at determining precisely where the activity occurred whereas other techniques are less accurate.

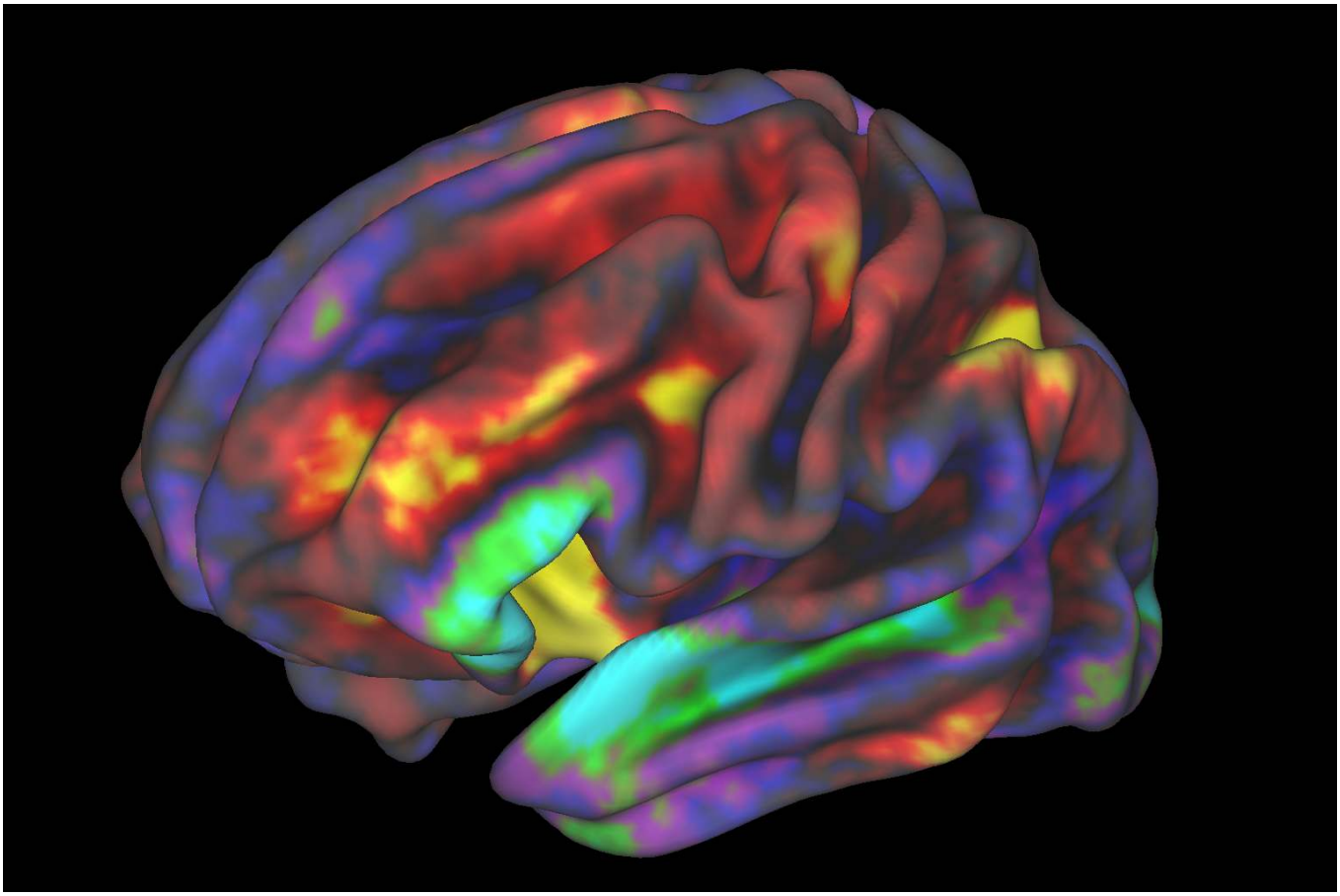


Figure 2.1.2: Functional MRI of a teenage brain conducting a working memory test. The regions in red and yellow, primarily in the frontal lobe and occipital lobe, are the most active. fMRI Image of Preteen Brain"(opens in new window) by NIH Image Gallery(opens in new window) is licensed under CC BY-NC 2.0(opens in new window)

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2.2: Non-Invasive Techniques- Structural Imaging

Learning Objectives

1. Explain how X-rays, CT scans, and MRI scans differ.
2. Describe the pros and cons of the three main structural imaging techniques.

2.2.1 Overview

Although there are many techniques, structural imaging typically come in three different options: X-rays, computed tomography (CT) or computed axial tomography (CAT) scans, and magnetic resonance imaging (MRI) scans. Each uses different types of technology to provide a representation of a structure without having to remove the skin or bone that protects that structure. Each of these non-invasive techniques has advantages and disadvantages.

2.2.2 **X-Rays**

German physicist Wilhelm Röntgen (1845–1923) was experimenting with electrical current when he discovered that a mysterious and invisible “ray” would pass through his flesh but leave an outline of his bones on a screen coated with a metal compound. In 1895, Röntgen made the first durable record of the internal parts of a living human: an “X-ray” image (as it came to be called) of his wife’s hand. Scientists around the world quickly began their own experiments with X-rays, and by 1900, X-rays were widely used to detect a variety of injuries and diseases. In 1901, Röntgen was awarded the first Nobel Prize for physics for his work in this field.

The **X-ray** is a form of high energy electromagnetic radiation with a short wavelength capable of penetrating solids and ionizing gases. As they are used in medicine, X-rays are emitted from an X-ray machine and directed toward a specially treated metallic plate placed behind the patient’s body. The beam of radiation results in darkening of the X-ray plate. X-rays are slightly impeded by soft tissues, which show up as gray on the X-ray plate, whereas hard tissues, such as bone, largely block the rays, producing a light-toned “shadow.” **Thus, X-rays are best used to visualize hard body structures such as teeth and bones**.

Figure 2.2.1 depicts an X-ray of a knee. Like many forms of high energy radiation, however, X-rays are capable of damaging cells and initiating changes that can lead to cancer. This danger of excessive exposure to X-rays was not fully appreciated for many years after their widespread use. Due to the development of other techniques that are considerably better at looking at soft tissue, X-rays are largely not used for studying the brain anymore.



Figure 2.2.1: X-Ray of a Knee: High energy electromagnetic radiation allows the internal structures of the body, such as bones, to be seen in X-rays like these."Plain radiograph of the right knee"(opens in new window) by Ptrump16 is licensed under CC BY-SA 4.0(opens in new window)

2.2.3 **Modern Medical Imaging**

X-rays can depict a two-dimensional image of a body region, and only from a single angle. In contrast, more modern medical imaging technologies produce data that are integrated and analyzed by computers to produce three-dimensional (3D) images or images that reveal aspects of the body functioning.

2.2.3.1 Computed Tomography

Tomography refers to imaging by sections. **Computed (or computerized) tomography (CT)** is a noninvasive imaging technique that uses computers to analyze several cross-sectional X-rays in order to reveal small details about structures in the body. The technique was invented in the 1970s and is based on the principle that, as X-rays pass through the body, they are absorbed or reflected at different levels. In the technique, a patient lies on a motorized platform while a computerized axial tomography (CAT) scanner rotates 360 degrees around the patient, taking X-ray images.

Figure 2.2.2 shows a CT scanner with a platform for the subject to lie on. A computer combines these images into a two-dimensional view of the scanned area, or "slice." Figure 2.2.3 shows a series of slices of the brain for one subject.



Figure 2.2.2: A CT scanner at the University of Pittsburg Medical Center East."New UPMC East"(opens in new window) by Davey Nin(opens in new window) is licensed under CC BY 2.0(opens in new window).

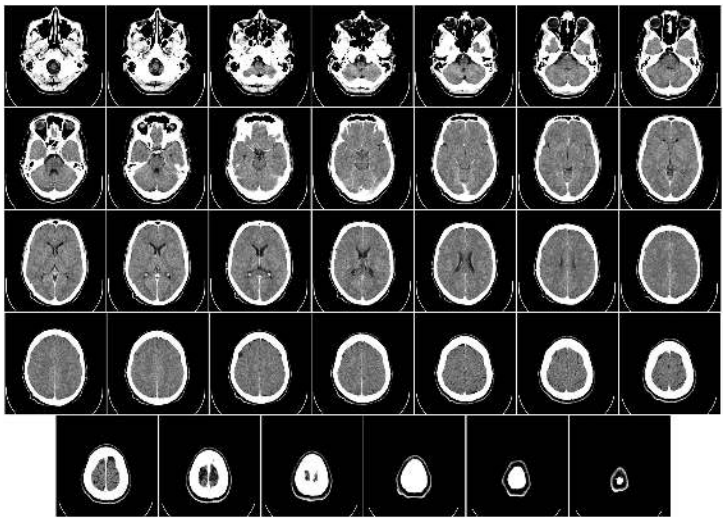


Figure 2.2.3: A series of axial CT scans of the brain of one subject. Each image is a slice of the brain starting with a bottom slice and incrementally moving to higher and higher slices. "Computed tomography of human brain - large - CT scan"(opens in new window) is in the Public Domain, CC0(opens in new window)

Since 1970, the development of more powerful computers and more sophisticated software has made CT scanning routine for many types of diagnostic evaluations. It is especially useful for soft tissue scanning, such as of the brain and the thoracic and abdominal viscera. Its level of detail is so precise that it can allow physicians to measure the size of a mass down to a millimeter. The main disadvantage of CT scanning is that it exposes patients to a dose of radiation many times higher than that of X-rays. Whether this is particularly dangerous is still being debated (McCollough et al., 2015).

2.2.3.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a noninvasive medical imaging technique based on a phenomenon of nuclear physics discovered in the 1930s, in which matter exposed to magnetic fields and radio waves was found to emit radio signals. In 1970, a physician and researcher named Raymond Damadian noticed that malignant (cancerous) tissue gave off different signals than

normal body tissue. He applied for a patent for the first MRI scanning device, which was in use clinically by the early 1980s. The early MRI scanners were crude, but advances in digital computing and electronics led to their advancement over any other technique for precise imaging, especially to discover tumors. MRI also has the major advantage of not exposing patients to radiation.

Drawbacks of MRI scans include their much higher cost, and patient discomfort with the procedure. The MRI scanner subjects the patient to such powerful electromagnets that the scan room must be shielded. The patient must be enclosed in a metal tube-like device for the duration of the scan, sometimes as long as thirty minutes, which can be uncomfortable and impractical for ill patients. The device is also so noisy that, even with earplugs, patients can become anxious or even fearful. These problems have been overcome somewhat with the development of “open” MRI scanning, which does not require the patient to be entirely enclosed in the metal tube.

Figure 2.2.4 shows an MRI machine with a platform for the patient to lie on. Patients with iron-containing metallic implants (internal sutures, some prosthetic devices, and so on) cannot undergo MRI scanning because it can dislodge these implants.



Figure 2.2.4: An MRI machine. "MRI"(opens in new window) by Liz West(opens in new window) is licensed under CC BY 2.0(opens in new window)

2.2.3.3 Using Structural Imaging Techniques to Study a Disorder: Autism Spectrum Disorder

One example that we will use throughout this chapter is that of how we use these research techniques to study Autism Spectrum Disorder (ASD). ASD is a developmental disorder frequently characterized by issues including various combinations of interaction issues, communication difficulties, and even repetitive behaviors. Throughout each section, we will discuss some of the ways the main tools of brain research have been used to examine this disorder.

Structural imaging techniques with ASD have focused on which brain structures have physical differences. MRIs have found a thicker frontal cortex (Carper & Courchesne, 2005) and a thinner temporal cortex (Hardan et al., 2006) in patients with ASD. These areas are notable because the frontal cortex is linked to communication and language abilities and the temporal cortex is linked to auditory processing (ie. language input), both of which are issues that many with ASD struggle with.

2.2.4 References

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2.2.5 Attributions

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2.3: Non-Invasive Techniques- Direct Functional Imaging Techniques

Learning Objectives

1. Apply the terms spatial and temporal resolution to EEG and MEG.
2. In basic terms, describe EEG and MEG.
3. Describe the key characteristic of direct functional imaging techniques.

2.3.1 Overview

In this section, we will discuss the two main direct functional imaging techniques, electroencephalography (EEG) and magnetoencephalography (MEG). We will also generally discuss what makes a technique a direct brain imaging technique.

2.3.2 EEG

Electroencephalography (EEG) is one technique for studying brain activity. This technique uses at least two and up to 256 electrodes to measure the difference in electrical charge (the **voltage**) between pairs of points on the head. These electrodes are typically fastened to a flexible cap (similar to a swimming cap) that is placed on the participant's head. Figure 2.3.1 shows a patient wearing such a cap. From the scalp, the electrodes measure the electrical activity that is naturally occurring within the brain. They do not introduce any new electrical activity.



Figure 2.3.1: A subject with a group of EEG electrodes on their head."EEG Brain Scan"(opens in new window) by Tim Sheerman-Chase(opens in new window) is licensed under CC BY 2.0(opens in new window)

Given that this electrical activity must travel through the skull and scalp before reaching the electrodes, localization of activity is less precise when measuring from the scalp, but it can still be within several millimeters when localizing activity that is near the scalp. While EEG is lacking with respect to spatial resolution, one major advantage of EEG is its temporal resolution. Data can be recorded thousands of times per second, allowing researchers to document events that happen in less than a millisecond. EEG analyses typically investigate the change in amplitude (wave height) or frequency (number of waves per unit of time) components of the recorded EEG on an ongoing basis or averaged over dozens of trials (see Figure 2.3.2). The EEG has been used extensively in the study of sleep. When you hear references to "brain waves", those are references to information obtained using EEG.

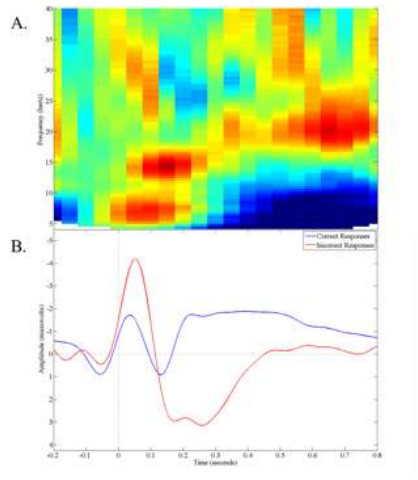


Figure 2.3.2: Example of EEG analysis output. Panel A represents changes in the relative strength of different frequencies in the EEG data over time. Panel B represents changes in the amplitude in the instantaneous EEG voltage over time. Noba Psychophysiological Methods in Neuroscience. CC BY SA-NC 4.0 International License.

2.3.3 MEG

Magnetoencephalography (MEG) is another technique for noninvasively measuring neural activity. The flow of electrical charge (the current) associated with neural activity produces very weak magnetic fields that can be detected by sensors placed near the participant's scalp. Figure 2.3.3 depicts a subject in an MEG machine. The number of sensors used varies from a few to several hundred. Due to the fact that the magnetic fields of interest are so small, special rooms that are shielded from magnetic fields in the environment are needed in order to avoid contamination of the signal being measured. MEG has the same excellent temporal resolution as EEG. Additionally, MEG is not as susceptible to distortions from the skull and scalp. Magnetic fields are able to pass through the hard and soft tissue relatively unchanged, thus providing better spatial resolution than EEG. MEG analytic strategies are nearly identical to those used in EEG. However, the MEG recording apparatus is much more expensive than EEG, so MEG is much less widely available.



Figure 2.3.3: A subject/patient getting an MEG.Figure 2.3.3: "170321-F-LW859-017"(opens in new window) by Airman Magazine(opens in new window) is licensed under CC BY-NC 2.0(opens in new window)

2.3.4 General Information About Direct Imaging Techniques

EEG and MEG both have excellent temporal resolution and are useful when someone is particularly interested in studying the timing of brain activity. For example, if someone is reading a sentence that ends with an unexpected word, how long after reading the unexpected word does the brain react to it? In addition to these types of questions, EEG and MEG methods allow researchers to investigate the degree to which different parts of the brain "talk" to each other. This allows for a better understanding of brain networks, such as their role in different tasks and how they may function abnormally in psychopathology.

Direct imaging techniques are those that allow for a direct measure of brain activity. EEG and MEG are both considered direct brain imaging techniques since EEG measures the electrical activity from groups of neurons and MEG measures the magnetic fields that the electrical activity gives off. Neither of these techniques relies on measuring something else with an assumption that they are linked. This is not true of other non-invasive, indirect imaging techiniques.

2.3.4.1 Using Direct Functional Imaging Techniques to Study a Disorder: Autism Spectrum Disorder

EEG and MEG have been used to examine ASD. One of the findings included a delay in the brain wave associated with auditory stimuli. In short, there are differences in the time for processing auditory sounds in children with ASD compared to those without ASD. Furthermore, this delay appears more pronounced in children with ASD who have language developmental delays as opposed to children with ASD without linguistic delays (Roberts et al., 2019). This delay has even been proposed to help clinicians diagnose autism in young children.

2.3.5 References

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2.3.6 Attributions

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2.4: Non-Invasive Techniques- Indirect Functional Imaging Techniques

Learning Objectives

1. Describe the key characteristics of indirect functional brain imaging techniques.
2. In basic terms, describe functional MRI (fMRI) and positron emission tomography (PET).
3. Discuss the pros and cons of FMRI and PET.

2.4.1 Overview

In this section, we will discuss what makes a technique an *indirect* brain imaging technique and the two main indirect imaging techniques used to assess brain function: functional MRI (fMRI) and positron emission tomography (PET).

2.4.2 FMRI and PET

Indirect brain imaging techniques rely on an assumption that activity in the brain correlates to something else that we are able to measure. In these cases, these techniques measure blood flow in the brain. The assumption is that blood flow in the brain is related to the activity level in that area of the brain. Of course, with any assumption, there is always the risk that it could be wrong. Thankfully there is extensive research examining this assumption and the scientific consensus currently is that blood flow is an appropriate indication of brain activity. The two main indirect brain imaging techniques that we will cover are functional MRI (fMRI) and positron emission tomography (PET).

Functional magnetic resonance imaging (fMRI) is a method that is used to assess changes in the activity of tissue, such as measuring changes in neural activity in different areas of the brain during thoughts or experiences. This technique builds on the principles of structural MRI techniques and also uses the property that, when neurons fire, they use energy, which must be replenished. Glucose and oxygen, two key components for energy production, are supplied to the brain from the blood stream as needed. Oxygen is transported through the blood using hemoglobin, which contains binding sites for oxygen. When these sites are saturated with oxygen, it is referred to as oxygenated hemoglobin. When the oxygen molecules have all been released from a hemoglobin molecule, it is known as deoxygenated hemoglobin. As a set of neurons begin firing, oxygen in the blood surrounding those neurons is consumed, leading to a reduction in oxygenated hemoglobin. The body then compensates and provides an abundance of oxygenated hemoglobin in the blood surrounding that activated neural tissue. When activity in that neural tissue declines, the level of oxygenated hemoglobin slowly returns to its original level, which typically takes several seconds.

Figure 2.4.1 shows a subject about to go into a functional MRI machine.



Figure 2.4.1: A Functional MRI machine. While it is pictured here with the patient outside of the magnet, to scan the patient, they would be moved into the circular magnet.

fMRI measures the change in the concentration of oxygenated hemoglobin, which is known as the blood-oxygen-level-dependent (BOLD) signal. This leads to two important facts about fMRI. First, fMRI measures blood volume and blood flow, and from this

we infer neural activity; as stated previously, fMRI does not measure neural activity directly. Second, fMRI data typically have poor temporal resolution; however, when combined with structural MRI, fMRI provides excellent spatial resolution. Temporal resolution for fMRI is typically on the order of seconds, whereas its spatial resolution is on the order of millimeters. Generally speaking, under most conditions there is an inverse relationship between temporal and spatial resolution—one can increase temporal resolution at the expense of spatial resolution and vice versa. In other words, as one increases the other decreases.

This method is valuable for identifying specific areas of the brain that are associated with different physical or psychological tasks. Clinically, fMRI may be used prior to neurosurgery in order to identify the brain areas that are associated with language so that the surgeon can avoid those areas during the operation. fMRI allows researchers to identify differential or convergent patterns of activation associated with tasks. For example, if participants are shown words on a screen and are expected to indicate the color of the letters, are the same brain areas recruited for this task if the words have emotional content or not? Does this relationship change in psychological disorders such as anxiety or depression? Is there a different pattern of activation even in the absence of obvious performance differences? fMRI is an excellent tool for comparing brain activation in different tasks and/or populations.

Figure 2.4.2 provides an example of results from fMRI analyses overlaid on a structural MRI image. The blue and orange shapes represent areas with significant changes in the BOLD signal, thus changes in neural activation.

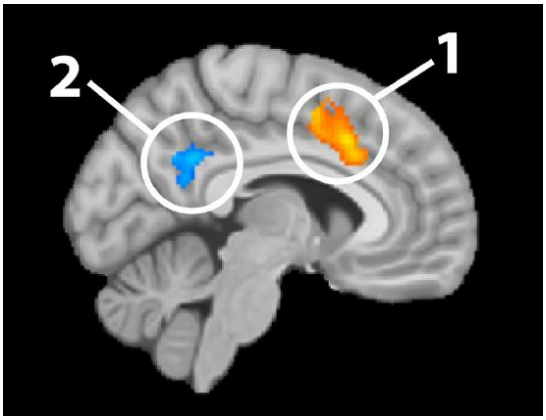


Figure 2.4.2: Example of fMRI analyses overlaid on an sMRI image. Area 1 (orange) indicates an increase in the BOLD signal, and Area 2 (blue) indicates a decrease in the BOLD signal. We infer that neural activity increased in the Area 1 and decreased in Area 2.

Positron emission tomography (PET) is a medical imaging technique that is used to measure processes in the body, including the brain (see Figure 2.4.3 for a PET scanner). This method relies on a positron-emitting tracer atom that is introduced into the blood stream in a biologically active molecule, such as glucose, water, or ammonia. A positron is a particle much like an electron but with a positive charge. One example of a biologically active molecule is fludeoxyglucose, which acts similarly to glucose in the body. Fludeoxyglucose will concentrate in areas where glucose is needed—commonly areas with higher metabolic (energy) needs. Over time, this tracer molecule emits positrons, which are detected by a sensor. The spatial location of the tracer molecule in the brain can be determined based on the emitted positrons. This allows researchers to construct a three-dimensional image of the areas of the brain that have the highest metabolic needs, typically those that are most active. Images resulting from PET usually represent neural activity that has occurred over tens of minutes, which is very poor temporal resolution for some purposes. PET images are often combined with computed tomography (CT) images to improve spatial resolution, as fine as several millimeters. Tracers can also be incorporated into molecules that bind to neurotransmitter receptors, which allow researchers to answer some unique questions about the action of neurotransmitters. Unfortunately, very few research centers have the equipment required to obtain the images or the special equipment needed to create the positron-emitting tracer molecules, which typically need to be produced on site.



Figure 2.4.3: A PET scanner.

2.4.2.1 Using Indirect Functional Imaging Techniques to Study a Disorder: Autism Spectrum Disorder

PET and fMRI studies of ASD have found different levels of neuronal activity in the amygdala and the hippocampus compared to subjects without ASD. These areas are notable because they are a part of the "social brain." These studies have largely focused on patients with ASD when they are viewing faces. As the viewing of faces is a large part of socializing (for example, reading expressions and making eye contact) and socializing is one area where many autistic patients have issues, these studies help provide further information for doctors and researchers to use. (See Philip et al. (2012) for a review of the fMRI studies of ASD.)

2.4.3 Transcranial Magnetic Stimulation

Another technique that is worth mentioning is transcranial magnetic stimulation (TMS). TMS is a noninvasive method that causes **depolarization** or **hyperpolarization** in neurons near the scalp. Depolarizations are increases in the electrical state of the neuron, while hyperpolarizations are decreases. In TMS, a coil of wire is placed just above the participant's scalp (as shown in Figure 2.4.4). When electricity flows through the coil, it produces a magnetic field. This magnetic field travels through the skull and scalp and affects neurons near the surface of the brain. When the magnetic field is rapidly turned on and off, a current is induced in the neurons, leading to depolarization or hyperpolarization, depending on the number of magnetic field pulses. Single- or paired-pulse TMS depolarizes site-specific neurons in the cortex, causing them to fire. If this method is used over certain brain areas involved with motor control, it can produce or block muscle activity, such as inducing a finger twitch or preventing someone from pressing a button. If used over brain areas involved with visual perception, it can produce sensations of flashes of light or impair visual processes. This has proved to be a valuable tool in studying the function and timing of specific processes such as the recognition of visual stimuli.

Repetitive TMS produces effects that last longer than the initial stimulation. Depending on the intensity, coil orientation, and frequency, neural activity in the stimulated area may be either attenuated or amplified. Used in this manner, TMS is able to explore **neural plasticity**, which is the ability of connections between neurons to change. This has implications for treating psychological disorders, such as depression, as well as understanding long-term changes in neuronal excitability.

Note that TMS is different from the previous techniques in that we are not taking images of what the brain is doing. TMS disrupts or stimulates the brain and actively changes what the brain is doing.



Figure 2.4.4: Woman with TMS wand pressed against the back right side of her head.

Figure 2.4.4: Woman with TMS wand pressed against the back right side of her head. Credit: "TMS"(opens in new window) by Baburov(opens in new window) is licensed under CC BY-SA 4.0(opens in new window)

2.4.3.1 Using Transcranial Magnetic Imaging to Study a Disorder: Autism Spectrum Disorder

TMS studies, as with most research techniques, can come in the form of basic research (research intended to inform our understanding) and applied research (research intended to solve a problem). Basic research in neuroscience is typically driven by research questions aimed at a general understanding of how the brain and nervous system work. Some TMS studies have used TMS to reduce brain activity in the right amygdala during the processing of faces with negative emotions (Baeken et al., 2010). Although this research wasn't specific to autism, it is not hard to see the connection between understanding how the amygdala works and ASD. Furthermore, studies have tried to use TMS to treat ASD. Studies thus far have focused on using TMS to change activity levels and possibly stimulate neural plasticity. There was even a transcranial magnetic stimulation therapy for autism conference held in 2014 to discuss the use of the tool in the treatment of ASD. Indeed, there are myriad of possibilities for how this tool can be used in the future. (See Oberman et al. (2015) for a review of TMS treatments for ASD.)

2.4.4 References

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2.5: Invasive Techniques

Learning Objectives

1. Describe what single cell recordings, lesion studies, direct cortical stimulation, split-brain studies, and the Wada procedure each refer to.
2. Explain the pros and cons of single cell recordings.
3. Describe when lesion studies, direct cortical stimulation, split-brain studies, and the Wada procedure may be used.
4. Discuss the limitations of lesion/surgery studies.

2.5.1 Overview

In this section, we will discuss some of the other ways that researchers and doctors study the brain. These techniques are different from what was previously discussed in that they are more invasive, techniques that require entering the brain as opposed to taking measurements from the skull. Each of the following techniques are not used on everyday "healthy" human volunteers. Rather, these techniques are typically used when there is something going on in the brain of interest and doctors/researchers need to investigate.

2.5.1.1 Single Cell Recordings

One technique that is used to study animals in neuroscience, known as **single cell recordings** allows for us to record the activity of a cell, at least in theory. The idea of single cell recordings is that we can place a very tiny recording device, known as a microelectrode, into a single neuron and then we can try and figure out what will “activate” that particular neuron. For example, in the visual system, you may find a neuron that activates when a line moves in a certain direction in a certain location. We would then conclude that this neuron processes moving lines from a particular location.

Furthermore, single cell recordings have excellent spatial and temporal resolution. The researcher can tell exactly where the activity is coming from and exactly when the activity is occurring.

However, single cell recordings are usually extracellular (outside of the cell). That is, they don’t record from inside a single cell but, rather, they record from outside a few cells. Also, consider that the neuron that responds to a line in a particular location that is moving in a particular direction likely does not respond to much else. So, it is extremely difficult to determine what exactly each cell does through single cell recordings. Recording from one area ignores what is happening everywhere else in the brain.

2.5.1.2 Lesion Studies

A **lesion** is a site of damage in the brain. In neuroscience, we conduct lesion studies on both animals and human subjects. In animals, lesions can be made in a specific area by the researcher. Researchers are able to correlate the deficits in function with the area of damage. For example, if a researcher damages area X, and now the animal is unable to enter into REM (rapid eye movement) sleep, one can reasonably conclude that area X serves some function related to REM sleep. Although the same can be said for lesion studies of humans, accidents, or medical necessities are generally the source of human lesion subjects. You'll recall that we began this chapter by mentioning the tragic - but educational - case of Phineas Gage.

Lesion studies can allow for very specific conclusions to be made about very specific brain areas. However, in human subjects, many of the lesion patients have damage to multiple areas. In general, this makes it more difficult to make conclusions about the function of the brain areas. If the person has damage to areas X, Y, and Z, and is unable to enter into REM sleep, we are uncertain whether the area that is related to REM sleep is area X, Y, or Z or some combination of them.

2.5.1.3 Neurosurgical Techniques

Another way the brain has been studied by neuroscientists is through various techniques that are employed before or during brain surgery. One such technique, **direct cortical stimulation**, occurs when a researcher applies a small electrical current directly to the brain itself. This stimulation can cause excitation or inhibition depending on how much stimulation is given. In order to do direct cortical stimulation, the subject must have their brain exposed during surgery. One may reasonably ask the question, “Why would we ever do this?” Well, when someone is having brain surgery, there is likely a reason. For example, if a patient has a tumor in a medial portion of the brain, doctors may have to go through healthy brain tissue in order to reach the tumor so that they can remove it. Doctors must choose carefully which part of the healthy brain tissue they will damage in order to get to the tumor. One way of figuring out which area would do the least damage is to do a technique known as **cortical mapping**. During cortical mapping,

direct cortical stimulation is applied to various parts of the healthy brain tissue to map out their functions. This allows doctors to choose the path of least damage.

Alternatively, cortical mapping can now occur through surgically implanted subdural strip and grid electrodes that will allow the researchers/doctors to stimulate the brain areas in between surgeries, as opposed to during surgery. Additionally, in recent years, researchers have been examining whether TMS is an appropriate (and non-surgical) substitution for direct cortical stimulation.

2.5.1.3.1 Split Brain Studies

Sometimes when surgeons perform surgery to improve the lives of their patients, they can unintentionally create other issues. One famous example of this involves patients who were subjected to a procedure that effectively disrupts the communication between the two sides of the brain. Split-brain research refers to the study of those who received this treatment and the knowledge resulting from this work (Rosen, 2018). Under what circumstances would such a seemingly radical procedure be used - and what are its effects?

In order to treat patients with severe epilepsy, doctors cut the corpus callosum in the brain, which is the main structure that connects the two hemispheres. Doing this kept the electrical activity that was causing the epileptic seizures confined to one hemisphere and helped get the epilepsy under control. However, this also disconnected the two hemispheres from each other, which led to some interesting studies, where researchers were able to study the functions of each hemisphere independently. These studies will be discussed later when we cover lateralization of functions.

2.5.1.3.2 Wada Procedure

One additional way to study the contributions of each hemisphere separately is through a procedure known as a Wada. In a Wada procedure, a barbiturate (a depressant drug used for various purposes including sedation) is used to put one half of the brain “to sleep” and then the contributions of the other hemisphere can be studied. Wada procedures are typically used for similar purposes as are cortical mapping techniques such as direct cortical stimulation. But, instead of mapping specific functions to specific areas (as with direct cortical stimulation), the Wada procedure maps functions to hemispheres. Usually, the Wada is used to identify which hemisphere is responsible for language processing and memory tasks. Although scientists know that language functions are usually in the left hemisphere, it is not always the case (particularly in left-handed individuals), so the Wada will help determine which hemisphere is dominant for language functions. For memory functions, both hemispheres play a significant role, but during the Wada, doctors are able to determine which hemisphere has stronger memory function.

2.5.1.4 One Major Concern With Lesion/Surgery Studies

One thing to remember about all studies of lesion or surgical patients is that the ability to generalize to the population during these studies may be questionable. It is important to keep in mind that that the reason these patients are studied is because they had some sort of issue with their brain. It is reasonable to wonder whether their brains are representative of “normal subjects,” that is, subjects who do not have lesions or other issues.

For example, perhaps someone with epilepsy, after having years of seizures, has a different brain organization than someone without epilepsy. In that circumstance, what we learn from them in a split brain study may not be applicable to a non-epileptic population.

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2.6: Ethical Considerations

Learning Objectives

1. Explain the "Three R's".
2. Explain why research is still conducted on nonhuman animal subjects.
3. Describe the Tuskegee Syphilis Study and explain the ramifications of studies like these on research.

2.6.1 Overview

In this section, we will discuss the ethics of conducting research, both on nonhuman animal subjects and on human subjects. We will discuss a handful of examples of ethical violations and how these violations have led to negative outcomes in some situations.

2.6.2 Ethics in Neuroscience Research

Research has a very complicated history with respect to ethics. This is true when discussing our treatment of nonhuman animal subjects and our treatment of human subjects as well. Let's start by discussing the ethical considerations for nonhuman animal subject research.

2.6.2.1 Nonhuman Animal Subject Research

One area of controversy regarding research techniques is the use of nonhuman animal subjects. One of the keys to behaving in an ethical manner is to ensure that one has given informed consent to be a subject in a study. Obviously, animals are unable to give consent. For this reason and others related to animal welfare, there are some who believe that researchers should not use nonhuman animal subjects in any case.

There are others that advocate for using nonhuman animal subjects because nonhuman animal subjects many times will have distinct advantages over human subjects. Their nervous systems are frequently less complex than human systems, which facilitates the research. It is much easier to learn from a system with thousands of neurons compared to one with billions of neurons like humans. Also, nonhuman animals may have other desirable characteristics such as shorter life cycles, larger neurons, and translucent embryos. However, it is widely recognized that this research must proceed with explicit guidelines ensuring the safe treatment of the animals. For example, any research institution that will be conducting research using nonhuman animal subjects must have an **Institutional Animal Care and Use Committee (IACUC)**. IACUCs review the proposed experiments to ensure an appropriate rationale for using nonhuman animals as subjects and ensure ethical treatment of those subjects.

Furthermore, many researchers who work with nonhuman animal subjects adhere to the **Three R's: Replacement, Reduction, and Refinement** (Russell & Burch, 1959).

Replacement suggests that researchers should seek to use inanimate systems as a replacement for nonhuman animal subjects whenever possible. Furthermore, replacement is also suggested to replace higher level organisms with lower level organisms whenever possible. The idea is that instead of choosing a primate to conduct the study, researchers are encouraged to use a lower level animal such as an invertebrate (a sea slug, for example) to conduct the study.

Reduction refers to reducing the number of nonhuman animal subjects that will be used in the particular study. The idea here is that if a study can learn sufficient information from one nonhuman animal, then they should only use one.

Finally, refinement is about how the nonhuman animals are cared for. The goal is to minimize discomfort that the subject experiences and to enhance the conditions that the subject experiences throughout their life. For a full discussion of the Three R's, see Tannenbaum and Bennett (2015).

In conclusion, many researchers argue that what we have learned from nonhuman animal subjects has been invaluable. These studies have led to drug therapies for treating pain and other disorders; for instance, most drugs are studied using animals first, to ensure they are safe for humans. Animal nervous systems are used as models for the human nervous systems in many areas. Sea slugs (Aplysia californica) have been used to learn about neural networks involved in learning and memory. Cats have been studied to learn about how our brain's visual system is organized. Owls have been used to learn about sound localization in the auditory system. Indeed, research using nonhuman animal subjects has led to many important discoveries.

2.6.2.2 Human Subject Research

What about research on human subjects? We do not have to go very far back in history to find situations where researchers behaved in unethical ways towards their human subjects. One of the most famous ethical violations in history is that many experiments were conducted using concentration camp prisoners as subjects during the holocaust.

Throughout the years, psychologists have engaged in various studies that have pushed the envelope of ethical research, such as Milgram's study of obedience or Zimbardo's Stanford prison study. Studies such as these have led to the development of strict ethical guidelines for human research. As with research on nonhuman animal subjects, there is a committee known as an **Institutional Review Board (IRB)** whose role is to approve research proposals. These committees ensure that there is an appropriate reason for completing the research with human subjects and that the safety of the human subjects are appropriately considered.

To further complicate matters, here in the United States, we have our own history of when ethical violations intersected with racial/ethnic divides.

Indeed, members of groups have historically faced more than their fair share of the risks of scientific research, including people of color, institutionalized individuals, the disabled, or other marginalized individuals. A particularly tragic example is the Tuskegee syphilis study conducted by the US Public Health Service from 1932 to 1972 (Reverby, 2009). The participants in this study were African American men in the vicinity of Tuskegee, Alabama, who were told that they were being treated for “bad blood.” Although they were given some free medical care, they were not treated for their syphilis. Instead, they were observed to see how the disease developed in untreated patients. Even after the use of penicillin became the standard treatment for syphilis in the 1940s, these men continued to be denied treatment without being given an opportunity to leave the study. The study was eventually discontinued only after details were made known to the general public by journalists and activists. It is now widely recognized that researchers need to consider issues of justice and fairness at the societal level.

“They Were Betrayed”

In 1997— 65 years after the Tuskegee Syphilis Study began and 25 years after it ended— President Bill Clinton formally apologized on behalf of the US government to those who were affected. Here is an excerpt from the apology:

So today America does remember the hundreds of men used in research without their knowledge and consent. We remember them and their family members. Men who were poor and African American, without resources and with few alternatives, they believed they had found hope when they were offered free medical care by the United States Public Health Service. They were betrayed.

Read the full text of the apology at http://www.cdc.gov/tuskegee/clintonp.htm.



Figure 2.6.1: President Bill Clinton greets a survivor of the Tuskegee Syphilis Study on African-American men.

The racism behind the unethical behavior in the Tuskegee study (and other studies) has led to a general distrust of research from some minorities. This distrust in research has led to a lack of volunteers from minority communities in research. Distrust in research also has other consequences, and as recently as 2021 has been cited as a contributing factor for the disproportionate impact of the COVID-19 pandemic on minority communities (Carson, et all., 2021). Unfortunately, when a large portion of the research conducted is on Caucasian samples, it is unclear whether or not the results generalize to non-

Caucasian groups. Given the complexities of the human brain, researchers continue to push for a sample that is truly representative of the population at large to ensure that their research results are generalizable.

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2.6.4 Attributions

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CHAPTER OVERVIEW

3: Nature and Nurture- Evolutionary Theories, Basic Genetics, Epigenetics, and Environmental Interactions

3.1: Evolutionary Theories in Psychology

3.2: Nature and Nurture

3.3: Epigenetics

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3.1: Evolutionary Theories in Psychology

Learning Objectives

- Demonstrate an understanding of what "evolution" means.
- Describe the primary mechanisms by which evolution takes place.
- Define sexual and gene selection theories.
- Define gene selection theory.
- Explain psychological adaptations.

Overview

Evolution or change over time occurs through the processes of natural and sexual selection. In response to problems in our environment, we adapt both physically and psychologically to ensure our survival and reproduction. Sexual selection theory describes how evolution has shaped us to provide a mating advantage rather than just a survival advantage and occurs through two distinct pathways: intrasexual competition and intersexual selection. Gene selection theory, the modern explanation behind evolutionary biology, occurs through the desire for gene replication. Evolutionary psychology connects evolutionary principles with modern psychology and focuses primarily on psychological adaptations: changes in the way we think in order to improve our survival.

Basics of Evolutionary Theory

Evolution simply means change over time. Many think of evolution as the development of traits and behaviors that allow us to survive this "dog-eat-dog" world, like strong leg muscles to run fast, or fists to punch and defend ourselves. However, physical survival is only important if it eventually contributes to successful reproduction. That is, even if you live to be a 100-year-old, if you fail to mate and produce children, your genes will die with your body. Thus, *reproductive* success, not *survival* success, is the engine of evolution by **natural selection**. Every mating success by one person means the loss of a mating opportunity for another. Yet every living human being is an evolutionary success story. Each of us is descended from a long and unbroken line of ancestors who triumphed over others in the struggle to survive (at least long enough to mate) and reproduce. However, in order for our genes to endure over time—to survive harsh climates, to defeat predators—we have inherited adaptive, psychological processes designed to ensure success.

At the broadest level, we can think of organisms, including humans, as having two large classes of **adaptations**—or traits and behaviors that evolved over time to increase our reproductive success. The first class of adaptations are called survival adaptations: mechanisms that helped our ancestors handle the "hostile forces of nature." For example, in order to survive very hot temperatures, we developed sweat glands to cool ourselves. In order to survive very cold temperatures, we developed shivering mechanisms (the speedy contraction and expansion of muscles to produce warmth). Other examples of survival adaptations include developing a craving for fats and sugars, encouraging us to seek out particular foods rich in fats and sugars that keep us going longer during food shortages. Some threats, such as snakes, spiders, darkness, heights, and strangers, often produce fear in us, which encourages us to avoid them and thereby stay safe. These are also examples of survival adaptations. However, all of these adaptations are for physical *survival*, whereas the second class of adaptations are for *reproduction*, and help us compete for mates. These adaptations are described in an evolutionary theory proposed by Charles Darwin, called **sexual selection** theory.

Sexual Selection Theory

Darwin noticed that there were many traits and behaviors of organisms that could not be explained by "survival selection." For example, the brilliant plumage of peacocks should actually lower their rates of survival. That is, the peacocks' feathers act like a neon sign to predators, advertising "Easy, delicious dinner here!" But if these bright feathers only lower peacocks' chances at survival, why do they have them? The same can be asked of similar characteristics of other animals, such as the large antlers of male stags or the wattles of roosters, which also seem to be unfavorable to survival. Again, if these traits only make the animals less likely to survive, why did they develop in the first place? And how have these animals continued to survive with these traits over thousands and thousands of years? Darwin's answer to this conundrum was the theory of sexual selection: the evolution of characteristics, not because of survival advantage, but because of ***mating*** **advantage**.

Sexual selection occurs through two processes. The first, **intrasexual competition**, occurs when members of one sex compete against each other, and the winner gets to mate with a member of the opposite sex. The second process of sexual selection is

preferential mate choice, also called **intersexual selection**. In this process, if members of one sex are attracted to certain qualities in mates—such as brilliant plumage, signs of good health, or even intelligence—those desired qualities get passed on in greater numbers, simply because their possessors mate more often.

Gene Selection Theory

In modern evolutionary theory, all evolutionary processes boil down to an organism's genes. Genes are the basic "**units of heredity**," or the information that is passed along in DNA that tells the cells and molecules how to "build" the organism and how that organism should behave. Genes that are better able to encourage the organism to reproduce, and thus replicate themselves in the organism's offspring, have an advantage over competing genes that are less able. For example, take female sloths: In order to attract a mate, they will scream as loudly as they can, to let potential mates know where they are in the thick jungle. Now, consider two types of genes in female sloths: one gene that allows them to scream extremely loudly, and another that only allows them to scream moderately loudly. In this case, the sloth with the gene that allows her to shout louder will attract more mates—increasing reproductive success—which ensures that her genes are more readily passed on than those of the quieter sloth.

Essentially, genes can boost their own replicative success in two basic ways. First, they can influence the odds for survival and reproduction of the organism they are in (individual reproductive success or fitness—as in the example with the sloths). Second, genes can also influence the organism to help other organisms who also likely contain those genes—known as "genetic relatives"—to survive and reproduce (which is called inclusive fitness).

Evolutionary Psychology

Evolutionary psychology aims the lens of modern evolutionary theory on the workings of the human mind. It focuses primarily on **psychological adaptations**: mechanisms of the mind that have evolved to solve specific problems of survival or reproduction. These kinds of adaptations are in contrast to *physiological* adaptations, which are adaptations that occur in the body as a consequence of one's environment. One example of a physiological adaptation is how our skin makes calluses. First, there is an "input," such as repeated friction to the skin on the bottom of our feet from walking. Second, there is a "procedure," in which the skin grows new skin cells at the afflicted area. Third, an actual callus forms as an "output" to protect the underlying tissue—the final outcome of the physiological adaptation (i.e., tougher skin to protect repeatedly scraped areas). On the other hand, a *psychological* adaptation is a development or change of a mechanism in the mind. For example, take sexual jealousy. First, there is an "input," such as a romantic partner flirting with a rival. Second, there is a "procedure," in which the person evaluates the threat the rival poses to the romantic relationship. Third, there is a behavioral output, which might range from vigilance (e.g., snooping through a partner's email) to violence (e.g., threatening the rival). Although such behaviors serve a purpose for the jealous person, they can be harmful to others.

Evolutionary psychology is fundamentally an *interactionist* framework, or a theory that takes into account multiple factors when determining the outcome. For example, jealousy, like a callus, doesn't simply pop up out of nowhere. There is an "interaction" between the environmental trigger (e.g., the flirting; the repeated rubbing of the skin) and the initial response (e.g., evaluation of the flirter's threat; the forming of new skin cells) to produce the outcome.

Evolutionary Psychology and Cultural Influences

In evolutionary psychology, culture also has a major effect on psychological adaptations. For example, status within one's group is important in all cultures for achieving reproductive success, because higher status makes someone more attractive to mates. In **individualistic cultures**, such as the United States, status is heavily determined by individual accomplishments. But in more **collectivist cultures**, such as Japan, status is more heavily determined by contributions to the group and by that group's success. For example, consider a group project. If you were to put in most of the effort on a successful group project, the culture in the United States reinforces the psychological adaptation to try to claim that success for yourself (because individual achievements are rewarded with higher status). However, the culture in Japan reinforces the psychological adaptation to attribute that success to the whole group (because collective achievements are rewarded with higher status). Evolutionary psychology, in short, does not predict rigid robotic-like "instincts." That is, there isn't one rule that works all the time. Rather, evolutionary psychology studies flexible, environmentally-connected and culturally-influenced adaptations that vary according to the situation.

Psychological adaptations are hypothesized to be wide-ranging, and include food preferences, habitat preferences, mate preferences, and specialized fears. These psychological adaptations also include many traits that improve people's ability to live in groups, such as the desire to cooperate and make friends, or the inclination to spot and avoid frauds, punish rivals, establish status

hierarchies, nurture children, and help genetic relatives. Research programs in evolutionary psychology develop and empirically test predictions about the nature of psychological adaptations.

Attributions

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3.2: Nature and Nurture

Learning Objectives

- Understand what the nature–nurture debate is and why the problem fascinates us.
- Understand why nature–nurture questions are difficult to study empirically.
- Know the major research designs that can be used to study nature–nurture questions.
- Appreciate the complexities of nature–nurture and why questions that seem simple turn out not to have simple answers.

Overview

There are three related problems at the intersection of philosophy and science that are fundamental to our understanding of our relationship to the natural world: the mind–body problem, the free will problem, and the **nature–nurture** problem. It seems that most people, even those without much knowledge of science or philosophy, have opinions about the answers to these questions that come simply from observing the world we live in. Our feelings about our relationship with the physical and biological world often seem incomplete. We are in control of our actions in some ways, but at the mercy of our bodies in others; it feels obvious that our consciousness is some kind of creation of our physical brains, at the same time we sense that our awareness must go beyond just the physical. This incomplete knowledge of our relationship with nature leaves us fascinated and a little obsessed, like a cat that climbs into a paper bag and then out again, over and over, mystified every time by a relationship between inner and outer that it can see but can't quite understand.

It may seem obvious that we are born with certain characteristics while others are acquired, and yet of the three great questions about humans' relationship with the natural world, only nature–nurture gets referred to as a "debate." In the history of psychology, no other question has caused so much controversy and offense: We are so concerned with nature–nurture because our very sense of moral character seems to depend on it.

The problem is, most human characteristics aren't usually as clear-cut as, for example 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—perfect pitch, or long, nimble fingers—that support and reward his hard work. And the basketball player might have eaten a diet while growing up that promoted her genetic tendency for being tall. When we think about our own qualities, they seem under our control in some respects, yet beyond our control in others. And 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 own control.



Figure 3.2.1: Researchers have learned a great deal about the nature-nurture dynamic by working with animals. But of course many of the techniques used to study animals cannot be applied to people. Separating these two influences in human subjects is a greater research challenge. (CC BY-NC 2.0; Sebastián Dario via Flickr)

One major problem with answering nature-nurture questions about people is, how do you set up an experiment? In nonhuman animals, there are relatively straightforward experiments for tackling 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 being raised by nonaggressive parents (the Beagles), and vice versa, in litters that mirror each other in puppy distribution. The big questions are: Would the Chihuahua parents raise aggressive beagle puppies? Would the beagle parents raise *non*aggressive 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 very 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 do 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 in order to suit the particular interests of a scientist) but adoption still tells us some interesting things, or at least confirms some basic expectations. 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?



Figure 3.2.2: Studies focused on twins have led to important insights about the biological origins of many personality characteristics. From Psychology as a Biological Science, The Nature-Nurture Question, NOBA; CC Attribution-NC SA 4.0

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 take a look at how nature and nurture apply: Identical twins, unsurprisingly, are almost perfectly similar for 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, twins who have been separated at birth and raised separately (Bouchard, Lykken, McGue, & Segal, 1990; such twins are very rare and play a smaller role than is commonly believed in the science of nature–nurture), or with entire extended families (see Plomin, DeFries, Knopik, & Neiderhiser, 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 among 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.

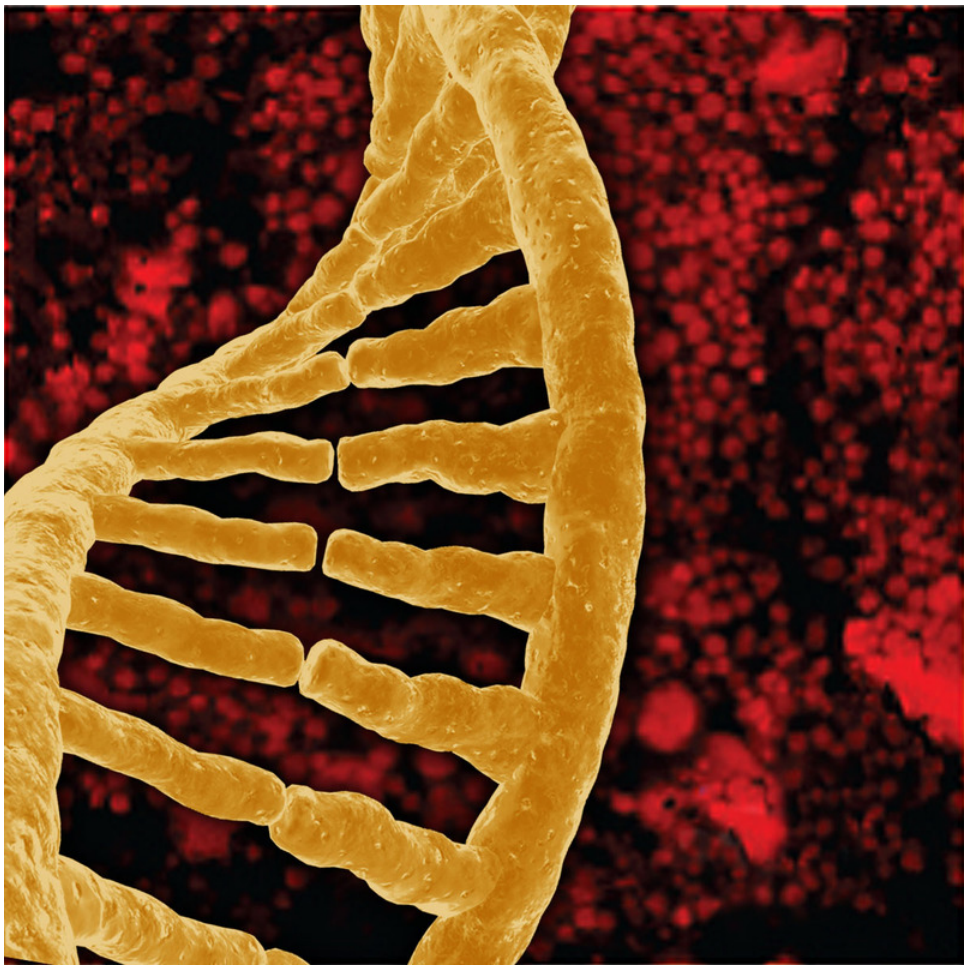


Figure 3.2.3: Quantitative genetics uses statistical methods to study the effects that both heredity and environment have on test subjects. These methods have provided us with the heritability coefficient which measures how strongly differences among individuals for a trait are related to differences among their genes. [Image: EMSL, https://goo.gl/IRfn9g, CC BY-NC-SA 2.0, https://goo.gl/fbv27n]

One reason nature–nurture continues to fascinate us so much is that we live in an era of great scientific discovery in genetics. Every day, it seems, new discoveries are made, new possibilities proposed. When Francis Galton first started thinking about nature–nurture in the late-19th century he was very influenced by his cousin, Charles Darwin, but genetics *per se* was unknown. Mendel's famous work with peas, conducted at about the same time, went undiscovered for 20 years; quantitative genetics was developed in the 1920s; the structure of DNA was discovered by Watson and Crick in the 1950s; the human genome 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. 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, 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. And 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, Corley, DeFries, & Fulker, 1990), and whether or not they get divorced (McGue & Lykken, 1992).



Figure 3.2.4: 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. [Image: Paul Altobelli, https://goo.gl/SWLwm2, CC BY-NC 2.0, https://goo.gl/9uSnqN]

Whatever the outcome of our broader discussion of nature–nurture, the basic fact that the best predictors of an adopted child's personality or mental health are found in the biological parents he or she has never met, rather than in the adoptive parents who raised him or her, presents a significant challenge to purely environmental explanations of personality or psychopathology. 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.

The outcomes of nature–nurture studies have fallen short of our expectations (of establishing clear-cut bases for traits) in many ways. The most disappointing outcome has been the inability to organize traits from *more*- to *less*-genetic. As noted earlier, everything has turned out to be at least *somewhat* heritable (passed down), yet nothing has turned out to be *absolutely* heritable (Turkheimer, 2000). The problem is conceptual: The heritability coefficient, and, in fact, the whole quantitative structure that underlies it, does not match up with our nature–nurture intuitions. We want to know how "important" the roles of genes and environment are to the development of a trait, but in focusing on "important" maybe we're emphasizing the wrong thing. First of all, genes and environment are both crucial to *every* trait; without genes the environment would have nothing to work on, and too, genes cannot develop in a vacuum. Even more important, because nature–nurture questions look at the differences among people, the cause of a given trait depends not only on the trait itself, but also on the differences in that trait between members of the group being studied.

The classic example of the heritability coefficient defying intuition is the trait of having two arms. No one would argue against the development of arms being a biological, genetic process. But fraternal twins are just as similar for "two-armedness" as identical twins, resulting in a heritability coefficient of zero for the trait of having two arms. Normally, according to the heritability model, this result (coefficient of zero) would suggest all nurture, no nature, but we know that's not the case. The reason this result is not a tip-off that arm development is less genetic than we imagine is because people *do not vary* in the genes related to arm development —which essentially upends the heritability formula. In fact, in this instance, the opposite is likely true: the extent that people differ in arm number is likely the result of accidents and, therefore, environmental. For reasons like these, we always have to be very careful when asking nature–nurture questions, especially when we try to express the answer in terms of a single number. The heritability of a trait is not simply a property of that trait, but a property of the trait in a particular context of relevant genes and environmental factors.

Another 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. It turns out to be the case that, for many traits, genetic differences affect behavior under some environmental circumstances but not others —a phenomenon called gene-environment interaction. In one well-known example, Caspi et al. (2002) showed 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. Whereas, in children who had not been maltreated, the gene had no effect. Making matters even more complicated are very recent studies of what is known as epigenetics, a process in which the DNA itself is modified by environmental events, and those genetic changes transmitted to children. Epigenetics will be discussed in detail in the next section.



Figure 3.2.5: 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. [Image: Sundaram Ramaswamy, https://goo.gl/Bv8lp6, CC BY-NC 2.0, https://goo.gl/9uSnqN]

Some common questions about nature–nurture are, how susceptible is a trait to change, how malleable is it, and do we "have a choice" about it? These questions are much more complex than they may seem at first glance. Height seems like a trait firmly rooted in our nature and unchangeable, but the average height of many populations in Asia and Europe has increased significantly in the past 100 years, due to changes in diet and the alleviation of poverty. There are a few rare genes that have been found to have significant (almost always negative) effects, such as the single gene that causes Huntington's disease, or the Apolipoprotein gene that causes early onset dementia in a small percentage of Alzheimer's cases. Aside from these rare genes, however, the genetic impact on behavior is broken up over many genes, each with very small effects. In fact, the same is true of environmental effects. We know that extreme environmental hardship causes catastrophic effects for many behavioral outcomes, however, within the average range of environmental events, those responsible for differences (e.g., why some children in a suburban third-grade classroom perform better than others) are much more difficult to grasp.

The difficulties with finding clear-cut solutions to nature–nurture problems bring us back to the other great questions about our relationship with the natural world: the mind-body problem and free will. Investigations into what we mean when we say we are aware of something reveal that consciousness is not simply the product of a particular area of the brain, nor does choice turn out to

be an orderly activity that we can apply to some behaviors but not others. So it is with nature and nurture: What at first may seem to be a straightforward matter, able to be indexed with a single number, becomes more and more complicated the closer we look.

It is tempting to predict that the more we understand the wide-ranging effects of genetic differences on all human characteristics—especially behavioral ones—our cultural, ethical, legal, and personal ways of thinking about ourselves will have to undergo profound changes in response. One of the most important things modern genetics has taught us is that almost all human behavior is too complex to be nailed down, even from the most complete genetic information, unless we're looking at identical twins. The science of nature and nurture has demonstrated that genetic differences among people are vital to human moral equality, freedom, and self-determination, not opposed to them. As Mordecai Kaplan said about the role of the past in Jewish theology, genetics gets a vote, not a veto, in the determination of human behavior. We should indulge our fascination with nature–nurture while resisting the temptation to oversimplify it.

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Attributions

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3.3: Epigenetics

Learning Objectives

- Explain what the term epigenetics means and the molecular machinery involved.
- Name and discuss important neural and developmental pathways that are regulated by epigenetic factors, and provide examples of epigenetic effects on personality traits and cognitive behavior.
- Understand how misregulation of epigenetic mechanisms can lead to disease states, and be able to discuss examples.
- Recognize how epigenetic machinery can be targets for therapeutic agents, and discuss examples.

Overview

Early life experiences exert a profound and long-lasting influence on physical and mental health throughout life. The efforts to identify the primary causes of this have significantly benefited from studies of the epigenome—a dynamic layer of information associated with DNA that differs between individuals and can be altered through various experiences and environments. The epigenome has been heralded as a key "missing piece" of the puzzle for understanding how development of psychological disorders may be influenced by the surrounding environment, in concordance with the genome. Understanding the mechanisms involved in the initiation, maintenance, and heritability of epigenetic states is thus an important aspect of research in current biology, particularly in the study of learning and memory, emotion, and social behavior in humans. Moreover, epigenetics in psychology provides a framework for understanding how the expression of genes is influenced by experiences and the environment to produce individual differences in behavior, cognition, personality, and mental health. In this section, we survey recent developments revealing epigenetic aspects of mental health and review some of the challenges of epigenetic approaches in psychology to help explain how nurture shapes nature.

Epigenetics



Figure 3.3.1: DNA stands for Deoxyribonucleic Acid, and although each person's DNA is unique to that individual, it is 99.9% similar to every other human on the planet. [Image: CC0 Public Domain, https://goo.gl/m25gce]

Early childhood is not only a period of physical growth; it is also a time of mental development related to changes in the anatomy, physiology, and chemistry of the nervous system that influence mental health throughout life. Cognitive abilities associated with learning and memory, reasoning, problem solving, and developing relationships continue to emerge during childhood. Brain

development is more rapid during this critical or sensitive period than at any other, with more than 700 neural connections created each second. Herein, complex **gene–environment interactions** serve to increase the number of possible contacts between neurons, as they hone their adult synaptic properties and excitability. Many weak connections form to different neuronal targets; subsequently, they undergo remodeling in which most connections vanish and a few stable connections remain. These structural changes (or plasticity) may be crucial for the development of mature neural networks that support emotional, cognitive, and social behavior.

The challenge for psychology has been to integrate findings from genetics and environmental (social, biological, chemical) factors into the study of personality and our understanding of the emergence of mental illness. These studies have demonstrated that common DNA sequence variation and rare mutations account for only a small fraction (1%–2%) of the total risk for inheritance of personality traits and mental disorders (Dick, Riley, & Kendler, 2010; Gershon, Alliey-Rodriguez, & Liu, 2011). Additionally, studies that have attempted to examine the mechanisms and conditions under which DNA sequence variation influences brain development and function have been confounded by complex cause-and-effect relationships (Petronis, 2010).

Epigenetics has the potential to provide answers to these important questions. It refers to the transmission of **observable characteristics (phenotype)** in terms of gene expression in the absence of changes in DNA sequence (Waddington, 1942; Wolffe & Matzke, 1999). The advent of advanced techniques to study the distributions of regulators of gene expression throughout the genome led to the collective description of the "epigenome." In contrast to the genome sequence, which is static and the same in almost all cells, the **epigenome** is highly dynamic, differing among cell types, tissues, and brain regions (Gregg et al., 2010). Recent studies have provided insights into epigenetic regulation of developmental pathways in response to a range of external environmental factors (Dolinoy, Weidman, & Jirtle, 2007). These environmental factors during early childhood and adolescence can cause changes in expression of genes conferring risk of mental health and chronic physical conditions. Thus, the examination of genetic–epigenetic–environment interactions from a developmental perspective may determine the nature of gene misregulation in psychological disorders.

This module will provide an overview of the main components of the epigenome and review themes in recent epigenetic research that have relevance for psychology, to form the biological basis for the interplay between environmental signals and the genome in the regulation of individual differences in physiology, emotion, cognition, and behavior.

Molecular control of gene expression: the dynamic epigenome



Figure 3.3.2: 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. [Caption: Valentina and Nina are 73 year old twins, both Doctors of Philology. They were dressed exactly the same, down to their shoes and hairdo, and they both voted. Image: M., https://goo.gl/VU5iJv, CC BY-NC-SA 2.0, https://goo.gl/Toc0ZF]

Almost all the cells in our body are genetically identical, yet our body generates many different cell types, organized into different tissues and organs, and expresses different proteins. Within each type of mammalian cell, about 2 meters of genomic DNA is divided into nuclear chromosomes. Yet the nucleus of a human cell, which contains the chromosomes, is only about 2 μm in diameter. To achieve this 1,000,000-fold compaction, DNA is wrapped around a group of 8 proteins called histones. This combination of DNA and histone proteins forms a special structure called a "nucleosome," the basic unit of chromatin, which represents a structural solution for maintaining and accessing the tightly compacted genome. These factors alter the likelihood that a gene will be expressed or silenced. Cellular functions such as gene expression, DNA replication, and the generation of specific cell types are therefore influenced by distinct patterns of chromatin structure, involving covalent modification of both histones (Kadonaga, 1998) and DNA (Razin, 1998).

Importantly, epigenetic variation also emerges across the lifespan. For example, although **identical twins** share a common **genotype** and are genetically identical and epigenetically similar when they are young, as they age they become more dissimilar in their epigenetic patterns and often display behavioral, personality, or even physical differences, and have different risk levels for serious illness. Thus, understanding the structure of the nucleosome is key to understanding the precise and stable control of gene expression and regulation, providing a molecular interface between genes and environmentally induced changes in cellular activity.

The primary epigenetic mark: DNA modification

DNA methylation is the best-understood epigenetic modification influencing gene expression. DNA is composed of four types of naturally occurring nitrogenous bases: adenine (A), thymine (T), guanine (G), and cytosine (C). In mammalian genomes, **DNA methylation** occurs primarily at cytosine residues in the context of cytosines that are followed by guanines (CpG dinucleotides), to form 5-methylcytosine in a cell-specific pattern (Goll & Bestor, 2005; Law & Jacobsen, 2010; Suzuki & Bird, 2008). The enzymes that perform DNA methylation are called **DNA methyltransferases (DNMTs)**, which catalyze the transfer of a methyl group to the cytosine (Adams, McKay, Craig, & Burdon, 1979). These enzymes are all expressed in the central nervous system and are dynamically regulated during development (Feng, Chang, Li, & Fan, 2005; Goto et al., 1994). The effect of DNA methylation on gene function varies depending on the period of development during which the methylation occurs and location of the methylated cytosine. Methylation of DNA in gene regulatory regions (promoter and enhancer regions) usually results in gene silencing and reduced gene expression (Ooi, O'Donnell, & Bestor, 2009; Suzuki & Bird, 2008; Sutter and Doerfler, 1980; Vardimon et al., 1982). This is a powerful regulatory mechanism that ensures that genes are expressed only when needed. Thus DNA methylation may broadly impact human brain development, and age-related misregulation of DNA methylation is associated with the molecular pathogenesis of neurodevelopmental disorders.

Histone modification and the histone code

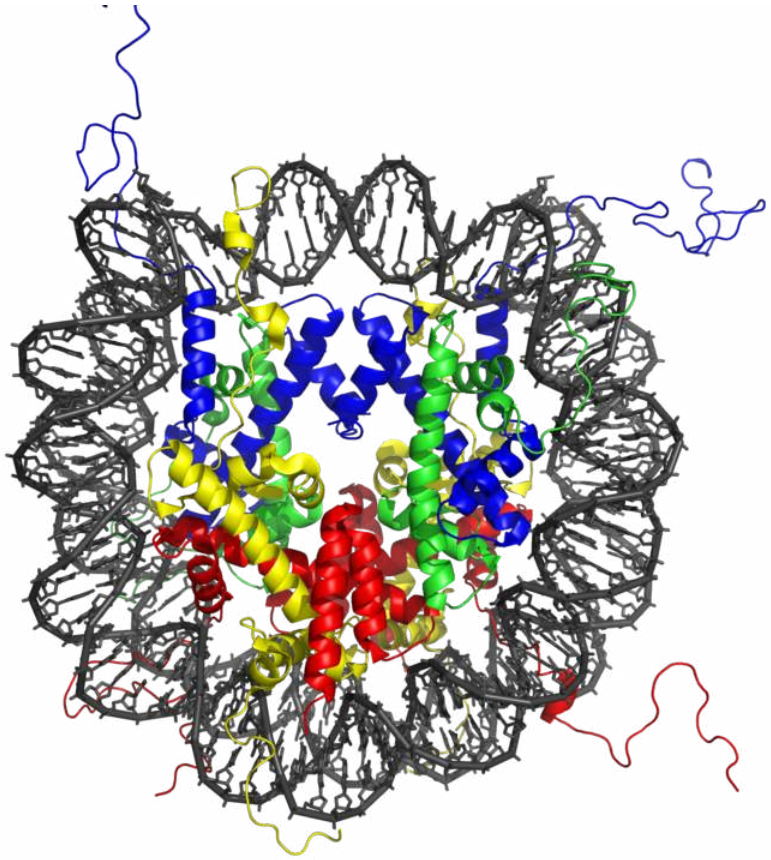


Figure 3.3.3: Life experiences, like a stressful event in childhood, can cause the modification of histone proteins (pictured) to help adapt to one's environment. For example, in response to a stressful event, histone modification of one's DNA might occur to encourage a more cautions personality—in order to avoid future, stressful encounters. [Image: Zephyris, https://goo.gl/gGrSQd, CC BY-SA 3.0, https://goo.gl/kB1Ogc]

The modification of histone proteins comprises an important epigenetic mark related to gene expression. One of the most thoroughly studied modifications is histone acetylation, which is associated with gene activation and increased gene expression (Wade, Pruss, & Wolffe, 1997). Acetylation on histone tails is mediated by the opposing enzymatic activities of **histone acetyltransferases (HATs) and histone deacetylases (HDACs)** (Kuo & Allis, 1998). For example, acetylation of histone in gene regulatory regions by HAT enzymes is generally associated with DNA demethylation, gene activation, and increased gene expression (Hong, Schroth, Matthews, Yau, & Bradbury, 1993; Sealy & Chalkley, 1978). On the other hand, removal of the acetyl group (deacetylation) by HDAC enzymes is generally associated with DNA methylation, gene silencing, and decreased gene expression (Davie & Chadee, 1998). The relationship between patterns of **histone modifications** and gene activity provides evidence for the existence of a "histone code" for determining cell-specific gene expression programs (Jenuwein & Allis, 2001). Interestingly, recent research using animal models has demonstrated that histone modifications and DNA methylation of certain genes mediates the long-term behavioral effects of the level of care experienced during infancy.

Parental investment and programming of stress responses in the offspring

The most comprehensive study to date of variations in parental investment and epigenetic inheritance in mammals is that of 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 individual differences in stress responsiveness, emotionality, cognitive performance, and reproductive behavior (Caldji et al., 1998; Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997; Myers, Brunelli, Shair, Squire, & Hofer, 1989; Stern, 1997). In adulthood, the offspring of mothers that exhibit increased levels of pup licking and grooming over the first week of life show increased expression of the glucocorticoid receptor in the hippocampus (a brain structure associated with stress responsivity as well as learning and memory) and a lower hormonal response to stress

compared with adult animals reared by low licking and grooming mothers (Francis et al., 1999; Liu et al., 1997). Moreover, rat pups that received low levels of maternal licking and grooming during the first week of life showed decreased histone acetylation and increased DNA methylation of a neuron-specific promoter of the glucocorticoid receptor gene (Weaver et al., 2004). The expression of this gene is then reduced, the number of glucocorticoid receptors in the brain is decreased, and the animals show a higher hormonal response to stress throughout their life.



Figure 3.3.4: Parental care during one's childhood has important and consequential effects on the development of an individual, effects that persist even into adulthood. [Image: The White Ribbon Alliance, https://goo.gl/KgY6N5, CC BY-NC-SA 2.0, https://goo.gl/Toc0ZF]

Several studies have attempted to determine to what extent the findings from model animals are transferable to humans. Examination of post-mortem brain tissue from healthy human subjects found that the human equivalent of the glucocorticoid receptor gene promoter (NR3C1 exon 1F promoter) is also unique to the individual (Turner, Pelascini, Macedo, & Muller, 2008). A similar study examining newborns showed that methylation of the glucocorticoid receptor gene promoter maybe an early epigenetic marker of maternal mood and risk of increased hormonal responses to stress in infants 3 months of age (Oberlander et al., 2008).

Epigenetic Mechanisms in Psychological Disorders

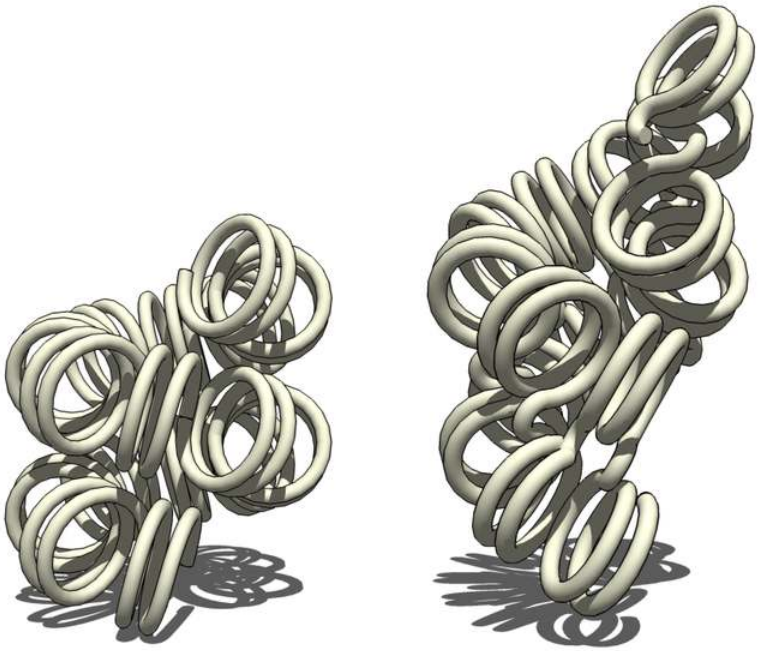


Figure 3.3.5: Pictured above is a chromatin, the spiral-looking macromolecule involved in depression. [Image: Zephyris, https://goo.gl/6DBQ1g, CC BY-SA 3.0, https://goo.gl/eLCn2O]

Epigenome-wide studies have identified several dozen sites with DNA methylation alterations in genes involved in brain development and neurotransmitter pathways, which had previously been 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. It has become evident that the efforts to identify the primary causes of complex psychiatric disorders may significantly benefit from studies linking environmental effects with changes observed within the individual cells.

Epigenetic events that alter chromatin structure to regulate programs of gene expression have been associated with depression-related behavior and action of antidepressant medications, with increasing evidence for similar mechanisms occurring 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). Similarly, chronic social defeat stress was found to decrease expression of genes implicated in normal emotion processing (Lutter et al., 2008). Consistent with these findings, levels of histone markers of increased gene expression were down regulated 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, Wynder, Schmidt, McCafferty, & Shiekhattar, 2006; Tsankova et al., 2006; Wilkinson et al., 2009). These results provide support for the use of HDAC inhibitors against depression. Accordingly, several HDAC inhibitors have been found to exert antidepressant effects by each modifying distinct cellular targets (Cassel et al., 2006; Schroeder, Lin, Crusio, & Akbarian, 2007).

Epigenetics and Understanding Gene-Environment Interactions



Figure 3.3.6: Although there is some evidence that a dysfunctional upbringing can increase one's likelihood for schizophrenia (an epigenetically inherited disease), some people who have both the predisposition and the stressful environment never develop the mental illness. [Image: Steve White, CC0 Public Domain, https://goo.gl/m25gce]

While the cellular and molecular mechanisms that influence on physical and mental health have long been a central focus of neuroscience, only in recent years has attention turned to the epigenetic mechanisms behind the dynamic changes in gene expression responsible for normal cognitive function and increased risk for mental illness. Ongoing research will show if this increased attention on epigenetics can be exploited in the development of new therapeutic options that may alter the traces that early environment leaves on the genome.

However, as discussed in this module, the epigenome is not static and can be molded by developmental signals, environmental perturbations, and disease states, which present an experimental challenge in the search for epigenetic risk factors in psychological disorders (Rakyan, Down, Balding, & Beck, 2011). The combination of genetic association maps studies with epigenome-wide developmental studies may help identify novel molecular mechanisms to explain features of inheritance of personality traits and transform our understanding of the biological basis of psychology. Importantly, these epigenetic studies may lead to identification of novel therapeutic targets and enable the development of improved strategies for early diagnosis, prevention, and better treatment of psychological and behavioral disorders.

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Attributions

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CHAPTER OVERVIEW

4: Nervous System Anatomy

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4.1: Nervous System Tissue
4.2: Nervous System Structure and Terminology
4.3: Nervous System Development
4.4: The Central Nervous System
4.5: The Peripheral Nervous System
4.6: Communication and the Endocrine System

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4.1: Nervous System Tissue

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Differentiate the central nervous system from the peripheral nervous system
2. Name the two types of cells found in nervous tissue
3. Explain the basic functions of neurons and glia
4. Describe the structures of a neuron
5. Give an example of a type of neuron that is classified by its structure, function, or other characteristic
6. Give an example of a glial cell and its function

4.1.1 Overview

This module presents a brief overview of the nervous system and goes into greater detail on nervous tissue cell types, including neurons (structure, types, and neurogenesis) and glia (types and functions).

In the Blink of an Eye

As you drive into a parking lot, a skateboarder suddenly flies in front of your car across your field of vision (Figure 4.1.1). You see the skateboarder in the nick of time and react immediately. You slam on the brakes and steer sharply to the right — all in the blink of an eye. You avoid a collision, but just barely. You're shaken up but thankful that no one was hurt. How did you respond so quickly? Such rapid responses are controlled by your nervous system.



Figure 4.1.1: Skateboarder

4.1.2 Overview of the Nervous System

The **nervous system**, illustrated in Figure 4.1.2, is the human organ system that coordinates all of the body's voluntary and involuntary actions by transmitting electrical and chemical signals to and from different parts of the body. Specifically, the nervous system extracts information from the internal and external environments using sensory receptors. It then usually sends signals encoding this information to the brain, which processes the information to determine an appropriate response. Finally, the brain sends signals to muscles, organs, or glands to bring about the necessary response. The two main divisions of the nervous system are the central nervous system (CNS), consisting of the brain and the spinal cord, and the peripheral nervous system (PNS), which includes all other nervous tissue, such as ganglia and nerves, outside the brain and spinal cord. The CNS and PNS are covered in greater detail in separate sections. In the example above, your eyes detected the skateboarder, the information traveled to your brain, and your brain instructed your body to act to avoid a collision.

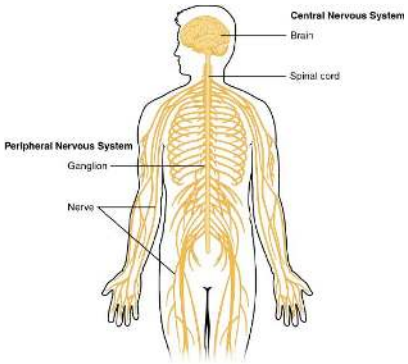


Figure 4.1.2: Overview of the Nervous System. The two main divisions of the nervous system are the central nervous system (the brain and the spinal cord) and the peripheral nerve system (which includes ganglia and nerves).

4.1.3 Nervous Tissue Cell Types

Nervous tissue is composed of two types of cells: neurons (also called nerve cells) and glia (also called glial cells or neuroglia), as shown in Figure 4.1.3. Neurons are responsible for the computation and communication that the nervous system provides. They are electrically active and release chemical signals to target cells. Glia are known to play a supporting role for nervous tissue. Ongoing research pursues an expanded role that glial cells might play in signaling, but neurons are still considered the basis of this function. Neurons are important, but without glial support they would not be able to perform their function.

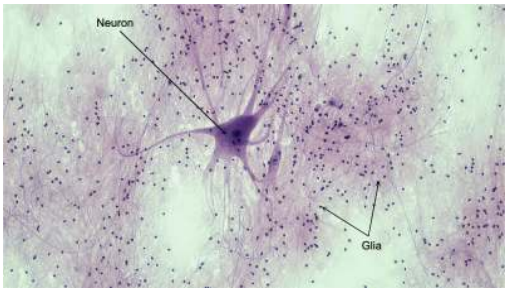


Figure 4.1.3: Labeled Nervous Tissue Smear. Nervous tissue from the spinal cord shows a neuron and glial cells. Glial cells are smaller and in larger quantities than neurons. The neuron shown is large and has multiple processes coming out of the soma (cell body). The magnification of the picture is 100X.

4.1.3.1 Neurons

Neurons, also called nerve cells, are electrically excitable cells that are the main functional units of the nervous system. Their function is to transmit nerve impulses. They are the only type of human cells that can carry out this function. Neurons are large cells with a high metabolic rate and they depend on a continuous and abundant supply of oxygen and glucose. Neurons are responsible for the electrical signals that communicate information about sensations, produce movements in response to those stimuli, and induce thought processes within the brain. An important part of the function of neurons is in their structure, or shape. The three-dimensional shape of these cells makes the immense numbers of connections within the nervous system possible. In the micrograph of human nervous tissue, Figure 4.1.4, the neon green structures in the forefront of the image are neurons.

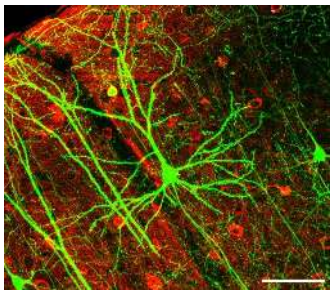


Figure 4.1.4: Interneurons of adult visual cortex.

4.1.3.1.1 Neuron Structure

The main thing that makes neurons special and differentiates them from other cells in the body is that they have many extensions of their cell membranes, generally referred to as processes. Neurons are usually described as having one, and only one, **axon**—a fiber that emerges from the cell body and projects to target cells. That single axon can branch repeatedly to communicate with many target cells. It is the axon that propagates the nerve impulse (also called an action potential), which is communicated to one or more cells. The other processes of the neuron are **dendrites**, which receive information from other neurons across specialized areas called **synapses**. The dendrites are usually highly branched processes, providing locations for other neurons to communicate with the cell body. Information flows through a neuron from the dendrites, across the cell body, and down the axon.

Figure 4.1.5 shows the structure of a typical neuron. The main parts of a neuron are labeled in the figure and described below.

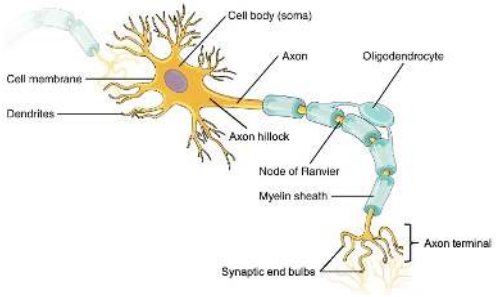


Figure 4.1.5: Neuron. A somatic motor neuron (in the CNS) with labeled structures: cell membrane, dendrites, cell body (soma), axon, axon hillock, node of Ranvier, myelin sheath, axon terminal, and synaptic end bulbs (also called axon terminal buttons). The oligodendrocyte shown to the side of the axon is a glial cell that forms the myelin sheath surrounding the axon.

- The **cell body** (or soma; soma = "body") is the part of a neuron that contains the nucleus (shown as an oval structure in the center of the cell body, but not labeled) and most of the major organelles. The cell body is usually quite compact, and may not be much wider than the nucleus. The **cell membrane** is the structure that surrounds all the surfaces of the cell (including the dendrites and axon) and separates the inside of the cell from the outside of the cell.
- **Dendrites** are thin structures that are extensions of the cell body. Their function is to receive messages (excitatory and inhibitory post-synaptic potentials, EPSPs/IPSPs- see the nervous system communication chapter) from other cells and carry them to the cell body. A neuron may have many dendrites, and each dendrite may branch repeatedly to form a dendrite “tree” with more than 1,000 **dendritic branches**. **Dendritic spines** (small extensions on the surface of the dendritic branches) further increase surface area for receiving messages, allowing a given neuron to communicate with thousands of other cells.
- The **axon** is a long, thin extension of the cell body. It transmits nerve impulses away from the cell body and toward other cells. The **axon hillock** is a small bulge found at the base of motor neuron axons. The nerve impulse (or action potential) starts from the axon hillock.
- The axon branches at the end, forming the **axon terminal**. Branches of the axon terminal end in **axon terminal buttons** (also called axon endings, synaptic end bulbs, synaptic buttons/boutons, bouton terminaux, etc.) These are the points where the message is transmitted to other cells (via the release of chemicals called neurotransmitters), often to the dendrites of other neurons. A small gap called a **synapse** (also called a synaptic gap or synaptic cleft) is located between the end of the axon terminal and the surface of the receiving cell. An axon may branch hundreds of times, but there is never more than one axon per neuron.
- Many axons (especially the long axons of nerves in the peripheral nervous system) are covered by sections of myelin (also called the **myelin sheath**). The myelin sheath is composed of lipid layers that surround the axon. Myelin is a very good electrical insulator, like the plastic or rubber that encases an electrical cord. Axons that are covered by sections of myelin are called **myelinated**, whereas axons without myelin sheaths are called **unmyelinated**.
- Regularly spaced gaps between sections of myelin occur along the axon. (The gaps are actually much further apart than is shown in the figure- it is necessary to shrink the distance to fit all the structures in a diagram!) These gaps are called **nodes of Ranvier**, and they allow the transmission of nerve impulses along the axon. Nerve impulses jump from node to node in a process called **saltatory conduction**, allowing nerve impulses to travel along the axon very rapidly.
- The **oligodendrocyte** shown in the figure is a glial cell that produces myelin sheaths in the central nervous system (brain and spinal cord)- see the Glia section below.

4.1.3.1.2 Classification of Neurons

There are many neurons in the nervous system- an estimated 86 billion in the brain alone (Lent et al., 2012). And there are many different types of neurons, exhibiting a variety of structures and functions. Neurons can be classified depending on their structure, function, or other characteristics.

4.1.3.1.3 Structural Classification

One type of structural classification depends on the number of processes attached to the cell body: one, two or multiple (Figure 4.1.6). The structures of these three different types of vertebrate neurons support their unique functions, as described below.

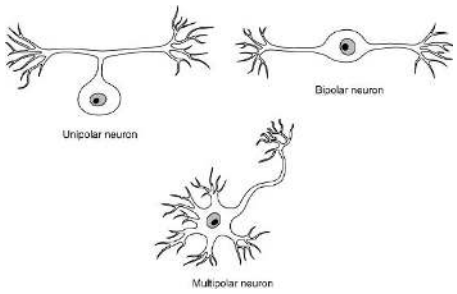


Figure 4.1.6: Neuron Classification by Structure. Unipolar neurons have one process emerging from the soma which contains both the axon and the dendrite. Bipolar neurons have two processes emerging from the soma: one is an axon and the other is a dendrite. Multipolar neurons have more than two processes emerging from the soma: one is an axon and two or more others are dendrites. (Note: True unipolar neurons are only found in invertebrates. The unipolar neuron pictured is technically a pseudo-unipolar neuron.)

Unipolar neurons have only one process emerging from the cell. True unipolar cells are only found in invertebrate animals, so the unipolar cells in humans are more appropriately called “pseudo-unipolar” cells. (Invertebrate unipolar cells do not have dendrites.) Human unipolar cells have an axon that emerges from the cell body, but it splits so that the axon can extend along a very long distance. At one end of the axon are dendrites, and at the other end, the axon forms synaptic connections with a target. Unipolar neurons are structured in a way that is ideal for relaying information forward. Unipolar cells are exclusively **sensory neurons** (see functional classification below), involved in processes like transmission of physiological information from the body’s periphery (such as communicating body temperature through the spinal cord up to the brain).

Bipolar neurons have two processes which extend from each end of the cell body opposite to each other. One is the axon and the other is the dendrite. Bipolar neurons help acquire and pass sensory information to various centers in the brain, and are not very common. Bipolar cells are are involved in sensory perception such as smell (from the olfactory epithelium), and light (in the retina of the eye). The bipolar cells of the retina are an intermediate layer of neurons between the deepest layer, the visual receptors (photoreceptors, comprised of the rods and cones), and the retinal ganglion cells, the most superficial layer of retinal neurons, whose axons bundle together to form the optic nerve (see the chapter on sensory systems for more information).

Multipolar neurons are all of the neurons that are not unipolar or bipolar, and are also the most common. They have one axon (which can branch forming multiple endings) and two or more dendrites (usually many more), which allows them to communicate with many other neurons. Multipolar neurons convey sensory and motor information in the brain, spinal cord, and throughout the body. With the exception of the unipolar sensory ganglion cells, and the two specific bipolar cells mentioned above, all other neurons are multipolar. Multipolar neurons can have multiple functions and include **motor neurons** (see functional classification below), which carry commands from the brain and spinal cord to muscles and glands, and **interneurons** (see functional classification below), which constitute the majority of neurons. One of the most prominent neuron types is a pyramidal neuron, which falls under the multipolar category. As mentioned below, it gets its name from the triangular or pyramidal shape of its soma (for examples see, Furtak, Moyer, & Brown, 2007).

4.1.3.1.4 Functional Classification

The main functional classification depends on which function the neuron is carrying out: sensation, integration or motor. A mnemonic to remember the functional classification and which direction the nerve impulses travel (towards the CNS= afferent; away from the CNS= efferent) is "***SAME***" (***S***ensory -- ***A***fferent and ***M***otor -- ***E***fferent).

Sensory (also called afferent) **neurons** carry nerve impulses from sensory receptors in tissues and organs to the central nervous system. They convert physical stimuli such as touch, light, and sound into nerve impulses.

Motor (also called efferent) **neurons**, like the one in Figure 4.1.5, carry nerve impulses from the central nervous system to muscles and glands. These signals then stimulate or inhibit the activity of these structures.

Interneurons carry out integrative functions (such as retrieving, processing, and storing information) and facilitate communication between sensory and motor neurons (inter = "between"). Interneurons are found in the brain and spinal cord, and their processes do not extend outside of the structure they occupy. In other words, a given interneuron will have its dendrites, cell body, and axon all contained within the brain region or spinal cord segment where it is located.

4.1.3.1.5 Other Classifications

Neurons can also be classified on the basis of what they look like, where they are found, who found them, what they do, or even what chemicals (neurotransmitters) they use to communicate with each other. Some of these classifications will be discussed in greater detail in the communication in the nervous system chapter. As a brief example, a multipolar neuron that has a very important role to play i

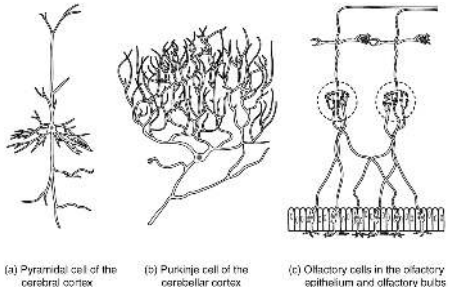


Figure 4.1.7: Other Neuron Classifications. Three examples of neurons that are named on the basis of other criteria. (a) The pyramidal cell is a multipolar cell with a cell body that is shaped something like a pyramid. (b) The Purkinje cell in the cerebellum was named after the scientist who originally described it. (c) Olfactory cells (located in the olfactory epithelium and olfactory bulbs) are named for the functional group to which they belong.

4.1.3.1.6 Gray Matter and White Matter

The nervous tissue in the brain and spinal cord consists of **gray matter** and **white matter**. Gray matter contains mainly the cell bodies and dendrites of neurons. It is gray only in cadavers; living gray matter is actually more pink than gray (Figure 4.1.8). White matter consists mainly of myelinated axons, giving it a white color. In the brain, the gray matter is on the outside surface (the **cortex**) and the white matter is on the interior; in the spinal cord it is reversed- the gray matter is inside and the white matter surrounds it.

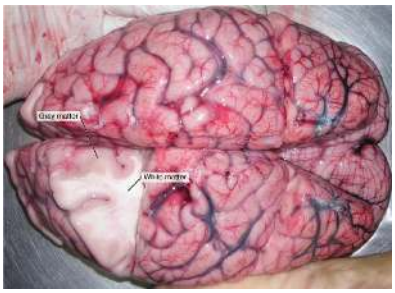


Figure 4.1.8: White and gray matter. You can see the layers of (pinkish) gray matter and white matter in this photo of a brain from a recently deceased human patient.

Nerves in the peripheral nervous system are also white matter. Nerves consist of long bundles of myelinated axons that extend to muscles, organs, or glands throughout the body. The axons in each nerve are bundled together like wires in a cable. Axons in nerves may be more than a meter long in an adult. The longest nerve runs from the base of the spine to the toes.

4.1.3.1.7 Neurogenesis

Fully differentiated neurons, with all their special structures, cannot divide and form new daughter neurons. Until recently, scientists thought that new neurons could no longer be formed after the brain developed prenatally (see the section on nervous system development). In other words, they thought that people were born with all the brain neurons they would ever have, and as neurons died, they would not be replaced. However, new evidence shows that additional neurons can form in certain areas of the brain, even in adults, from the division of undifferentiated neural stem cells that are found throughout the brain. The production of new neurons is called **neurogenesis.** The extent to which it can occur in adult humans is not known, but it is not likely to be very great.

Recent research indicated that new neurons formed in the amygdala of adult mice (Jhaveri at al., 2018). As the amygdala is important for emotional memory, particularly related to fearful experiences, future research may suggest new treatments for disorders such as post-traumatic stress disorder (PTSD) and depression.

If research on rats is found to apply also to humans, then sustained aerobic exercise such as running can increase neurogenesis in the adult brain, specifically in the hippocampus, a brain structure important for memory as well as learning temporally and/or spatially complex tasks. Although the research is still in the beginning stages, it suggests that exercise may actually lead to a “smarter” brain. Exercise is certainly beneficial for your body, even if it ends up not being confirmed to result in neurogenesis in humans, so it can’t hurt to get more aerobic exercise!

4.1.3.2 Glia

Glia (also called neuroglia or glial cells), are the other type of cell found in nervous tissue. They are considered to be vital supporting cells, and many functions are directed at helping neurons complete their function for communication. Although they do not participate in the communication between cells in the same fashion that neurons do, some researchers have found evidence that suggests that some glia may participate in information processing activities along with neurons (Fields & Stevens-Graham, 2002; Perea, et al., 2014). Some glial functions include digesting debris from dead neurons, carrying nutritional support from blood vessels to the neurons, and helping to regulate the ionic composition of the extracellular fluid.

The name glia comes from the Greek word that means “glue,” and was coined by the German pathologist Rudolph Virchow, who wrote in 1856: “This connective substance, which is in the brain, the spinal cord, and the special sense nerves, is a kind of glue (neuroglia) in which the nervous elements are planted.” Modern research into nervous tissue has shown that there are many deeper roles that these cells play. After his death in 1955, Albert Einstein's brain was studied by scientists worldwide—all wanting to gain insight into the anatomy of a genius. But it wasn't until the 1980s when Marian Diamond reported that Einstein had more glial cells than the average male brain (Diamond et al., 1985). Now it is clear that glia may play a more active role in brain activity, and research may reveal much more about them in the future.

One type of glial cell, radial glia, exist only during prenatal development, guiding migrating neurons to their final destinations. After this task is complete, most of these cells become neurons, but some become astrocytes or oligodendrocytes (Kalat, 2019), described below. There are six types of glial cells in the adult nervous system. Four of them are found in the CNS- astrocytes, oligodendrocytes, microglia and ependymal cells, and two are found in the PNS- satellite cells and Schwann cells. Table 4.1.1 outlines some common characteristics and functions of these glia.

Table 4.1.1: Glial Cell Types by Location and Basic Function.

CNS glia	PNS glia	Basic function
Astrocyte	Satellite cell	Support of the nervous tissue, form the blood-brain barrier (BBB)
Oligodendrocyte	Schwann cell	Insulation, myelination
Microglia	-	Immune surveillance and phagocytosis
Ependymal cell	-	Creating cerebrospinal fluid (CSF)

4.1.3.2.1 Important Functions of Some Glia

Astrocytes, named for their star-shaped appearance under the microscope (astro = “star”), have many processes extending from their main cell body (not axons or dendrites like neurons, just cell extensions). Those processes interact with neurons, blood vessels, or the connective tissue covering the CNS known as the pia mater. One important role of astrocytes is their contribution to the **blood-brain barrier**. The brain and spinal cord are isolated from the circulation — and most toxins or pathogens in the blood — by the blood-brain barrier, a highly selective membrane that separates the circulating blood from the extracellular fluid in the CNS. The barrier allows water, certain gases, glucose, and some other molecules needed by the brain and spinal cord to cross from the blood into the CNS while keeping out potentially harmful substances. Very little can pass through by diffusion. Most substances that cross the wall of a blood vessel into the CNS must do so through an active transport process. While this barrier protects the CNS from exposure to toxic or pathogenic substances and makes the CNS less susceptible to injury, it also keeps out the cells that could protect the brain and spinal cord from disease and damage (such as white blood cells, one of the body’s main lines of defense). Damage to the CNS is thus likely to have more serious consequences. The blood-brain barrier also causes problems with drug delivery to the CNS. Pharmaceutical companies are challenged to design drugs that can cross the blood-brain barrier as well as have an effect on the nervous system. Aside from finding efficacious substances, the means of delivery is also crucial.

Schwann cells and **oligodendrocytes** are the glia that produce the myelin sheath insulating axons. A single entire Schwann cell wraps around and surrounds a portion of only one axon segment in the peripheral nervous system, whereas oligodendrocytes have processes that reach out to multiple axon segments in the central nervous system. Oligodendrocyte (sometimes called just “oligo”), means “cell of a few branches” (oligo = “few”; dendro = “branches”; cyte = “cell”). Each dendritic process extends from the cell body and wraps around an axon many times to insulate it in myelin. One oligodendrocyte will provide the myelin for many axon segments- 30 to 50 (Kalat, 2019), either along the same axon or by branching out to separate axons.

The diagram (Figure 4.1.9) shows several types of central nervous system cells associated with two multipolar neurons. Astrocytes are star-shaped cells with many dendrite-like projections but no axon. They are connected with the multipolar neurons and other cells in the diagram through their dendrite-like projections. Ependymal cells have a teardrop shaped cell body and a long tail that branches several times before connecting with astrocytes and the multipolar neuron. Microglial cells are small cells with rectangular bodies and many dendrite-like projections stemming from their shorter sides. The projections are so extensive that they give the microglial cell a fuzzy appearance. The oligodendrocytes have circular cell bodies with dendrite-like projections. Each projection is connected to a segment of myelin sheath on the axons of the multipolar neurons. In the diagram, the oligodendrocytes are the same color as the myelin sheath segment and are adding layers to the sheath using their projections.

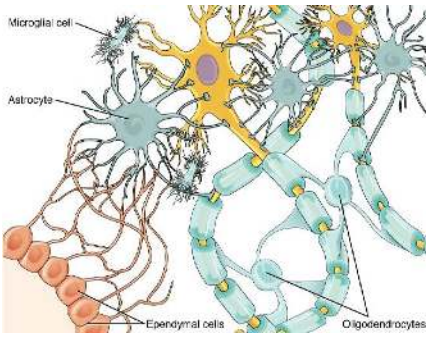


Figure 4.1.9: Glial Cells of the CNS. This diagram shows several types of central nervous system cells (astrocytes, oligodendrocytes, microglia, and ependymal cells) associated with two multipolar neurons.

4.1.4 Summary

The nervous system coordinates all of the body's voluntary and involuntary actions by transmitting electrical and chemical signals to and from different parts of the body. The two main divisions of the nervous system are the central nervous system (CNS, the brain and the spinal cord), and the peripheral nervous system (PNS, all other nervous tissue in the body).

Nervous tissue contains two major cell types, neurons and glial cells. Neurons are the cells responsible for communication through electrical signals. Glial cells are supporting cells, maintaining the environment around the neurons.

The structures that differentiate neurons from other body cells are the extensions of their cell membranes, namely one axon that projects to target cells, and one or more dendrites, which receive information from other neurons across specialized areas called synapses. The axon propagates nerve impulses (action potentials), which are communicated to one or more cells.

Neurons can be classified depending on their structure, function, or other characteristics. One structural classification is based on the number of processes the neuron has- one (unipolar), two (bipolar) or many (multipolar). One functional classification groups neurons into those that participate in sensation (sensory neurons), integration (interneurons) or motor (motor neurons) functions. Some other ways of classifying neurons include what they look like, where they are found, who found them, what they do, or what neurotransmitters they use.

The nervous tissue in the brain and spinal cord consists of gray matter and white matter. Gray matter contains the cell bodies and dendrites of neurons and white matter contains myelinated axons. Typically, neurons cannot divide to form new neurons. Recent animal research indicates that some limited neurogenesis is possible, but the extent to which this applies to adult humans is unknown.

Several types of glial cells are found in the nervous system, including astrocytes, oligodendrocytes, microglia, and ependymal cells in the CNS, and satellite cells and Schwann cells in the PNS. Astrocytes contribute to the blood-brain barrier that protects the brain. Oligodendrocytes and Schwann cells create the myelin that insulates many axons, allowing nerve impulses to travel along the axon very rapidly.

4.1.5 References

Note: These references are specifically those added to the content of this page by Naomi Bahm and do not include citations from the outside sources used. Refer to the text attributions to locate citations for articles from other sources.

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4.1.6 Additional Resources

4.1.7 Attributions

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4.2: Nervous System Structure and Terminology

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Describe anatomical position and describe the location of at least two structures using anatomical direction terms
2. Explain the difference between frontal (/coronal), transverse (/horizontal), and sagittal sectional planes
3. Understand the six common divisions of the nervous system
4. List the four major regions of the central nervous system
5. Explain the structures that protect the brain and spinal cord
6. Describe the components of the ventricular system in the brain and spinal cord

4.2.1 Overview

This module starts with anatomical position, sectional planes and directional terms and continues with the divisions of the nervous system. Some areas and structures of the central nervous system (brain and spinal cord) are then discussed, including the four major regions, the protective coverings, and the ventricular system.

4.2.2 Anatomical Orientation and Directions

4.2.2.1 Anatomical Position

When anatomists or health professionals identify the location of a structure in the human body, they do so in reference to a body in anatomical position. That is, they figure out the location based on the assumption that the body is starting out in anatomical position. Anatomical position for a human is when the human is standing up, facing forward, with arms extended to the sides, and palms facing out, as illustrated by two human models in Figure 4.2.1.



Figure 4.2.1:
Female (left) and male (right) human body in anatomical position seen from anterior (upper) and posterior (lower) views.

When referencing a structure that is on one side of the body or the other, we use the terms “anatomical right” and “anatomical left.” Anatomical right means that the structure is on the side that a person in anatomical position would consider their right-hand side (not necessarily on the right of the viewer) and anatomical left means that the structure is the side that a person in anatomical position would consider their left-hand side (which likewise is not necessarily the left side of the viewer.)

4.2.2.2 Anatomical Planes

To view the interior of a body, we expose the organs and structures that are visible when that body is cut open along one of three commonly used sectional planes. These planes are the different directions a body is cut to reveal different views of its internal structures.

- **Frontal** (or **coronal**) **plane—**A vertical cut that separates the front from the back of the individual/structure.
- **Transverse** (or **horizontal**) **plane—**A horizontal cut that separates the top from the bottom of the individual/structure. (May also be called cross-sections.)
- **Sagittal plane—**A vertical cut that separates the left half from the right half of the individual/structure.

- **Midsagittal** (or **median**) **plane—**A vertical cut down the exact center line of the individual/structure that separates the left half from the right half.
- **Parasagittal plane—**A vertical cut that is off-center that separates the left of the individual/structure from the right in unequal portions. It does not matter whether it is the left side or the right side that is larger, as long as they are not equal.

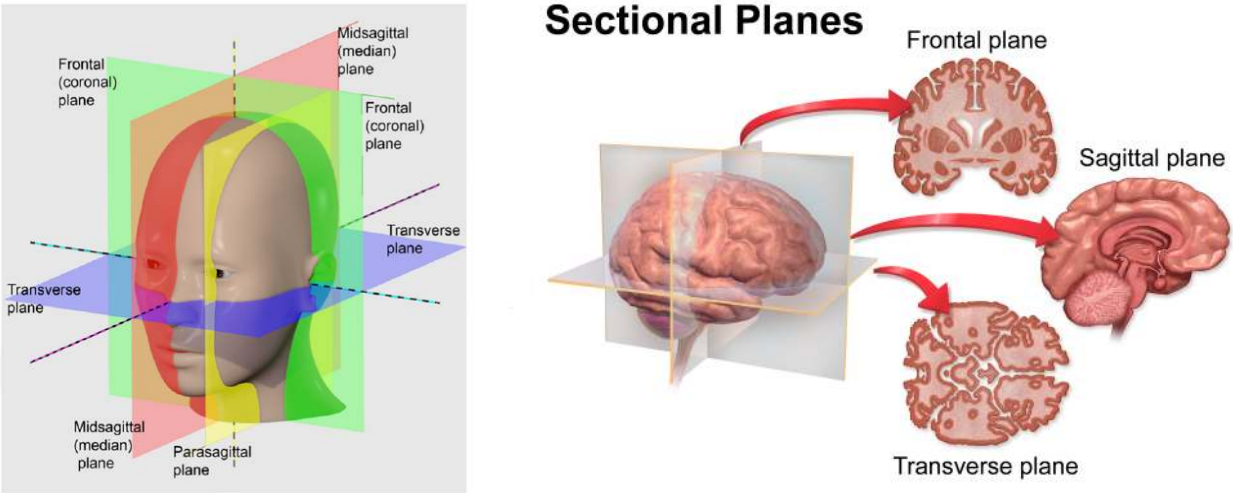


Figure 4.2.2: The different sectional planes used to expose internal structures, and examples of these planes through the human brain.

4.2.2.3 Anatomical Directional Terms

To be able to direct others to specific anatomical structures, or to find structures based on someone else's directions, it is useful to have specific pairs of terms that allow you to orient your search with respect to the location of another known structure. The following pairs of terms are used to make comparisons. Each term is used to orient a first structure or feature with respect to the position of a second structure or feature. All of these terms refer to the body in anatomical position, and are illustrated in Figure 4.2.3.

- **Superior/Inferior**–Equivalent to above (superior) versus below (inferior) when moving along the long axis of the body. A structure that is superior to another is above the second structure. A feature that is inferior to another is below the second feature.
- **Proximal/Distal**–Equivalent to near (proximal) versus far (distal). Usually used to orient the positions of structures and features along the limbs with respect to the trunk of the body. A feature that is proximal to something else is closer to the limb's point of attachment to the trunk. A structure that is distal to something else is farther away from the limb's point of attachment. Although less precise, these terms are occasionally used in the trunk of the body itself to indicate whether something is closer to (proximal) or farther away from (distal) something else.
- **Medial/Lateral**–Equivalent to towards the middle (medial) versus towards the edge (lateral). These terms are used with respect to the midline of the trunk of the body. A structure that is medial to another is closer to the midline of the body's trunk. A feature that is lateral to another is farther away from the midline of the trunk.
- **Anterior/Posterior**–Equivalent to the front (anterior) versus the back (posterior) of the body. A structure that is anterior to another is closer to the front of the body. A feature that is posterior to another is closer to the back of the body.
- **Ventral/Dorsal**–Equivalent to belly-side (ventral) versus back-side (dorsal) of the body. For a human in anatomical position, this pair of terms is largely equivalent to anterior versus posterior. However, for the head and brain, dorsal is on the top (superior) and ventral is on the bottom (inferior), whereas the front of the face would be anterior and the back of the head would be posterior. These terms match four-legged animals in what is considered their anatomical position, where the belly-side is not equivalent to the front of the animal. A structure below the human head that is ventral to another is closer to the belly-side of the body, whereas a feature that is dorsal to another is closer to the back of the body.
- **Superficial/Deep**–Equivalent to closer to the surface (superficial) versus farther from the surface (deep). A structure that is superficial to another is closer to the surface of the body. A feature that is deep to another is farther from the surface of the body.
- (**Cephalic/Caudal**–Equivalent to closer to the head (cephalic) versus closer to the tail (caudal). These terms are more useful for four-legged animals with tails than for upright humans with only a few vestigial tail bones and no visible tail- an area which is

also not at the end of the body like the tail is in four-legged animals.)

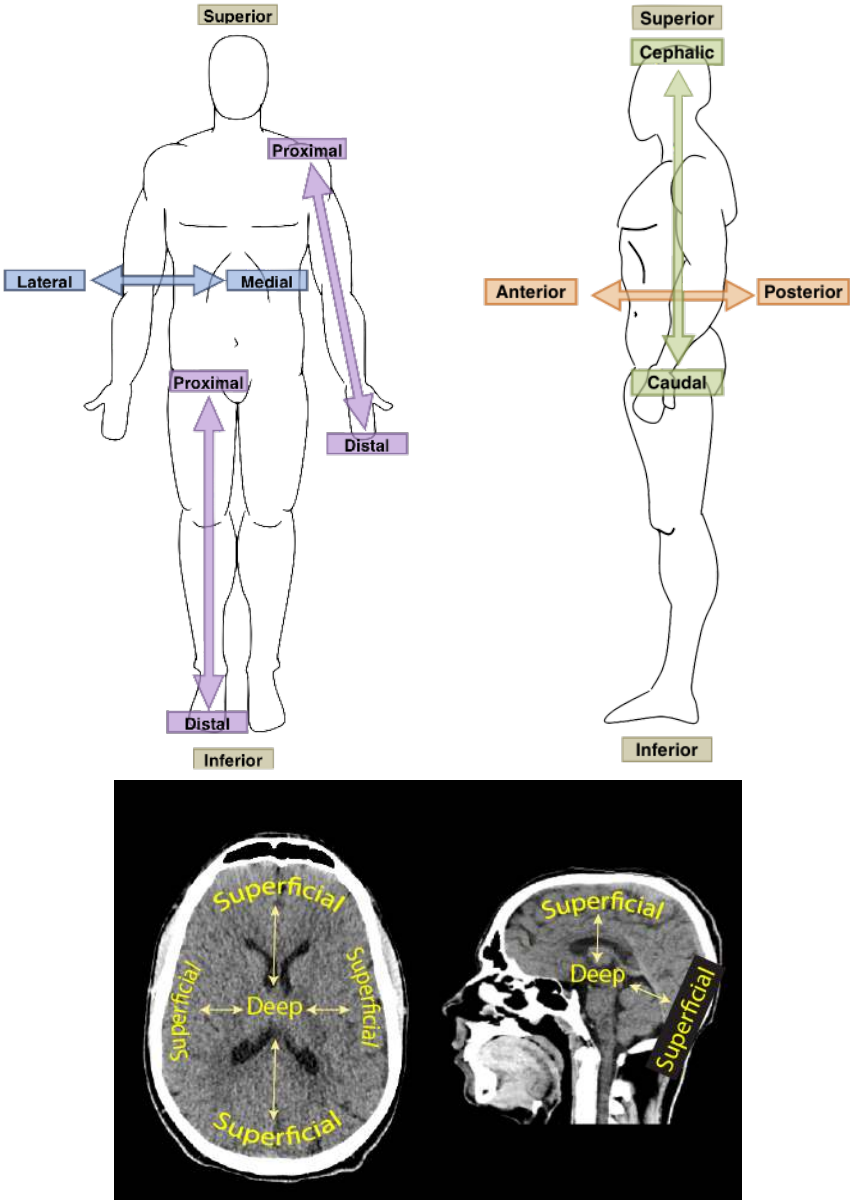


Figure 4.2.3: Pairs of terms providing anatomical direction or orientation, shown on body outlines in the first image, and in a cross-section (left) and sagittal section (right) of the brain in the second image.

4.2.3 Organization of the Nervous System

As you might predict, the human nervous system is very complex. It has multiple divisions, beginning with its two main parts, the **central nervous system** (CNS) and the **peripheral nervous system** (PNS), as shown in Figure 4.2.4. The CNS includes the brain and spinal cord, and the PNS consists of all other nervous tissue in the body- mainly nerves, which are bundles of axons from sensory and motor neurons. The nerves of the PNS connect the CNS to the rest of the body.

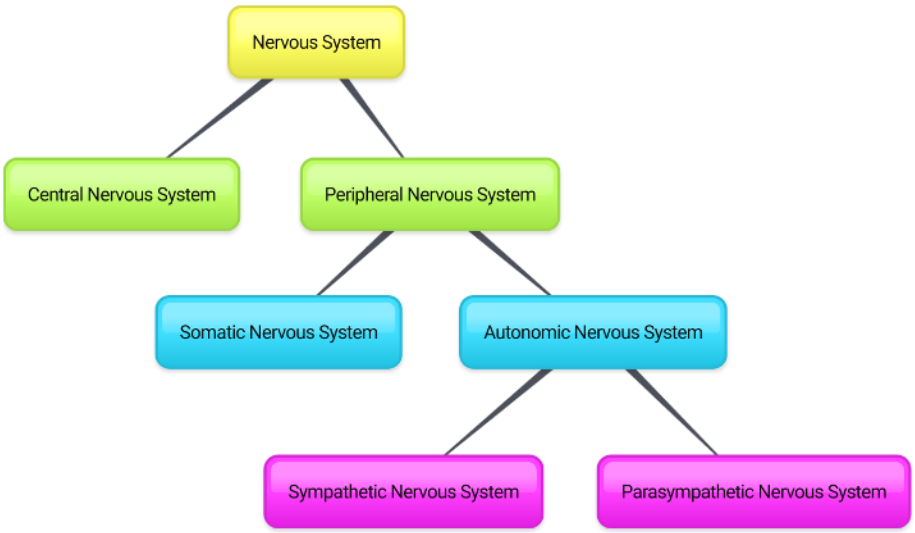


Figure 4.2.4: This concept map illustrates that the nervous system is divided into the central and peripheral systems. The peripheral nervous system is further divided into the somatic and autonomic systems. The autonomic nervous system is further divided into the sympathetic and parasympathetic systems.

The PNS is divided into two major parts, called the autonomic and somatic nervous systems. The **somatic nervous system** (SNS) is responsible for activities that are under voluntary control and awareness, such as turning a steering wheel or feeling water splashing on your hands. The **autonomic nervous system** (ANS) controls involuntary activities, such as digesting a meal or regulating your heartbeat. The autonomic nervous system also has two divisions: the sympathetic and parasympathetic nervous systems. The **sympathetic nervous system** controls the "fight-or-flight" response during emergencies, and the **parasympathetic nervous system** controls the routine “housekeeping” functions of the body (sometimes referred to as the "rest and digest" division). Generally speaking, your body is usually activating a balance of sympathetic and parasympathetic functions.

The CNS and the sympathetic and parasympathetic branches of the ANS (itself a division of the PNS) are described in greater detail in other modules of this chapter. The other division of the PNS, the SNS, is composed largely of sensory receptors and their connections (covered in the sensory system chapter) and structures related to voluntary motor control (addressed in the movement chapter).

4.2.4 Central Nervous System Regions

Some commonly used terms referring to regions in the central nervous system (such as forebrain, midbrain, and hindbrain) derive from embryonic development and are discussed separately (see the module on development of the nervous system).

In its fully formed state, the CNS may be described in terms of four major regions: the cerebrum, the brainstem (comprised of the diencephalon, the midbrain, the pons, and the medulla- note that some definitions separate the diencephalon out as an additional separate region- Basinger and Hogg, 2021), the cerebellum, and the spinal cord. These regions are colored in on an MRI of an adult in Figure 4.2.5.

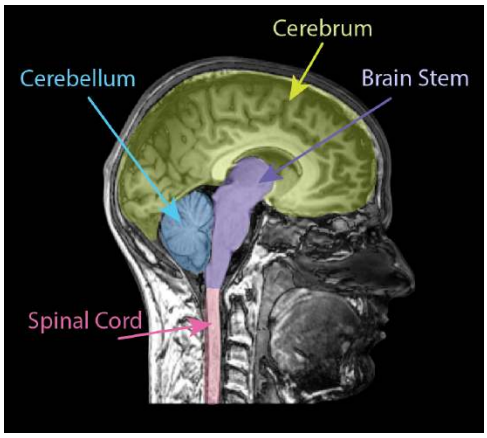


Figure 4.2.5: Regions of the adult central nervous system: The cerebrum, cerebellum, brainstem (including the diencephalon) and spinal cord.

4.2.5 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 4.2.6 shows a segment of the spinal cord within its protective vertebra.

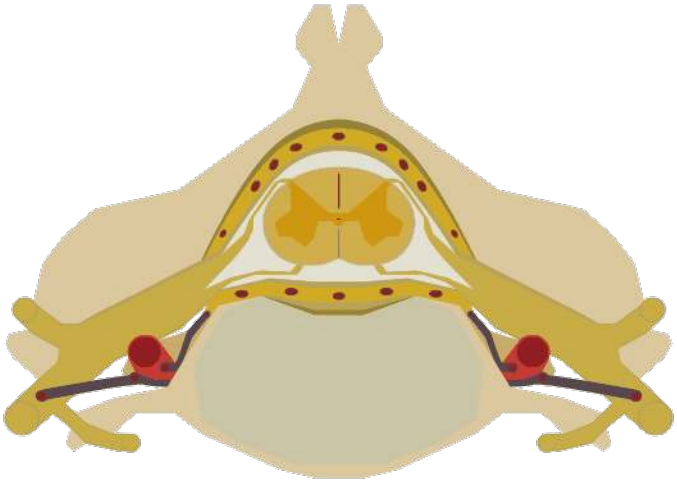


Figure 4.2.6: Cross-section of a spinal cord segment shown encased in its vertebra. The back of the person is at the top of the image.

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 4.2.7 shows the three layers of meninges covering the spinal cord and Figure 4.2.8 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.

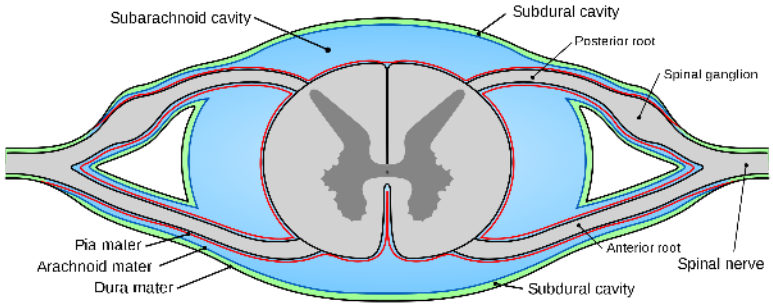


Figure 4.2.7: Cross-section of a spinal cord segment with the meninges and other structures labeled.

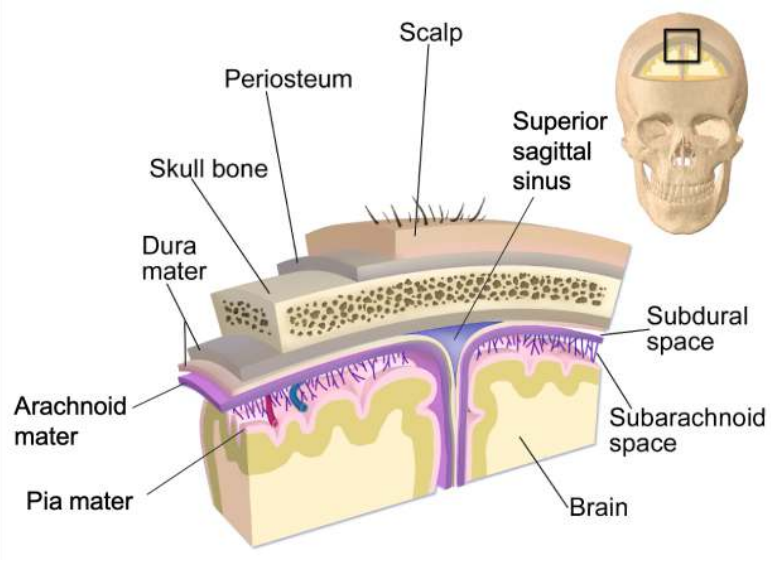


Figure 4.2.8: Protective structures of the brain. Superficially, the skin of the scalp and components of the skull bone create the first layer of protection. Deep to these layers, the meninges (the dura mater, arachnoid mater and pia mater) cover and partition the brain.

4.2.6 Ventricular System

There are four **ventricles** within the brain, all of which developed from the original hollow space within the neural tube, the **central canal**. The ventricles are lined with **ependymal cells** (a type of glia) that produce cerebrospinal fluid (CSF). The first two ventricles are named the **lateral ventricles** and are deep within the brain. The two lateral ventricles are shaped like a letter "C" and are located in the left and right hemispheres. (They were originally referred to as the first and second ventricles.) These ventricles are connected to the **third ventricle** by two openings called the **interventricular foramina** (plural; "foramen" is the singular term). The third ventricle opens into a canal called the **cerebral aqueduct** that passes through the midbrain and connects the third ventricle to the **fourth ventricle**. The fourth ventricle is the space between the cerebellum and the pons and upper medulla. From the fourth ventricle, CSF continues down the central canal of the spinal cord. Figure 4.2.9 illustrates the ventricles, from both a lateral and anterior viewpoint. CSF circulates through the brain and the spinal cord within these structures.

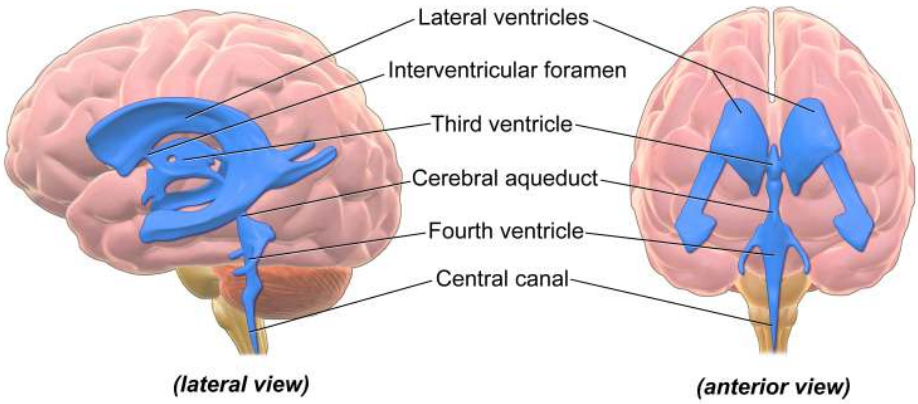


Figure 4.2.9: Ventricles. Deep within the brain are the lateral ventricles, which are connected to the third ventricle by two openings called interventricular foramina. The third ventricle opens into a canal called the cerebral aqueduct which connects to the fourth ventricle. The fourth ventricle is connected to the central canal of the spinal cord.

4.2.7 Summary

Anatomical position for humans is standing up, facing forward, with arms extended to the sides, and palms facing out. Anatomical planes are the different directions a body is cut to reveal different views of its internal structures, which include frontal (coronal) planes, separating the front from the back, transverse (horizontal) planes, separating the top from the bottom, and sagittal planes, separating the left and right halves. A midsagittal (or median) plane is exactly on the center line and a parasagittal plane divides the left and right halves unevenly. Pairs of anatomical directional terms are used to make comparisons between one structure with respect to the position of a second structure. These include superior (above) versus inferior(below), proximal (near) versus distal (far), medial (towards the middle) versus lateral (towards the edge, anterior (front) versus posterior (back), ventral (belly-side) versus dorsal (back-side), and superficial (closer to the surface) versus deep (farther from the surface).

The organization of the nervous system includes six divisions. The CNS includes the brain and spinal cord, and the PNS consists of all other nervous tissue in the body. The nerves of the PNS connect the CNS to the rest of the body. The PNS is further divided into the autonomic and somatic nervous systems. The somatic nervous system (SNS) is responsible for activities that are under voluntary control and awareness. The autonomic nervous system (ANS) controls involuntary activities. The autonomic nervous system also has two divisions: the sympathetic and parasympathetic nervous systems. The sympathetic nervous system controls response during emergencies, and the parasympathetic nervous system controls the routine functions of the body.

The adult CNS is separated into four major regions: the cerebrum, the brainstem, the cerebellum, and the spinal cord. Anatomical structures help to protect and isolate the CNS, including the skull (surrounding the brain) and the vertebral column (surrounding the spinal cord). Layers of connective tissue called meninges support and stabilize the brain and spinal cord, as well as partition the brain into specific regions. The outer layer is the dura mater, the middle layer is the arachnoid mater and the inner layer is the pia mater.

The ventricular system is composed of four fluid-filled ventricles in the brain (two lateral ventricles, the third ventricle and the fourth ventricle) which connect to each other (via the interventricular foramina and the cerebral aqueduct) and the central canal of the spinal cord. Cerebrospinal fluid (CSF) circulates through the brain and the spinal cord within these structures.

4.2.8 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/

4.2.9 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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4.3: Nervous System Development

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Explain how the neural tube forms
2. Describe the growth and differentiation of the anterior neural tube into primary and secondary vesicles
3. Understand the mechanisms of postnatal brain development
4. Describe the development of the posterior neural tube into the adult spinal cord
5. Identify at least four stages of neuron development

4.3.1 Overview

This module starts with the value of an embryologic perspective, and then discusses the formation of the neural tube, embryonic brain development (the process of the anterior neural tube differentiates into primary and secondary vesicles), postnatal brain development, spinal cord development, and neuron development.

4.3.2 An Embryologic Perspective

The brain is a complex organ composed of gray and white matter, which can be hard to distinguish. Starting from an embryologic perspective allows you to understand more easily how the parts relate to each other. The embryonic nervous system begins as a very simple structure—essentially a plate of tissue, which then gets increasingly complex. Looking at the development of the nervous system through a few early snapshots makes it easier to understand the whole complex system. Many structures that appear to be adjacent in the adult brain are not connected, and the connections that exist may seem arbitrary. But there is an underlying order to the system that comes from how different parts develop. By following the developmental pattern, it is possible to distinguish the major regions of the nervous system.

4.3.3 Neural Tube

To begin, a sperm cell and an egg cell fuse to become a fertilized egg. The fertilized egg cell, or zygote, starts dividing to generate the cells that make up an entire organism. Sixteen days after fertilization, the developing embryo's cells belong to one of three germ layers that give rise to the different tissues in the body (Figure 4.3.1). 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 integumentary system (the skin) and the nervous system. It is probably not difficult 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?

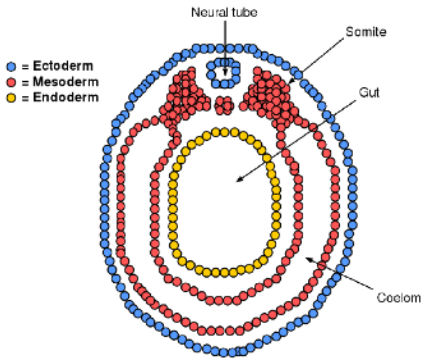


Figure 4.3.1: Cross section of a vertebrate embryo in the neurula stage. This stage is characterized by development of the nervous system through the formation of the neural tube, shown as a small circle of ectoderm tissue at the top of the image, just inside the large outer circle of ectoderm tissue. The neural tube later develops into the brain and the spinal cord. The middle horseshoe-shaped loop of two layers of mesoderm tissue has clumps of cells at the upper closed ends representing somites. The somites become the vertebral column and the skeletal muscles. The coelom is the open space inside the two layers of mesoderm forming the loop- internal organs develop here. The innermost circle is endoderm tissue; the gut is enclosed in the center.

As the embryo develops, a portion of the ectoderm differentiates into tissue that will become the nervous system. Molecular signals induce cells in this region to form a **neural plate**. The cells then begin to change shape, causing the tissue to buckle and fold inward (Figure 4.3.2). A **neural groove** forms, visible as a line along the dorsal surface of the embryo. The ridge-like edge on either side of the neural groove is referred to as the **neural fold**. As the neural folds come together and converge, the underlying structure forms into a tube called the **neural tube,** located just beneath the remaining ectoderm (which will form the epidermis).

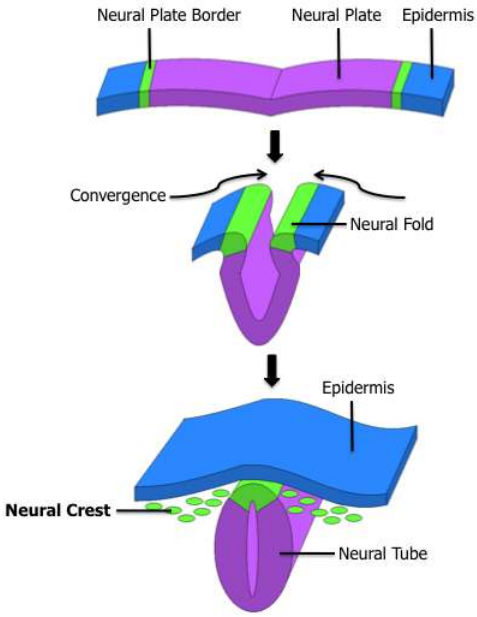


Figure 4.3.2: Formation of the Neural Tube. The ectoderm layer forms the epidermis and the nervous system. The neural plate (with a border on either side separating that tissue from tissue that forms the epidermis) begins to fold inward to form the neural groove (visible in the middle drawing but not labeled), with the neural plate borders becoming the neural folds on either side. As the two sides of the neural groove converge, the neural folds fuse together and form the neural tube, which lies beneath the epidermis tissue (similarly merged to form a continuous outer plate). The anterior end of the neural tube will develop into the brain, and the posterior portion will become the spinal cord. The neural crest (formed from part of the neural folds) sits laterally to the neural tube and develops into structures in the peripheral nervous system.

At this point, the early nervous system is a simple, hollow tube. It runs from the anterior end of the embryo to the posterior end. Beginning at 25 days, the anterior end develops into the brain, and the posterior portion becomes the spinal cord. This is the most basic arrangement of tissue in the nervous system, and by the fourth week of development it gives rise to the more complex structures.

4.3.4 Brain Development

4.3.4.1 Embryonic Brain Development

4.3.4.1.1 Overview

The vertebrate brain has three major regions based on embryonic development: the forebrain (including the cerebrum, thalamus, hypothalamus, and limbic system structures), the midbrain, and the hindbrain (including the medulla, pons, and cerebellum). Figure 4.3.3 shows the embryologic vesicles (originating from bulges in the neural tube, explained in greater detail below) that contribute to these regions. The prosencephalon (forebrain) is composed of the telencephalon and the diencephalon, the mesencephalon is the midbrain, and the rhombencephalon (hindbrain) is composed of the metencephalon and the myelencephalon. The spinal cord extends below the hindbrain.

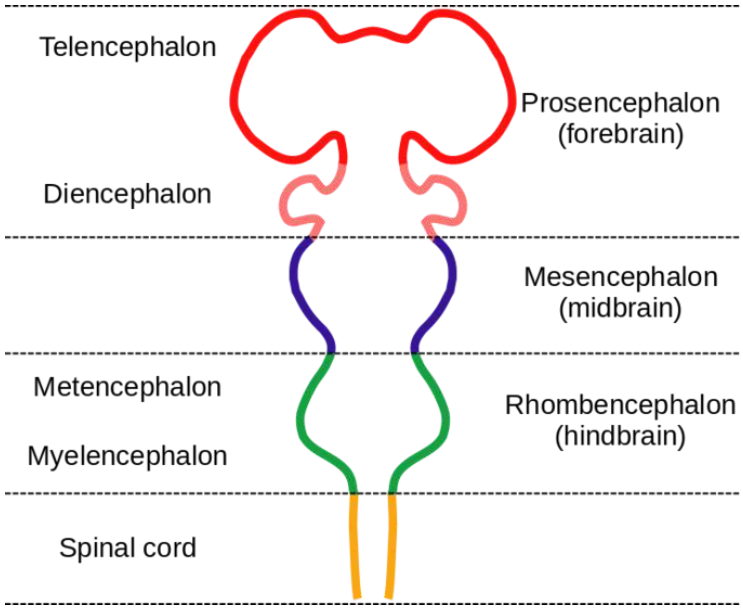


Figure 4.3.3: Terms for the regions of the central nervous system during embryonic development. The anterior end of the neural tube forms vesicles that become the brain. The left side of the figure lists the five secondary vesicles, which differentiate from the three primary vesicles listed on the right side. The telencephalon and diencephalon differentiate from the prosencephalon (forebrain), The mesencephalon (midbrain) is fully differentiated at the primary vesicle stage (and thus does not form any additional secondary vesicle divisions). The metencephalon and myelencephalon differentiate from the rhombencephalon (hindbrain). The posterior end of the neural tube forms the spinal cord.

The diencephalon is the one region of the adult brain that retains its (Greek) embryonic name in common usage. This is because there is no better term for it (dia = “through”). The diencephalon is between the cerebrum and the rest of the nervous system and can be described as the region through which all projections have to pass. All vertebrate brains have these regions, but in humans the anterior forebrain is enlarged to the extent that the diencephalon (posterior forebrain), the midbrain, and even part of the hindbrain is hidden from view by the cerebrum.

Another aspect of the adult CNS structures that relates to embryonic development is the cerebral ventricles—open spaces within the CNS where cerebrospinal fluid circulates. They are the remnant of the hollow center of the neural tube. The four ventricles and the tubular spaces associated with them can be linked back to the hollow center of the embryonic brain.

4.3.4.1.2 Primary Vesicles

When the embryo is three to four weeks of age, the anterior end of the neural tube starts to develop into the brain. It undergoes a couple of enlargements; the result is the production of sac-like vesicles. Similar to a child’s balloon animal, the long, straight neural tube begins to take on a new shape. Three vesicles form at the first stage, which are called **primary vesicles**. These vesicles are given names that are based on Greek words, the main root word being *enkephalon*, which means “brain” (en- = “inside”; kephalon = “head”). The prefix to each generally corresponds to its position along the length of the developing nervous system.

The **prosencephalon** (pros- = “in front”) is the forward-most vesicle, and the term can be loosely translated to mean **forebrain**. The **mesencephalon** (mes- = “middle”) is the next vesicle, which can be called the **midbrain**. The third vesicle at this stage is the **rhombencephalon**. The first part of this word is also the root of the word rhombus, which is a geometrical figure with four sides of equal length (a square is a rhombus with 90° angles). Whereas prosencephalon and mesencephalon translate into the English words forebrain and midbrain, there is not a word for “four-sided-figure-brain.” Instead, the third vesicle is called the **hindbrain**. One way of thinking about how the brain is arranged is to use these three regions—forebrain, midbrain, and hindbrain—which are based on the primary vesicle stage of development (Figure 4.3.4a).

4.3.4.1.3 Secondary Vesicles

The brain continues to develop in a five-week old embryo, and the vesicles differentiate further (Figure 4.3.4b). The three primary vesicles become five **secondary vesicles**. The prosencephalon enlarges into two new vesicles called the **telencephalon** and the **diencephalon**. The telecephalon will become the cerebrum. The diencephalon gives rise to several adult structures; two that will be important are the thalamus and the hypothalamus.

The mesencephalon does not differentiate any further, but remains an established region of the brain. The rest of the brain develops around it and constitutes a large percentage of the mass of the brain. Dividing the brain into forebrain, midbrain, and hindbrain is useful in considering its developmental pattern, but the midbrain is a relatively small proportion of the entire brain.

The rhombencephalon develops into the **metencephalon** and **myelencephalon**. The metencephalon corresponds to the adult structure known as the pons and also gives rise to the cerebellum. The cerebellum (from the Latin meaning “little brain”) accounts for about 10 percent of the mass of the brain and is an important structure in itself. The most significant connection between the cerebellum and the rest of the brain is at the pons, because the pons and cerebellum develop out of the same vesicle. The myelencephalon corresponds to the adult structure known as the medulla (or medulla oblongata).

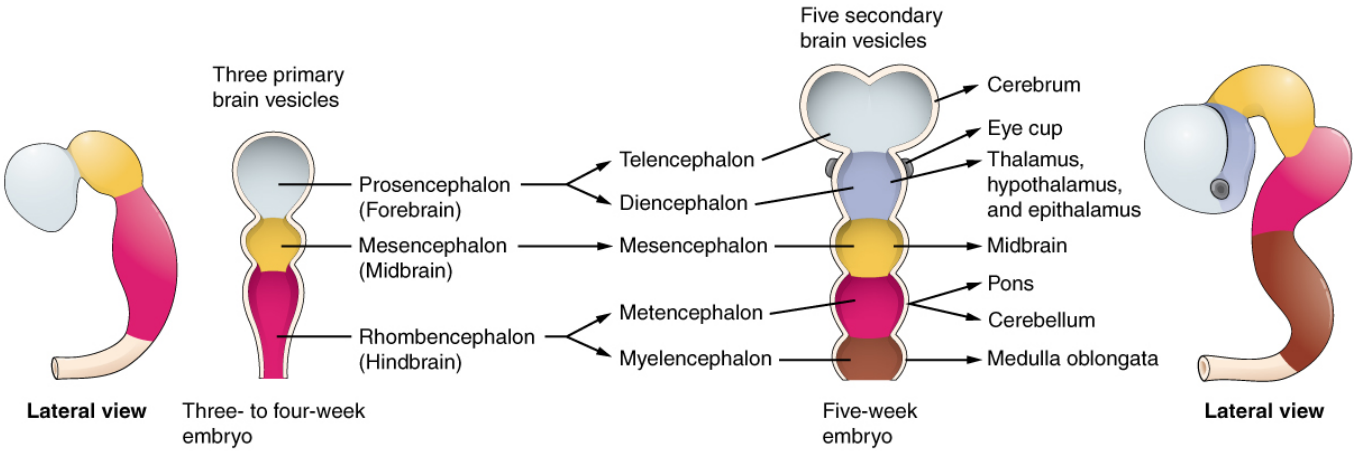


Figure 4.3.4: Primary and Secondary Vesicle Stages of Development. The embryonic brain develops complexity through enlargements of the neural tube called vesicles. In part a, the primary vesicle stage which happens around 3 to 4 weeks of embryonic development shows three vesicles: the prosencephalon (forebrain) is superior and anterior; the mesencephalon (midbrain) is inferior to the prosencephalon; and the rhombencephalon (hindbrain) is the most inferior vesicle. In part b, the secondary vesicle stage which happens at 5 weeks of embryonic development shows five regions. From anterior and superior to posterior and inferior, these regions (and structures that form from them) are: telencephalon (cerebrum), diencephalon (eye cup; thalamus, hypothalamus and epithalamus), mesencephalon (midbrain), metencephalon (pons; cerebellum), and myelencephalon (medulla oblongata). Lateral views of each stage are also depicted.

4.3.4.2 Postnatal Brain Development

As summarized by Stiles & Jernigan (2010, p. 328), "Human brain development is a protracted process that begins in the third gestational week ... and extends at least through late adolescence, arguably throughout the lifespan". During the preschool years (roughly age three to five years), the brain quadruples in size, attaining about 90% of adult volume by age six (Stiles & Jernigan, 2010). Figure 4.3.5 illustrates the growth between a one-month old baby and a six-year-old child, in both brain size and neuron complexity.

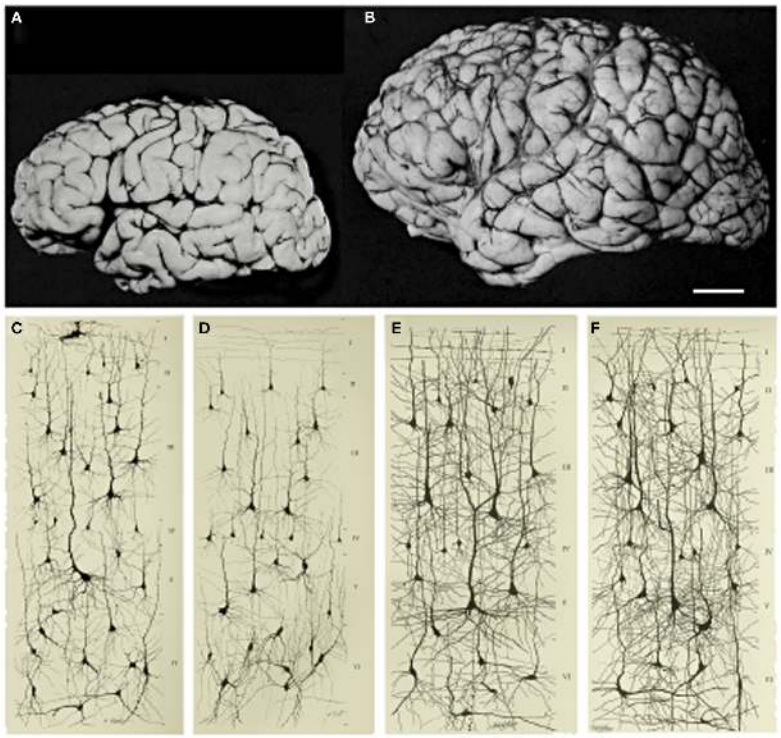


Figure 4.3.5: Increase in brain size and the maturation of cortical circuits. The maturation of mental processes and motor skills is associated with an approximately four-fold enlargement in brain size. Photographs of the brains of a A. 1-month and B. 6-year-old child. This size increase is accompanied by a dramatic development in the complexity of the neuronal processes, which in turn is influenced by the genetic background and the surroundings. This increase in the complexity is clearly evident in the drawings of Golgi-stained cortical neurons from the cerebral cortex of a 1-month-old child (C. showing the cortical area known as “pars triangularis of gyrus frontalis inferior”; D. showing “orbital gyrus”) and a 6-year-old child (E. “pars triangularis of gyrus frontalis inferior”; F. “orbital gyrus”). Scale bar for A and B: 2 cm.

Changes in the structure of both gray matter and white matter components of the brain continue through childhood and adolescence, accompanied by changes in both functional organization and behavior. Young children, particularly infants, have much higher connectivity between neurons in the brain than adults. As development continues, these connections become more specialized (through pruning of less efficient pathways, as determined by experience- see neuron development below). Correspondingly, "plasticity and capacity for adaptation ... is the hallmark of early brain development" (Stiles & Jernigan, 2010, p. 328). Plasticity (the ability of the brain to change based on experience) continues throughout life, but slows down with age. It is still possible to "teach an old dog new tricks"- it just takes longer!

Although the human brain increases five-fold in volume between infancy and adulthood, there is little change in the number of neurons present. Brain growth occurs as a result of axon myelination and increased connections between neurons (Budday et al., 2015).

4.3.5 Spinal Cord Development

While the brain is developing from the anterior neural tube, the spinal cord is developing from the posterior neural tube. However, its structure does not differ from the basic layout of the neural tube. It is a long, straight cord with a small, hollow space down the center. The neural tube is defined in terms of its anterior versus posterior portions, but it also has a dorsal–ventral dimension. As the neural tube separates from the rest of the ectoderm, the side closest to the surface is dorsal (toward the back), and the deeper side is ventral (toward the belly).

As the spinal cord develops, the cells making up the wall of the neural tube proliferate and differentiate into the neurons and glia of the spinal cord. The dorsal tissues will be associated with sensory functions, and the ventral tissues will be associated with motor functions

Development of the Nervous System: Spina Bifida

Early formation of the nervous system depends on the formation of the neural tube. A groove forms along the dorsal surface of the embryo, which becomes deeper until its edges meet and close off to form the tube. If this fails to happen in the posterior region where the spinal cord forms, a developmental defect called spina bifida occurs. The closing of the neural tube is important for more than just the proper formation of the nervous system. The surrounding tissues are dependent on the correct development of the tube. The connective tissues surrounding the CNS can be involved as well.

There are three classes of this disorder: occulta, meningocele, and myelomeningocele (Figure 4.3.6). The first type, spina bifida occulta, is the mildest because the vertebral bones do not fully surround the spinal cord, but the spinal cord itself is not affected. No functional differences may be noticed, which is what the word occulta means; it is hidden spina bifida. The other two types both involve the formation of a cyst—a fluid-filled sac of the connective tissues that cover the spinal cord called the meninges. “Meningocele” means that the meninges protrude through the spinal column but nerves may not be involved and few symptoms are present, though complications may arise later in life. “Myelomeningocele” means that the meninges protrude and spinal nerves are involved, and therefore severe neurological symptoms can be present.

Often surgery to close the opening or to remove the cyst is necessary. The earlier that surgery can be performed, the better the chances of controlling or limiting further damage or infection at the opening. For many children with meningocele, surgery will alleviate the pain, although they may experience some functional loss. Because the myelomeningocele form of spina bifida involves more extensive damage to the nervous tissue, neurological damage may persist, but symptoms can often be handled. Complications of the spinal cord may present later in life, but overall life expectancy is not reduced.

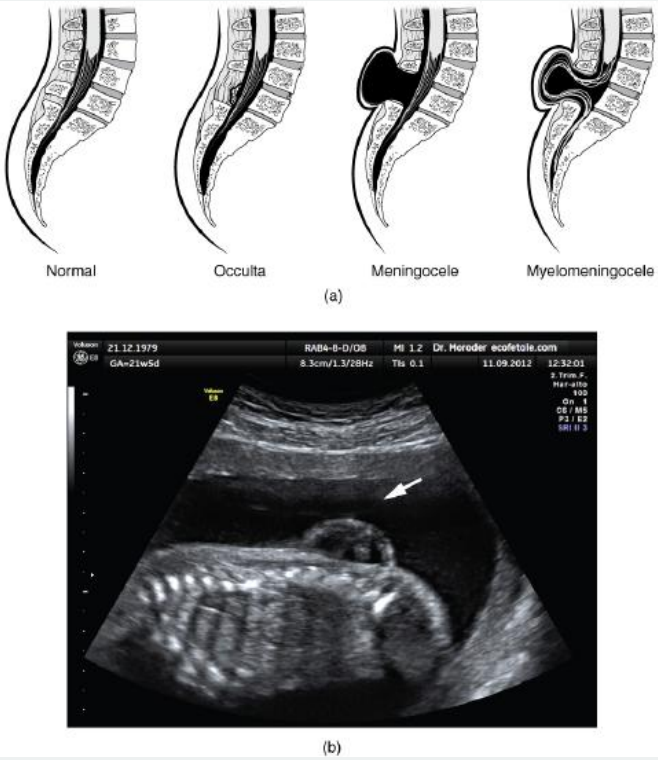


Figure 4.3.6: Spina Bifida. Spina bifida is a birth defect of the spinal cord caused when the neural tube does not completely close, but the rest of development continues. The result is the emergence of meninges and neural tissue through the vertebral column. Part (a) shows the difference between a normal spinal cord, and the three types of spina bifida: occulta, meningocele and myelomeningocele. In part (b), an ultrasound taken at 21 weeks shows a fetal myelomeningocele.

4.3.6 Neuron Development

Neuron development is typically divided into several stages, although the names of the stages may vary somewhat from one source to another. **Neuron production** (also called proliferation) is the first stage, when **neurogenesis**, the production of new neurons

from stem cells, occurs (Kalat, 2019). In humans, this begins around the fifth week of gestation (Budday et al., 2015), or on the 42nd day after conception (Stiles & Jernigan, 2010). It is mostly finished by 28 weeks gestational age, and if premature birth occurs before 28 weeks, further neurogenesis is inhibited (Kalat, 2019). Figure 4.3.7 shows a photograph of neurons developing in an embryo.

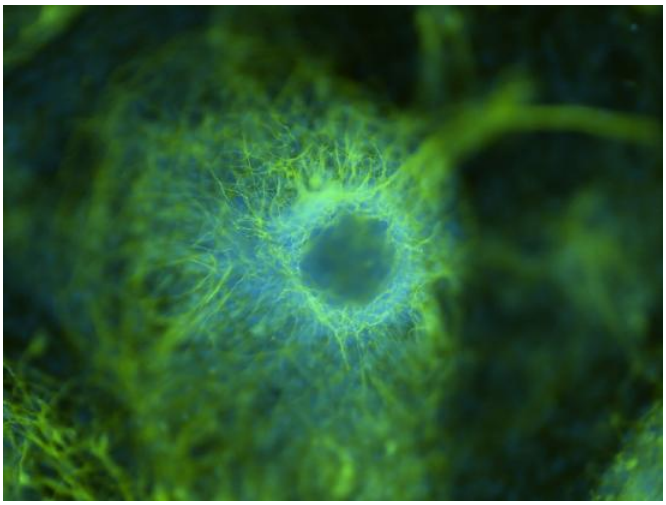


Figure 4.3.7: Neuron cluster. Human embryonic tissue can be differentiated into many different cell types, including neurons. BIII-tubulin (green) is used as a marker for immature neurons. DAPI (blue) staining identifies the cells' nuclei.

As the neurons are forming, **migration** (movement to their final destinations) starts, following chemical signals (Kalat, 2019). The six-layered mature structure of the cerebral cortex is formed via the orderly migration of neurons (Stiles & Jernigan, 2010). **Differentiation** is the process of a neuron achieving the features that make it distinct from other body cells- forming an axon and one or more dendrites (Kalat, 2019). The term differentiation also encompasses the formation of different types of neurons (Stiles & Jernigan, 2010), or gaining the features that distinguish one type of neuron from another.

Synaptogenesis is the creation of connections between neurons by forming synapses (Kalat, 2019). It begins mid-gestation, and as connectivity progresses, axons form and reach out to numerous targets "until each neuron connects with thousands of other neurons" by birth (Budday et al., 2015, p. 5). Synaptogenesis "continues throughout life, as neurons form new synapses and discard old ones" (Kalat, 2019, p. 118).

Myelination is the process of axons becoming insulated with a layer of myelin, which speeds up the transmission of nerve impulses. Myelination starts in the spinal cord and then progresses from the hindbrain to the midbrain and finally the forebrain. This occurs gradually over decades and may also be implicated in learning new motor skills (Kalay, 2019).

Synaptic **pruning** is the process of removing synapses that are not useful or efficient, based on the specific experiences of the individual. Pruning starts around birth and is completed during adolescence, by the time sexual maturity is attained. It is thought that learning corresponds with pruning (Budday et al., 2015).

An estimated timeline for these stages of neuron development is shown in Figure 4.3.8.

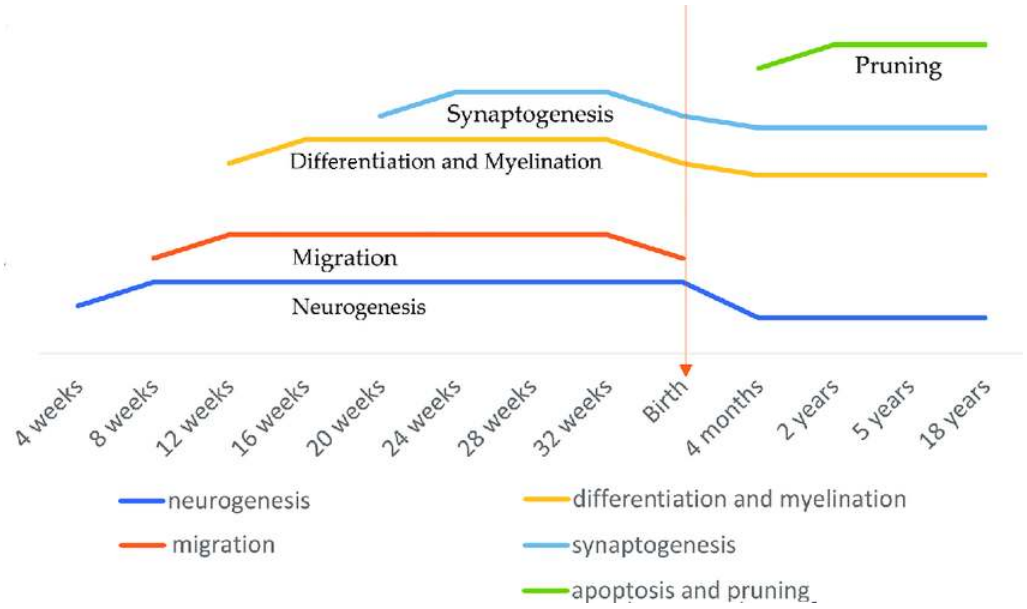


Figure 4.3.8: Timeline for stages of neuron development. GA= gestational age. The timeline ends with age 18 years, but some of these processes may continue throughout life. Neurogenesis starts at four weeks GA and decreases sharply after birth, to almost nothing by four months of age and beyond. Migration starts at eight weeks GA, increases through 12 weeks GA, stays steady through 32 weeks GA, and then decreases, ending at birth. Differentiation and Myelination start at 12 weeks GA, increase through 16 weeks GA, stay steady through 32 weeks GA, decrease through four months of age, and then stay steady through 18 years of age. Synaptogenesis starts at 20 weeks GA, increases through 24 weeks GA, stays steady through 32 weeks GA, decreases through four months of age, and then stays steady through 18 years of age. Pruning starts at four months of age, increases through two years of age, and then stays steady through 18 years of age.

4.3.7 Summary

The development of the nervous system starts early in embryonic development. The outer layer of the embryo, the ectoderm, gives rise to the skin and the nervous system. A specialized region of this layer becomes a groove that folds in and becomes the neural tube beneath the dorsal surface of the embryo. The anterior end of the neural tube develops into the brain, and the posterior region becomes the spinal cord.

The brain develops from this early tube structure and gives rise to specific regions of the adult brain. As the neural tube grows and differentiates, it enlarges into three vesicles that correspond to the forebrain, midbrain, and hindbrain regions of the adult brain. Later in development, two of these three vesicles differentiate further, resulting in five vesicles. Those five vesicles can be aligned with the four major regions of the adult brain. The cerebrum is formed directly from the telencephalon. The diencephalon is the only region that keeps its embryonic name, and includes the thalamus and the hypothalamus. The mesencephalon becomes the midbrain, the metencephalon forms the pons and the cerebellum, and the myelencephalon becomes the medulla.

Brain development is a lifelong process, and the brain retains plasticity (the ability to change based on experience) throughout life. The increase in brain size during postnatal brain development occurs largely due to the myelination of axons and increased connections between neurons.

The spinal cord develops from the remainder of the neural tube and retains the tube structure, with the nervous tissue thickening and the hollow center becoming a very small central canal through the cord. The rest of the hollow center of the neural tube corresponds to open spaces within the brain called the ventricles, where cerebrospinal fluid is found.

Several stages of neuron development have been identified- neuron production (or proliferation), migration, differentiation, synaptogenesis (increased connectivity), myelination, and synaptic pruning.

4.3.8 References

Budday, S., Steinmann, P., & Kuhl, E. (2015). Physical biology of human brain development. *Frontiers in Cellular Neuroscience 9*, 1-17. DOI=10.3389/fncel.2015.00257

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4.4: The Central Nervous System

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Name the structures that comprise the central nervous system
2. Identify the three main parts of the brain
3. Describe the lobes of the cerebrum and their locations
4. Identify the components of the diencephalon and describe their functions
5. Identify the regions of the brainstem and describe their functions
6. Identify the major structures of the limbic system and describe their functions
7. Describe the structure and function of the cerebellum
8. Describe the structure and function of the spinal cord

4.4.1 Overview

This module defines the central nervous system (the brain and spinal cord) and goes into detail on its components. Structures and functions of the brain are discussed, including the cerebrum: hemispheres and lateralization, the cerebral cortex, the frontal, parietal, temporal and occipital lobes; the brainstem: diencephalon, midbrain, pons and medulla; the limbic system; and the cerebellum; as well as structures, function and injury of the spinal cord.

Homunculus



Figure 4.4.1: Front and rear views of a sensory homunculus model.

Figure 4.4.1 is a very odd-looking model called a homunculus. This model shows the relative representation of different parts of the body in the primary sensory cortex, an area in the parietal lobe of the brain. As you can see, larger areas of the brain in this region are associated with the hands, face, and tongue than the arms, torso, legs and feet. Larger areas of representation in the brain result in greater sensitivity in those body areas. Given the importance of speech, manual dexterity, and face-to-face social interactions in human beings, it is not surprising that relatively large areas of the brain are needed to relay sensation from these body parts. (There is a similarly odd-looking representation of voluntary motor functions called the motor homunculus that is located in the primary motor cortex, an area in the frontal lobe of the brain.) The brain is the most complex organ in the human body and is part of the central nervous system.

4.4.2 What Is the Central Nervous System?

The central nervous system (CNS) is the part of the nervous system that includes the brain and spinal cord. Figure 4.4.2 shows the central nervous system both as it appears in the body dissected from the backside and also completely removed from the body. The central nervous sytem and the peripheral nervous system (PNS, the other main division, which is addressed in a separate module), work together to control virtually all body functions.

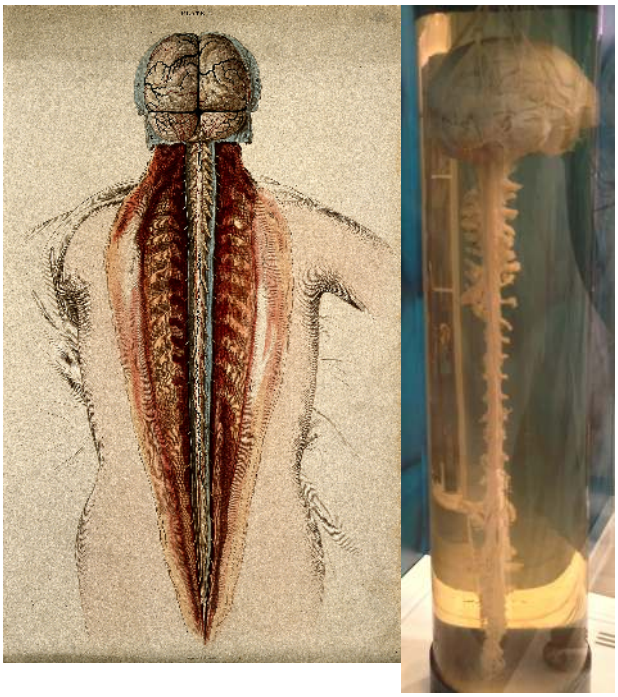


Figure 4.4.2: The human central nervous system. A back view dissection of the brain and spinal cord (colored line engraving by W.H. Lizars, circa 1827) and a preserved brain and spinal cord.

4.4.3 The Brain

The **brain** is the control center not only of the rest of the nervous system but of the entire organism. The adult brain makes up only about two percent of the body's weight, but it uses about 20 percent of the body's total energy. The brain contains an estimated 86 billion neurons (Lent et al., 2012), and each neuron has thousands of synaptic connections to other neurons. It is estimated that the brain also has about the same number of glial cells as neurons. No wonder the brain uses so much energy! In addition, the brain uses mostly glucose for energy. As a result, if the brain is deprived of glucose, it can lead to unconsciousness.

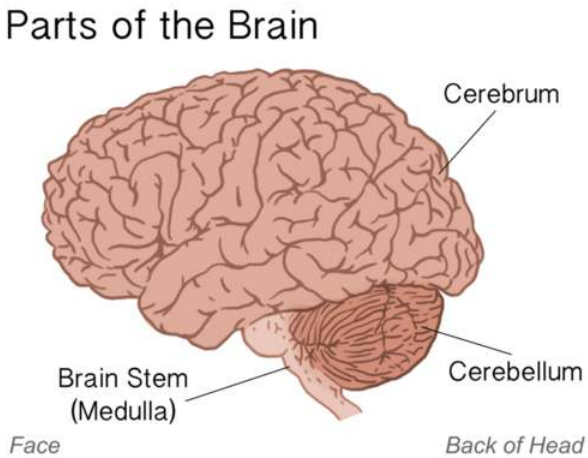


Figure 4.4.3: The major parts of the brain are the cerebrum, cerebellum, and brainstem. The medulla is part of the brainstem.

The brain controls such mental processes as reasoning, imagination, memory, and language. It also interprets information from the senses and commands the body's responses. It controls basic physiological processes such as breathing and heartbeat as well as voluntary activities such as walking and writing. The brain has three major parts: the cerebrum, cerebellum, and brainstem (Figure 4.4.3). The figure shows the brain from the left side of the head. It shows how the brain would appear if the skull and meninges were removed. The brainstem links to the spinal cord via the medulla. The cerebellum is a small structure at the back of the brain. The largest part of the brain is the cerebrum.

4.4.4 Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the **cerebrum**. It controls conscious, intellectual functions, such as reasoning, language, memory, sight, touch, and hearing. When you read a book, play a video game, or recognize a classmate, you are using your cerebrum. The wrinkled portion is the **cerebral cortex** (see below), and the rest of the structure is deep to that outer covering.

4.4.4.1 Hemispheres and Lateralization of the Cerebrum

There is a large separation between the two sides of the cerebrum called the **longitudinal fissure**. It separates the cerebrum into two distinct halves, the right and left **cerebral hemispheres**. The two hemispheres are connected by a thick bundle of axons, known as the **corpus callosum**, which lies deep within the cerebrum. The corpus callosum is the major pathway for communication between the two hemispheres, connecting each point in the cerebral cortex to the mirror-image point in the opposite hemisphere. The location of the corpus callosum is shown with a dotted outline in Figure 4.4.4, as though you are looking through the outside and deep inside the brain. Figure 4.4.5 shows a three-dimensional image of the corpus callosum in relation to other deep brain structures and surrounded by the cerebrum.

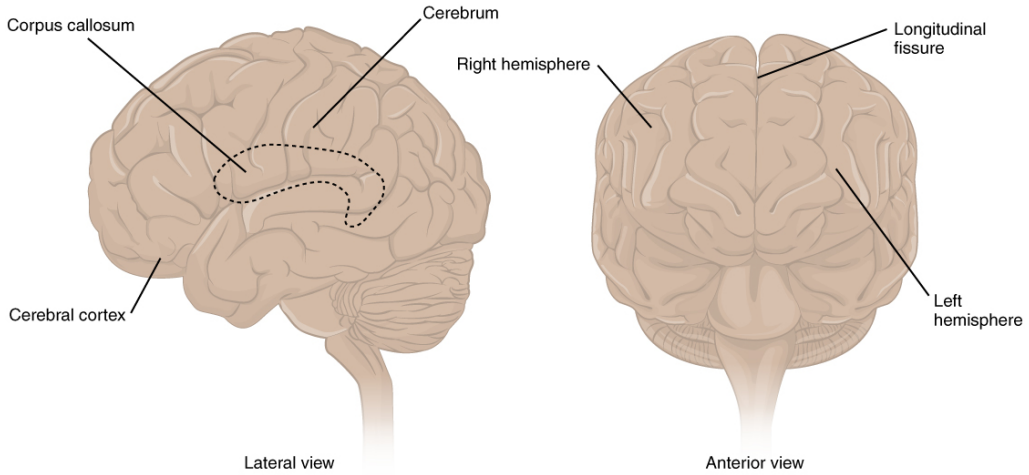


Figure 4.4.4: The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.

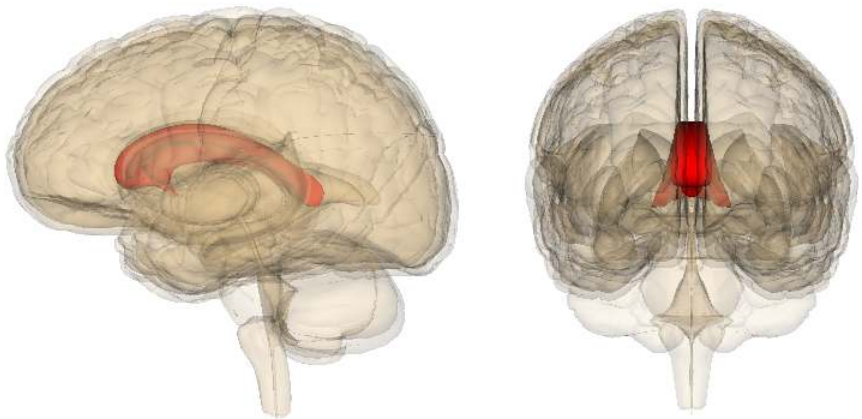


Figure 4.4.5: The corpus callosum (shown in red) is a thick bundle of axons connecting the left and right hemispheres of the brain. It is located deep within the cerebrum.

The right and left hemispheres of the cerebrum are similar in shape, and most areas of the cerebrum are found in both hemispheres. Some areas, however, show **lateralization,** or a concentration in one hemisphere or the other. For example, in most people,

language functions are more concentrated in the left hemisphere, whereas abstract reasoning and visual-spatial abilities are more concentrated in the right hemisphere.

For reasons that are not yet clear, each hemisphere of the brain interacts primarily with the **contralateral** (opposite) side of the body. The left side of the brain receives messages from and sends commands to the right side of the body, and the right side of the brain receives messages from and sends commands to the left side of the body. Sensory nerves from the spinal cord to the brain and motor nerves from the brain to the spinal cord both cross to the other side of the body.

4.4.4.2 Cerebral Cortex

The cerebrum is covered by a continuous layer of gray matter that wraps around either side of the forebrain—the **cerebral cortex**. This thin (just a few millimeters thick), extensive region of wrinkled gray matter is responsible for most of the information processing and higher functions of the nervous system. The cerebral cortex has many folds in it that greatly increase the surface area of the brain. A **gyrus** (plural = gyri) is the ridge of one of those wrinkles, and a **sulcus** (plural = sulci) is the groove between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex. At birth, the head of the newborn is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cerebral cortex in an adult were peeled off of the cerebrum and laid out flat, its surface area would be about 2,500 cm^2 (2.5 ft^2), or about the size of the top of a card table.

4.4.4.3 Lobes of the Cerebral Cortex

The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes (Figure 4.4.6). The **lateral sulcus** that separates the **temporal lobe** from the other regions is one such landmark.

Superior to the lateral sulcus are the **frontal lobe** and **parietal lobe**, which are separated from each other by the **central sulcus**. The most posterior gyrus of the frontal lobe is the **precentral gyrus**, which is where the primary motor cortex is located, while the most anterior gyrus of the parietal lobe is the **postcentral gyrus**, which is where the primary somatosensory cortex is located. (The primary somatosensory cortex is the area that the homonculus in Figure 4.4.1 represents.)

The posterior region of the cortex is the **occipital lobe**, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, the **parieto-occipital sulcus** separates the parietal and occipital lobes.

Figure 4.4.7 has only the four lobes labeled for quicker reference. The lobes are associated with multiple functions. The image shows one function of each lobe: frontal is associated with reasoning, parietal with touch, occipital with sight, and temporal with hearing. The lobes (found on each hemisphere of the cerebrum) are described in greater detail below.

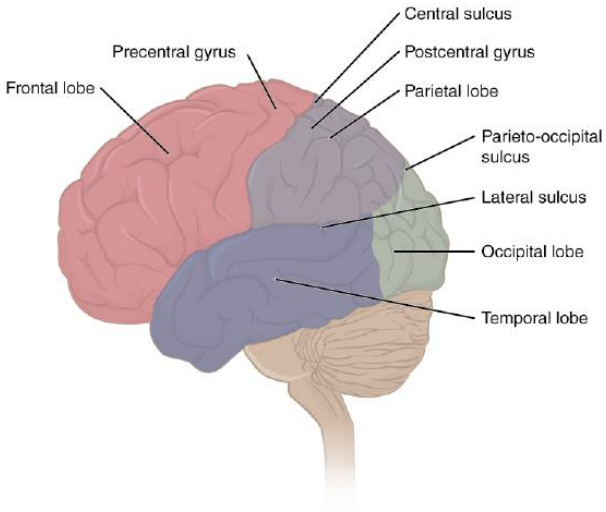


Figure 4.4.6: Major gyri, sulci and lobes of the cerebral cortex.

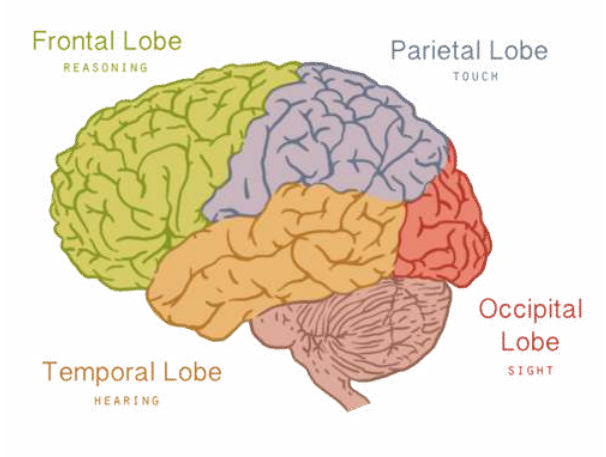


Figure 4.4.7: The four major lobes of the brain.

4.4.4.3.1 Frontal Lobe

The **frontal lobes** are located at the front of the brain behind the forehead. The frontal lobes are associated with executive functions such as attention, self-control, planning, problem-solving, reasoning, abstract thought, language, and personality. Another important function of the frontal lobes is movement- as mentioned above, the precentral gyrus (indicated on Figure 4.4.6) contains the primary motor cortex. Like the sensory homunculus pictured in the beginning of this section (Figure 4.4.1), there is a similarly disproportionate representation of voluntary motor control (the motor homunculus) located in the precentral gyrus. Figure 4.4.8 shows the areas of the primary motor cortex dedicated to movement of various body areas. Notice that like the sensory homunculus, the hands, fingers, thumb, and facial areas have a greater share of the cortex than areas with less fine-tuned movement (like the shoulders, trunk, and hips, for example).

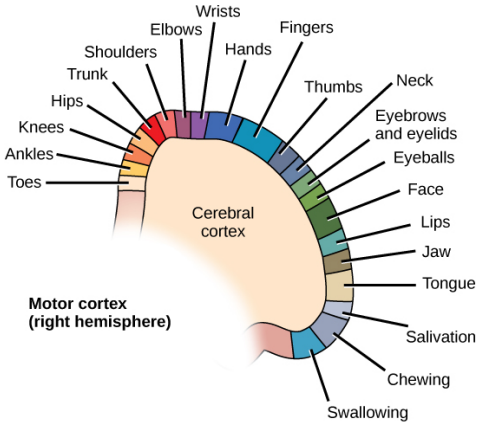


Figure 4.4.8: Different regions of the motor cortex control different muscle groups and their neighboring regions control neighboring muscle groups. Although the right hemisphere is shown, a mirror-image exists in the left hemisphere as well. Note that all areas of the body that have voluntary motor control are represented on the primary motor cortex.

4.4.4.3.2 Parietal Lobe

The **parietal lobes** are located posterior to the frontal lobes at the top of the head. The parietal lobes are involved in body sensations, including temperature, touch, and pain. As mentioned above, the postcentral gyrus (indicated on Figure 4.4.6) contains the primary somatosensory cortex. The sensory homunculus model pictured in the beginning of this section (Figure 4.4.1) shows the strange character that results from making the body areas proportional to their representation in the brain. The drawing in Figure 4.4.9 shows the sensory homunculus stretched out along the postcentral gyrus of the parietal lobe. Notice that areas that have sensation but no voluntary motor control (like the genitals and the intra-abdominal organs) are present on the primary somatosensory cortex but not on the primary motor cortex (Figure 4.4.8). Reading and arithmetic are also functions of the parietal lobes.

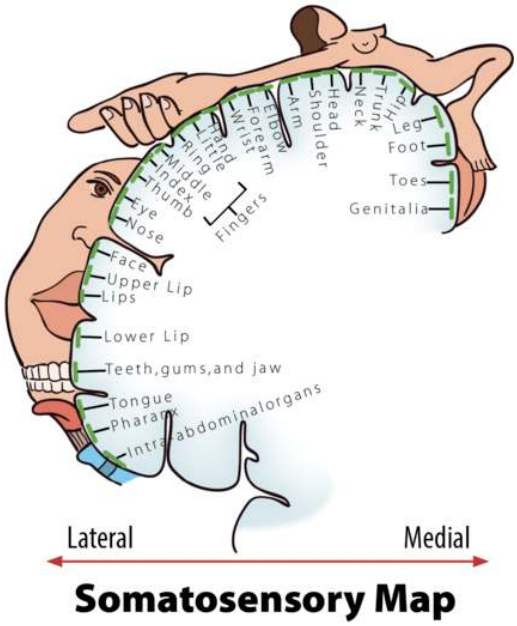


Figure 4.4.9: Somatosensory Map. The sensory map of your body represented on the primary somatosensory cortex in your brain is not proportional to the actual size of your body parts. Sensitive areas like your face (particularly your lips) and hands (particularly your fingers) occupy a larger section of cortex than less sensitive areas like your limbs (arms and legs) or trunk. Although the left hemisphere is shown, a mirror-image exists in the right hemisphere as well. Note that all areas of the body that register touch sensations are represented on the primary somatosensory cortex.

4.4.4.3.3 Temporal Lobe

The **temporal lobes** are located at the sides of the head below the frontal and parietal lobes. The temporal lobes enable the formation and retrieval of memories, the integration of memories and sensations, and perception of the senses of hearing (audition), and smell (olfaction)- primary auditory cortex and primary olfactory cortex are both located in the temporal lobes.

4.4.4.3.4 Occipital Lobe

The **occipital lobes** are located at the back of the head below the parietal lobes. The occipital lobes are the smallest of the four pairs of lobes. Primary visual cortex is located in the occipital lobes, and they are dedicated almost solely to vision.

4.4.5 Brainstem

As noted separately (see the nervous system structure module), sometimes the diencephalon is considered as a separate additional region, and sometimes it is included as the uppermost part of the brainstem (Basinger and Hogg, 2021), as it is here. The **brainstem** is the central region of the brain that connects the cerebrum (on the superior end) to the diencephalon, midbrain, pons, medulla, and ultimately joins the spinal cord (on the inferior end). The **cerebellum** is attached to the brainstem, but is considered a separate region of the adult brain.

One of the brainstem's most important roles is that of an "information highway." That is, all of the information coming from the body to the brain and the information from the cerebrum to the body go through the brainstem. Sensory pathways for such things as pain, temperature, touch, and pressure sensation go upward to the cerebrum, and motor pathways for movement and other body processes go downward to the spinal cord. Most of the axons in the motor pathways cross from one side of the CNS to the other as they pass through the medulla. As a result, the right side of the brain controls much of the movement on the left side of the body, and the left side of the brain controls much of the movement on the right side of the body. Similarly, axons in sensory pathways cross from one side of the CNS to the other either in the spinal cord or in the medulla (depending on the specific sensory information carried, such as pain versus localized touch), such that the right side of the brain receives sensation primarily from the left side of the body and vice versa.

4.4.5.1 Diencephalon

The diencephalon ("through brain") is the one region of the adult brain that retains its name from embryonic development. It connects the cerebrum and the rest of the nervous system, with one exception. The brainstem, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon, and output from the cerebrum then passes back through the diencephalon. The single exception to this pattern is the sense of smell (olfaction), which connects directly to the cerebrum first. The diencephalon comprises the ventral surface of the forebrain (and connects to the tapering cone of the midbrain, pons, and medulla, the remaining structures in the brainstem).

The diencephalon is located deep within the cerebrum and constitutes the walls of the third ventricle. The diencephalon can be described as any region of the brain with "thalamus" in its name. The two major regions of the diencephalon are the thalamus itself and the hypothalamus (Figure 4.4.10). There are other structures as well, such as the epithalamus, which contains the pineal gland.

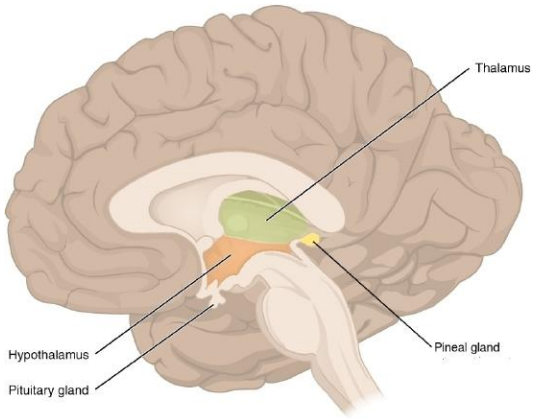


Figure 4.4.10: The diencephalon.

4.4.5.1.1 Thalamus

The **thalamus,** which is located above the hypothalamus (Figure 4.4.10 and Figure 4.4.11), is a major hub for information traveling back and forth between the spinal cord, brainstem, and cerebrum. It filters sensory information traveling to the cerebrum. It relays sensory signals to the cerebral cortex and motor signals to the spinal cord. It is also involved in the regulation of consciousness, sleep, and alertness. As noted above, olfaction (smell) is the only sense that travels directly to the cortex and does not travel through the thalamus (as part of the diencephalon) first. However, olfactory messages do travel from the cortex back to the thalamus, so smell is still a participant in the "sensory relay" functions of the thalamus.

4.4.5.1.2 Hypothalamus

The **hypothalamus** ("below thalamus") is about the size of an almond and is responsible for certain metabolic processes and other activities of the autonomic nervous system, including body temperature, heart rate, hunger, thirst, fatigue, sleep, wakefulness, and circadian (24-hour) rhythms. The hypothalamus is also an important emotional center of the brain. The hypothalamus can regulate so many body functions because it responds to many different internal and external signals, including messages from the brain, light, steroid hormones, stress, and invading pathogens, among others.

One way the hypothalamus influences body functions is by synthesizing hormones that directly influence body processes. For example, it synthesizes the hormone oxytocin, which stimulates penile and vaginal contractions during orgasm, uterine contractions during childbirth, and the letdown of milk during lactation. It also synthesizes the hormone vasopressin (also called antidiuretic hormone), which stimulates the kidneys to reabsorb more water and excrete more concentrated urine. These two hormones are sent from the hypothalamus via a stalk-like structure called the **infundibulum** ("pituitary stalk", see Figure 4.4.11) directly to the posterior (back) portion of the **pituitary gland**, which secretes them into the blood.

The main way the hypothalamus influences body functions is by controlling the pituitary gland, known as the "master gland" of the **endocrine system**. (The endocrine system is considered separately in the communication and the endocrine system module.) The hypothalamus synthesizes neurohormones called releasing factors that travel through the infundibulum directly to the anterior (front) part of the pituitary gland. The releasing factors generally either stimulate or inhibit the secretion of anterior pituitary hormones, most of which control other glands of the endocrine system.

Figure 4.4.11 shows where the thalamus, hypothalamus, and pituitary gland (typically considered an extension of the hypothalamus) are located in the brain. The cerebrum, hypothalamus, and thalamus exist in two halves, one in each hemisphere. The pituitary gland is a single structure in the center, connected to the hypothalamus by the infundibulum (or "pituitary stalk").

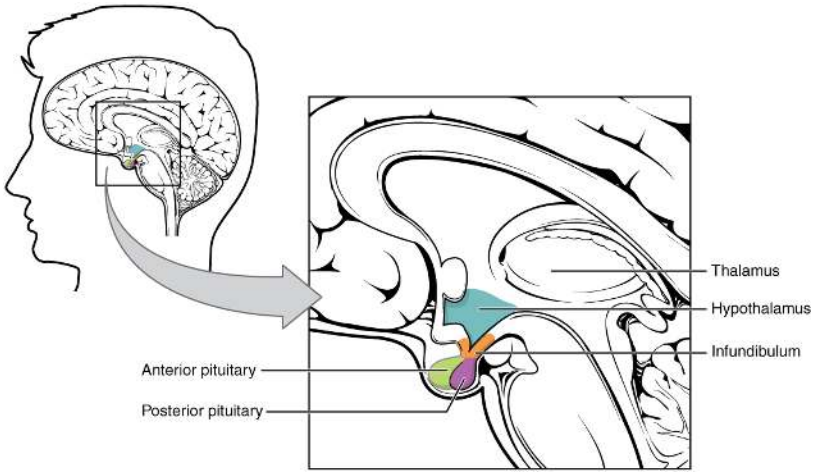


Figure 4.4.11: Just inferior (and deep) to the cerebrum is the thalamus. The hypothalamus is located a little bit anterior and inferior to the thalamus. The pituitary gland is attached to the hypothalamus via a stalk called the infundibulum.

The remaining parts to the brainstem are the midbrain, the pons, and the medulla, which are shown in Figure 4.4.12 below. These structures are primarily involved in the unconscious functions of the autonomic nervous system as well as several types of sensory information. They also help coordinate large body movements such as walking and running.

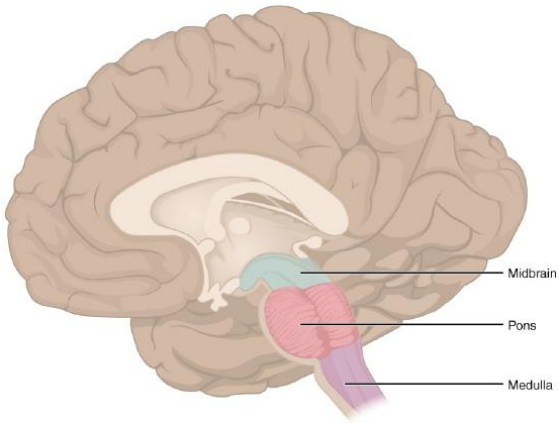


Figure 4.4.12: The brainstem includes the midbrain, pons, and medulla

4.4.5.2 Midbrain

The **midbrain** coordinates sensory representations of sight (visual system- the **superior colliculi**), sound (auditory system- the **inferior colliculi**), and somatosensory perceptual spaces, translating these inputs before sending them to the forebrain.

4.4.5.3 Pons

The **pons** ("bridge") is the main connection with the cerebellum. It relays messages between other parts of the brain (primarily the cerebrum and cerebellum) and sends messages to paralyze major body muscles during REM sleep. Some researchers have hypothesized that the pons plays a role in dreaming. Some of the functions of the pons are shared by the medulla, such as regulating several crucial functions including cardiovascular system and respiratory systems, and heartbeat and breathing rates.

4.4.5.4 Medulla

The **medulla** (also called the medulla oblongata) controls several subconscious homeostatic functions such as breathing, heart and blood vessel activity, swallowing, and digestion.

4.4.6 Limbic System

The **limbic system** is a collection of structures of the cerebrum and diencephalon that are involved in emotion, motivation and memory. Although still under debate, the structures most often recognized as belonging to this system are the cingulate gyrus, hippocampus, amygdala, olfactory structures, and various nuclei of the diencephalon. Here we will focus on the cingulate gyrus, the hippocampus, and the amygdala (Figure 4.4.13). The **cingulate gyrus** (colored green in the figure) is located on the midsagittal surface of the cortex, immediately superior to the corpus callosum and surrounding the diencephalon. The cingulate gyrus focuses attention on events that are emotionally salient. The **hippocampus** (colored purple in the figure) is a nucleus shaped like a seahorse, hence its name. The hippocampus is essential for forming memories and storing them long-term and is located deep in the temporal lobe. Lastly, the **amygdala** (also called the amygdaloid body, colored blue in the figure) is connected to the anterior end of the hippocampus and is involved in multiple aspects of emotion, including encoding memories related to highly emotional states. The amygdala is especially important for the emotion fear.

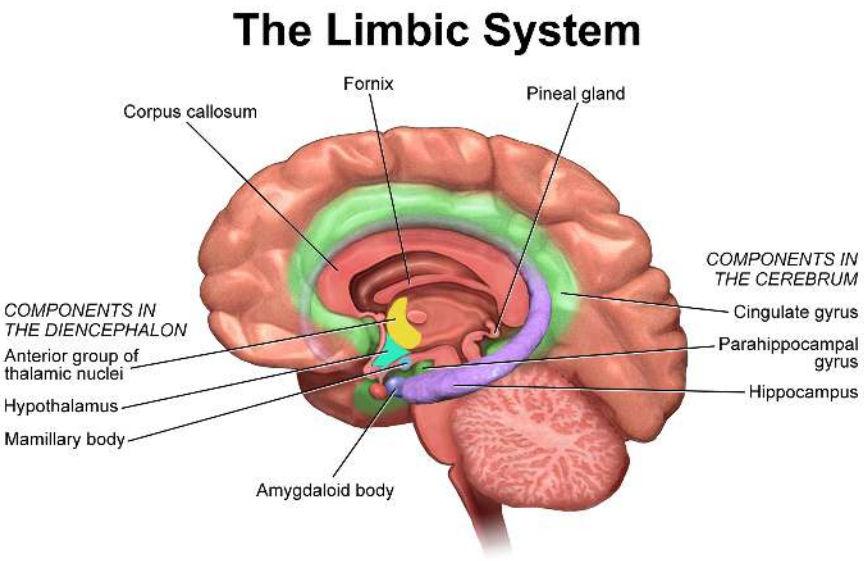


Figure 4.4.13: The Limbic System includes components from both the diencephalon (anterior group of thalamic nuclei, hypothalamus, and mammilary body) and the cerebrum (cingulate gyrus, parahippocampal gyrus, hippocampus, and amygdaloid body). Structures additionally labeled for reference are the corpus callosum, fornix, and pineal gland.

4.4.7 Cerebellum

The **cerebellum**, as the name suggests, is the "little brain", just below the cerebrum and at the back of the brain behind the brainstem. It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain Figure 4.4.14. The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain. The cerebellum coordinates body movements and is involved in movements that are learned with repeated practice. For example, when you hit a softball with a bat or touch type on a keyboard you are using your cerebellum. Many nerve pathways link the cerebellum with motor neurons throughout the body.

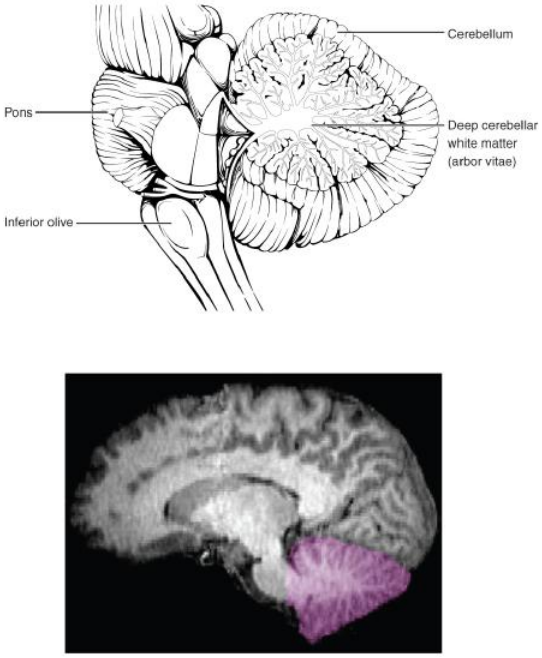


Figure 4.4.14: **The cerebellum.** The cerebellum is situated on the posterior surface of the brainstem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.

4.4.8 Spinal Cord

The above description of the CNS is concentrated on the structures of the brain, but the **spinal cord** is another major organ of the system. The spinal cord is a long, thin, tubular bundle of nervous tissues that extends from the brainstem down through the center of the back and pelvis. It is highlighted in yellow in Figure 4.4.15.



Figure 4.4.15: The spinal cord (shown in yellow) runs from the inferior aspect of the brain to the lower back. Spinal nerves are shown in black, and bones are shown in blue.

4.4.8.1 Structure of the Spinal Cord

The center of the spinal cord consists of **gray matter**, which is made up mainly of neuron cell bodies, including interneurons and motor neurons. The gray matter is surrounded by **white matter** that consists mainly of myelinated axons from motor and sensory neurons. Sensory neuron axons enter the posterior side through the **dorsal (/posterior) nerve root**. Motor neuron axons emerge from the anterior side through the **ventral (/anterior) nerve root**. Note that it is common to see the terms dorsal (dorsal = back) and ventral (ventral = belly) used interchangeably with posterior and anterior, particularly in reference to nerves and the structures of the spinal cord. The **central canal** travels through the center of the spinal cord. The central canal is filled with **cerebrospinal fluid** (CSF). Figure 4.4.16 shows the gray matter, white matter, central canal, dorsal roots and ventral roots of the spinal cord.

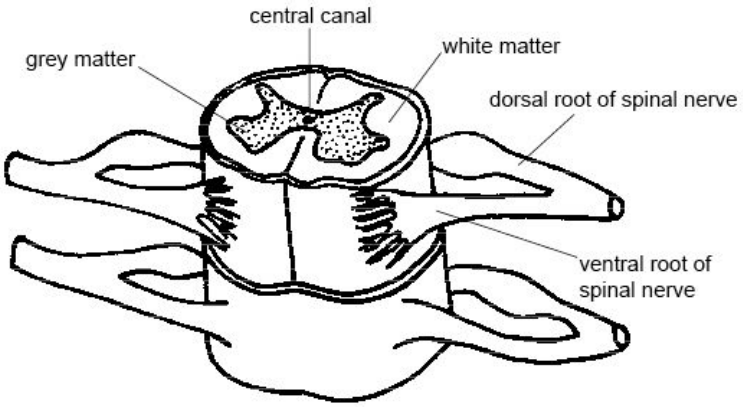


Figure 4.4.16: Cross section of spinal cord showing the central canal, gray and white matter, and the dorsal and ventral roots of the spinal nerves.

At each level of the spinal cord, the dorsal and ventral roots come together to form spinal nerves. Because the spinal cord is shorter than the vertebral column it is enclosed within, nerve roots must travel lower to exit at the associated vertebra. Spinal nerves connect the spinal cord to the PNS and enter/exit from the spinal cord between vertebrae (Figure 4.4.17).

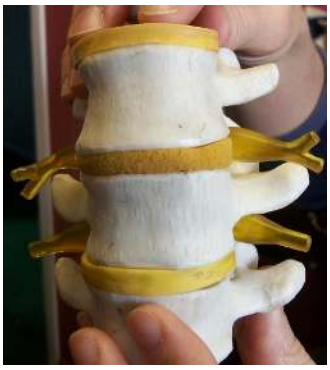


Figure 4.4.17: This model shows three vertebrae (white) with branching spinal nerves (yellow) emerging from either side of the spinal cord between vertebrae. Also shown in yellow are pancake-like disks between vertebrae that help cushion and maintain space between adjacent bony vertebrae.

4.4.8.2 Gray Horns

In cross-section, the gray matter of the spinal cord has the appearance of an ink-blot test, with the spread of the gray matter on one side replicated on the other—a shape reminiscent of a bulbous capital “H” or a butterfly. As shown in Figure 4.4.18, the gray matter is subdivided into regions that are referred to as horns.

The **posterior horn** is responsible for sensory processing. The **anterior horn** sends out motor signals to the skeletal muscles. The **lateral horn**, which is only found in the thoracic, upper lumbar, and sacral regions, is the central component of the sympathetic division of the autonomic nervous system.

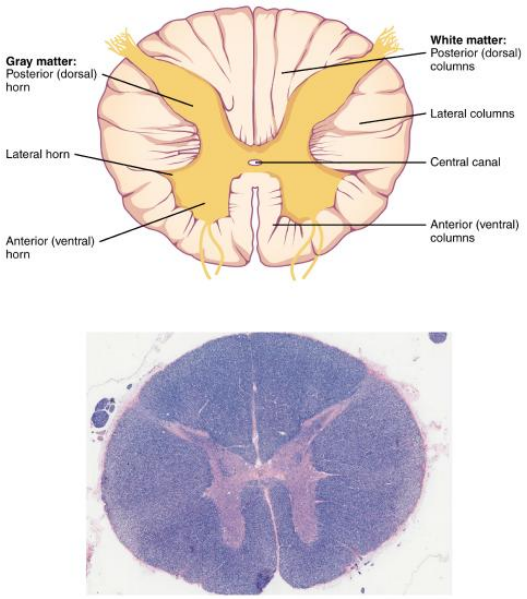


Figure 4.4.18: **Cross-section of Spinal Cord** The cross-section of a thoracic spinal cord segment shows the posterior (dorsal), anterior (ventral), and lateral horns of gray matter, as well as the posterior (dorsal), anterior (ventral), and lateral columns of white matter. Light Microscopy × 40 magnification.

4.4.8.3 Functions of the Spinal Cord

The spinal cord serves as an information superhighway. It passes messages from the body to the brain and from the brain to the body. Sensory (afferent) nerves carry nerve impulses to the brain from sensory receptor cells everywhere in and on the body. Motor (efferent) nerves carry nerve impulses away from the brain to glands, organs, or muscles throughout the body.

The spinal cord also independently controls certain rapid responses called **reflexes** without any input from the brain. A sensory receptor responds to a sensation and sends a nerve impulse along a sensory nerve to the spinal cord. In the spinal cord, the message passes to an interneuron and from the interneuron to a motor nerve, which carries the impulse to a muscle. The muscle contracts in response. These neuron connections form a reflex arc, which requires no input from the brain. No doubt you have experienced such

reflex actions yourself. For example, you may have reached out to touch a pot on the stove, not realizing that it was very hot. Virtually at the same moment that you feel the burning heat, you jerk your arm back and remove your hand from the pot.

4.4.8.4 Injuries to the Spinal Cord

Physical damage to the spinal cord may result in **paralysis,** which is a loss of sensation and movement in part of the body. Paralysis generally affects all the areas of the body below the level of the injury because nerve impulses are interrupted and can no longer travel back and forth between the brain and body beyond that point. If an injury to the spinal cord produces nothing more than swelling, the symptoms may be transient. However, if nerve fibers (axons) in the spinal cord are badly damaged, the loss of function may be permanent. Experimental studies have shown that spinal nerve fibers attempt to regrow, but tissue destruction usually produces scar tissue that cannot be penetrated by the regrowing nerves, as well as other factors that inhibit nerve fiber regrowth in the central nervous system.

Feature: My Human Body

Each year, many millions of people have a stroke, and stroke is the second leading cause of death in adults. **Stroke,** also known as **cerebrovascular accident**, occurs when poor blood flow to the brain results in the death of brain cells. There are two main types of strokes:

- **Ischemic** strokes occur due to a lack of blood flow because of a blood clot in an artery going to the brain.
- **Hemorrhagic** strokes occur due to bleeding from a broken blood vessel in the brain.

Either type of stroke may result in paralysis, loss of the ability to speak or comprehend speech, loss of bladder control, personality changes, and many other potential effects, depending on the part of the brain that is injured. The effects of a stroke may be mild and transient or more severe and permanent. A stroke may even be fatal. It generally depends on the type of stroke and how extensive it is.

Are you at risk of stroke? The main risk factor for stroke is age: about two-thirds of strokes occur in people over the age of 65. There is nothing you can do about your age, but most other stroke risk factors can be reduced with lifestyle changes or medications. The risk factors include high blood pressure, tobacco smoking, obesity, high blood cholesterol, diabetes mellitus, and atrial fibrillation.

Chances are good that you or someone you know is at risk of a stroke, so it is important to recognize a stroke if one occurs. Stoke is a medical emergency, and the more quickly treatment is given, the better the outcome is likely to be. In the case of ischemic strokes, the use of clot-busting drugs may prevent permanent brain damage if administered within 3 or 4 hours of the stroke. Remembering the signs of a stroke is easy. They are summed up by the acronym FAST, as explained in Figure 4.4.19.



Figure 4.4.19: The signs of stroke are abbreviated as FAST, where F stands for droopy face, A stands for arm weakness, S stands for slurry speech, and T stands for time to call 911.

4.4.9 Summary

The central nervous system (CNS) includes the brain and spinal cord, described in greater detail in this module. The adult brain is separated into three major regions: the cerebrum, the brainstem, and the cerebellum. The cerebrum is the largest portion and is

divided into two halves called hemispheres by the longitudinal fissure. The two hemispheres are connected by the corpus callosum, the major pathway for communication between the hemispheres.

The cerebral cortex, a continuous layer of gray matter covering the cerebrum, is the location of important cognitive functions. The cerebral cortex is separated into the frontal, parietal, temporal, and occipital lobes. The frontal lobe is responsible for executive functions and movements. The parietal lobe is involved in body sensations, reading, and arithmetic. The temporal lobe has regions crucial for memory formation, and contains cortical areas that process audition (hearing) and olfaction (smell). The occipital lobe is where visual processing begins.

The brainstem is composed of the diencephalon, midbrain, pons, and medulla. The brainstem serves as an "information highway", since all of the information coming from the body to the brain and the information from the cerebrum to the body go through the brainstem. The two major regions of the diencephalon are the thalamus and the hypothalamus. The thalamus is a relay between the cerebrum and the rest of the nervous system. The hypothalamus coordinates metabolic processes through the autonomic and endocrine systems. The midbrain coordinates sensory representations of sight, sound and somatosensation. The pons is the main connection between the cerebrum and the cerebellum. The pons and the medulla together regulate the cardiovascular and respiratory systems. The medulla also has important functions for swallowing and digestion.

The limbic system includes structures of the cerebrum and diencephalon that are responsible for emotion, motivation, and memory. The main structures are the cingulate gyrus, the hippocampus and the amygdala.

The cerebellum is connected to the brain stem and compares information from the cerebrum with sensory feedback from the spinal cord. The cerebellum coordinates body movements and is involved in movements that are learned with repeated practice.

The spinal cord extends from the brainstem down through the center of the back and pelvis. Sensory neuron axons enter through the dorsal (/posterior) nerve root and motor neuron axons emerge from the ventral (/anterior) nerve root. Gray matter (containing of neuron cell bodies) is located in the center of the spinal cord, surrounded by white matter (myelinated axons). The gray matter is subdivided into the posterior, anterior, and lateral horns. The spinal cord passes messages from the body to the brain and from the brain to the body. Sensory (afferent) nerves carry nerve impulses to the brain from sensory receptor cells everywhere in and on the body. Motor (efferent) nerves carry nerve impulses away from the brain to glands, organs, or muscles throughout the body. The spinal cord also independently controls reflexes without any input from the brain. Physical damage to the spinal cord may result in paralysis, which may be permanent.

4.4.10 References

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4.4.12 Attributions

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4.5: The Peripheral Nervous System

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Describe the structures found in the PNS
2. Distinguish between somatic and autonomic structures
3. Name the twelve cranial nerves and explain the functions associated with each
4. Describe the sensory and motor components of spinal nerves
5. Explain the functions of the sympathetic and parasympathetic divisions of the autonomic system

4.5.1 Overview

This module discusses the peripheral nervous system (PNS) in greater depth, including nervous tissues, the two major systems the PNS divides into (the somatic nervous system and the autonomic nervous system), names and functions of the twelve cranial nerves, and characteristics of the 31 pairs of spinal nerves. The subdivisions of the autonomic nervous system (the sympathetic nervous system and the parasympathetic nervous system) and their functions are also covered, as well as a brief mention of disorders of the PNS.

4.5.2 What Is the Peripheral Nervous System?

The **peripheral nervous system (PNS)** consists of all the nervous tissue that lies outside of the central nervous system (CNS). The main function of the PNS is to connect the CNS to the rest of the organism. It serves as a communication relay, going back and forth between the CNS and muscles, organs, and glands throughout the body. Figure 4.5.1 illustrates both the central and peripheral nervous systems, including many representative **spinal nerves**. Although an overview of spinal nerves is discussed in greater detail below, the identification and functions of specific spinal nerves are beyond the scope of this section.

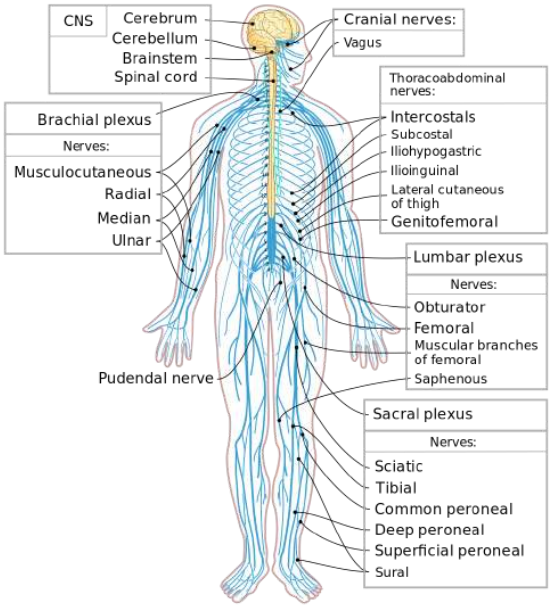


Figure 4.5.1: The central nervous system (CNS) is shown in yellow: Cerebrum, Cerebellum, Brainstem, Spinal cord. Some representative nerves of the peripheral nervous system (PNS) are shown in blue.

The representative nerves pictured are Cranial nerves: Vagus. Brachial plexus nerves: Musculotaneous, Radial, Median, Ulnar; Thoracoabdominal nerves: Intercostals, Subcostal, Iliohypogastric, Ilioinguinal, Lateral cutaneous of thigh, Genitofemoral; Lumbar plexus nerves: Obturator, Femoral, Muscular branches of femoral, Saphenous; Sacral plexus nerves: Sciatic, Tibial, Common peroneal, Deep peroneal, Superficial peroneal, Sural. The Pudendal nerve is also pictured.

4.5.3 Tissues of the Peripheral Nervous System

The primary structures that make up the PNS are nerves and ganglia. Ganglia are clusters of neuron cell bodies outside the CNS; they act as relay points for messages transmitted through nerves of the PNS. Nerves are cable-like bundles of axons that make up the majority of PNS tissues. Nerves are generally classified based on the type of information they carry (which coincides with the direction in which their nerve impulses travel) as sensory, motor, or mixed nerves. See an example of a sensory and motor nerve in Figure 4.5.2. (Note that the interneuron that is usually located between the sensory and motor neuron is not shown in this figure.)

- **Sensory nerves** transmit information from sensory receptors in the body to the CNS. Sensory nerves are also called afferent nerves.
- **Motor nerves** transmit information from the CNS to muscles, organs, and glands. Motor nerves are also called efferent nerves.
- **Mixed nerves** contain axons from both sensory and motor neurons, so they transmit information in both directions and have both afferent and efferent functions.

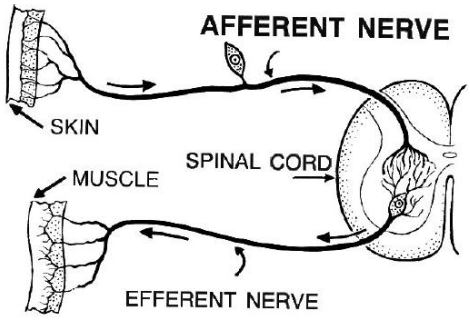


Figure 4.5.2: A sensory nerve is an afferent nerve. The one pictured here sends nerve impulses from sensory receptors in the skin to the CNS. A motor nerve is an efferent nerve. This one sends nerve impulses from the CNS to a muscle.

4.5.4 Divisions of the Peripheral Nervous System

The PNS is divided into two major systems, called the autonomic nervous system and the somatic nervous system. Both systems of the PNS interact with the CNS and include sensory and motor neurons, but they use different circuits of nerves and ganglia.

4.5.4.1 Somatic Nervous System

The **somatic nervous system** primarily senses the external environment and controls voluntary activities for which decisions and commands come from the cerebral cortex of the brain. For example, when you feel too cold, decide to turn on the heater, and walk across the room to the thermostat, you are using your somatic nervous system. In general, the somatic nervous system is responsible for all of your conscious perceptions of the outside world, and all of the voluntary motor activities you perform in response. Whether it's playing piano, driving a car, or playing basketball, you can thank your somatic nervous system for making it possible. Structurally, the somatic nervous system consists of 12 pairs of cranial nerves and 31 pairs of spinal nerves.

4.5.4.1.1 Cranial Nerves

Cranial nerves (Figure 4.5.3) 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 4.5.1 for a brief summary of the functions of each cranial nerve.

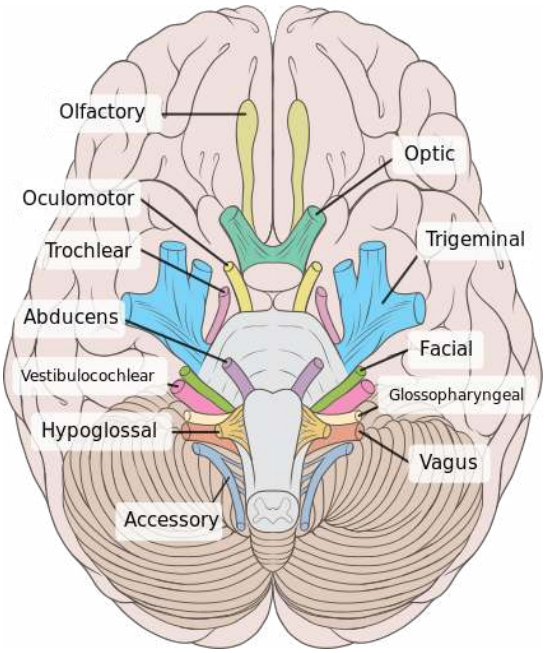


Figure 4.5.3: The twelve pairs of cranial nerves are located on the inferior aspect of the human brain.

4.5.4.1.2

Table 4.5.1: Cranial Nerves

Mnemonic	#	Name	Function (**S**ensory/**M**otor/**B**oth)	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)
Finn	VII	Facial	Motor – face; Taste (B)	Facial nucleus, solitary nucleus, superior salivatory nucleus	Facial muscles; Geniculate ganglion; Pterygopalatine ganglion (autonomic)

Mnemonic	#	Name	Function (**S**ensory/**M**otor/**B**oth)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
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

4.5.4.1.3 Spinal Nerves

The nerves connected to the spinal cord are the **spinal nerves**. The arrangement of these nerves is much more regular than that of the cranial nerves. All of the spinal nerves are combined sensory and motor axons that separate into two nerve roots. The sensory axons enter the spinal cord as the **dorsal nerve root**. The motor fibers, both somatic and autonomic, emerge as the **ventral nerve root**. The sensory neuron cell bodies (soma) are grouped in enlargements of the dorsal nerve root called **dorsal root ganglia**. See Figure 4.5.4 to locate these structures on a segment of the spinal cord. (As noted in the central nervous system module, it is common to see the terms dorsal (dorsal = back) and ventral (ventral = belly) used interchangeably with posterior and anterior in reference to nerves and the structures of the spinal cord.)

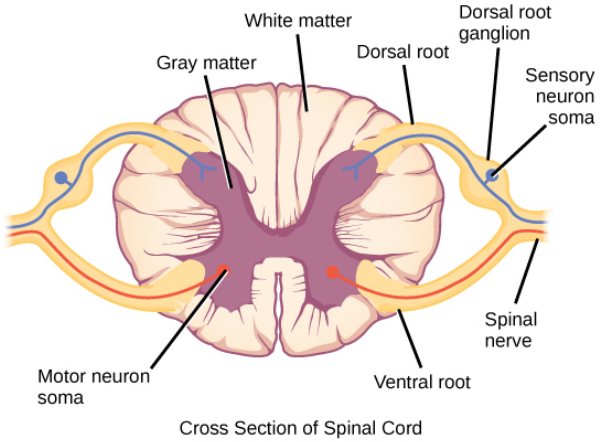


Figure 4.5.4: **Spinal nerves**: Spinal nerves contain both sensory and motor axons. The cell bodies of sensory neurons are located in dorsal root ganglia. The cell bodies of motor neurons are found in the ventral portion of the gray matter of the spinal cord.

Each sensory neuron has one projection with a sensory receptor ending in skin, muscle, or sensory organs, and another that synapses with a neuron in the dorsal spinal cord. Motor neurons have cell bodies (soma) in the ventral gray matter of the spinal cord that project to muscle through the ventral root. These neurons are usually stimulated by interneurons within the spinal cord,

but are sometimes directly stimulated by sensory neurons. Spinal nerves include the motor nerves that stimulate skeletal muscle contraction, allowing for voluntary body movements.

There are 31 pairs of spinal nerves, named for the level of the spinal cord at which they emerge, one on each side of the body. There are eight pairs of cervical nerves designated C1 to C8, twelve thoracic nerves designated T1 to T12, five pairs of lumbar nerves designated L1 to L5, five pairs of sacral nerves designated S1 to S5, and one pair of coccygeal nerves. The nerves are numbered from the superior to inferior positions, and each emerges from the vertebral column through the intervertebral foramen at its level. Thus, each spinal nerve corresponds to a segment of the spinal cord, carrying both sensory and motor information (as mentioned above) for the areas of the body represented. As such, all of the spinal nerves are mixed nerves and contain both sensory and motor neuron axons. Figure 4.5.5 illustrates the body areas represented by the spinal nerves and Figure 4.5.6 lists some of the functions of the spinal nerves.

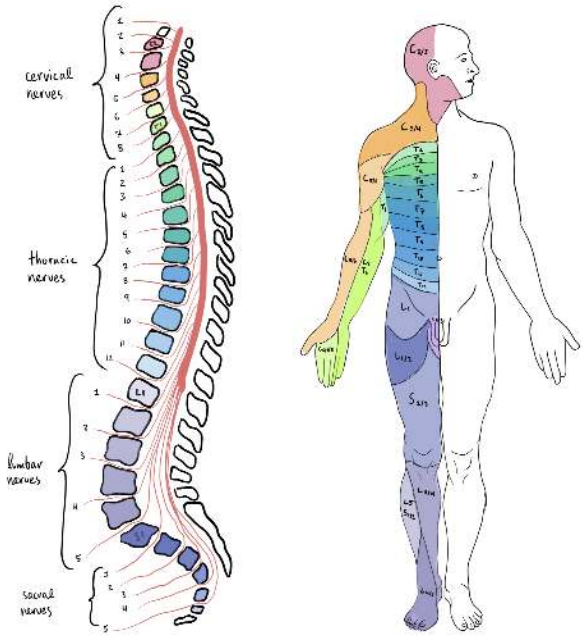


Figure 4.5.5: Spinal cord segments and body representation.

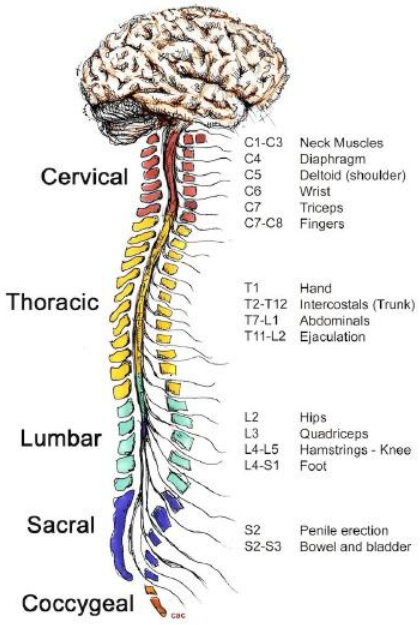


Figure 4.5.6: Vertebral location and some functions of spinal nerves.

4.5.4.2 Autonomic Nervous System

The **autonomic nervous system** primarily senses the internal environment and controls involuntary activities. It is responsible for monitoring conditions in the internal environment and bringing about appropriate changes in them. In general, the autonomic nervous system is responsible for all the activities that go on inside your body without your conscious awareness or voluntary participation.

Structurally, the autonomic nervous system consists of sensory and motor nerves that run between the CNS (especially the hypothalamus in the brain) and internal organs (such as the heart, lungs, and digestive organs) and glands (such as the pancreas and sweat glands). Sensory neurons in the autonomic system detect internal body conditions and send messages to the brain. Motor nerves in the autonomic system function by controlling the contractions of smooth or cardiac muscle or glandular tissue. For example, when sensory nerves of the autonomic system detect a rise in body temperature, motor nerves signal both the smooth muscles in blood vessels near the body surface to undergo vasodilation, and the sweat glands in the skin to secrete more sweat, to cool the body.

The autonomic nervous system, in turn, has two subdivisions: the sympathetic division and parasympathetic division. The functions of the two subdivisions of the autonomic system are summarized in Figure 4.5.5. Both affect most of the same organs and glands, but they generally do so in opposite ways.

- The **sympathetic division** controls the fight-or-flight response. Changes occur in organs and glands throughout the body that prepare the body to fight or flee in response to a perceived danger. For example, the pupils dilate, saliva production decreases, air passages in the lungs become wider (the bronchia dilate), heart rate speeds up, more blood flows to the skeletal muscles, and

the digestive system temporarily shuts down. With regard to urinary and sexual functions, the sympathetic division relaxes the urinary bladder and stimulates orgasm in both men and women.

- The **parasympathetic division** returns the body to normal after the fight-or-flight response has occurred. For example, pupils constrict, saliva production increases, air passages in the lungs narrow (the bronchia constrict), heart rate slows down, blood flow to the skeletal muscles is reduced, and the digestive system is stimulated to start working again. The parasympathetic division also maintains the internal homeostasis of the body at other times. With regard to urinary and sexual functions, the parasympathetic division constricts the urinary bladder and stimulates genital tissue erection in both men and women.

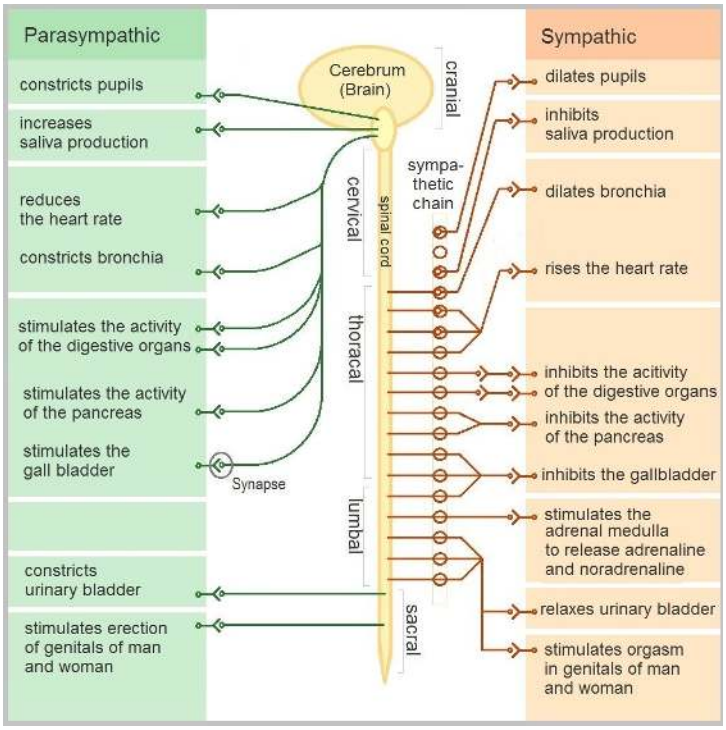


Figure 4.5.7: This diagram summarizes the structures and functions controlled by the parasympathetic and sympathetic divisions of the autonomic nervous system. The image shows how eyes, salivary gland, heart rate, bronchi, digestive system, bladder, and genitalia are affected in opposite ways by the two systems.

4.5.5 Disorders of the Peripheral Nervous System

Unlike the CNS, which is protected by bones, meninges, and cerebrospinal fluid (CSF), the PNS has no such protections. The PNS also has no blood-brain barrier to protect it from toxins and pathogens in the blood. Therefore, the PNS is more subject to injury and disease than is the CNS. Causes of nerve injury include diabetes, infectious diseases such as shingles, and poisoning by toxins such as heavy metals. Disorders of the PNS often have symptoms such as loss of feeling, tingling, burning sensations, or muscle weakness. If a traumatic injury results in a nerve being transacted (cut all the way through), it may regenerate, but this is a very slow process and may take many months.

4.5.6 Summary

The peripheral nervous system (PNS) is composed of the groups of neurons (ganglia) and bundles of axons (nerves) that are outside of the brain and spinal cord. The PNS connects the CNS to the rest of the body.

Sensory (/afferent) nerves transmit information from sensory receptors in the body to the CNS. Motor (/efferent) transmit information from the CNS to muscles, organs, and glands. Mixed nerves transmit information in both directions and have both sensory (/afferent) and motor (/efferent functions). The PNS is divided into the autonomic nervous system and the somatic nervous system.

The somatic nervous system senses the external environment and controls voluntary activities, and consists of 12 pairs of cranial nerves (connected to the brain) and 31 pairs of spinal nerves (connected to the spinal cord). Cranial nerves can be strictly sensory, strictly motor, or a combination of the two functions. The olfactory nerve (CN I) is responsible for smell and the optic nerve (CN II) is responsible for vision. The oculomotor nerve (CN III) is responsible for eye movements, lifting the upper eyelid, and

controlling the size of the pupil. The trochlear nerve (CN IV) and the abducens nerve (CN VI) are both responsible for eye movement, but control different extraocular muscles. The trigeminal nerve (CN V) is responsible for cutaneous (skin) sensations of the face and controlling the muscles of mastication (chewing). The facial nerve (VII) is responsible for the muscles involved in facial expressions, as well as part of the sense of taste. The vestibulocochlear nerve (VIII) is responsible for the senses of hearing and balance. The glossopharyngeal nerve (IX) is responsible for controlling muscles in the throat, as well as part of the sense of taste. The vagus nerve (CN X) is responsible for contributing to homeostatic control of the organs of the thoracic and upper abdominal cavities. The accessory nerve (CN XI, along with cervical spinal nerves) is responsible for controlling the muscles of the neck. The hypoglossal nerve (CN XII) is responsible for controlling the muscles of the lower throat and tongue.

Spinal nerves are all mixed nerves with both sensory and motor fibers. The sensory axons enter the spinal cord as the dorsal nerve root and the motor fibers (both somatic and autonomic) emerge as the ventral nerve root. The sensory neuron cell bodies (soma) are located in dorsal root ganglia. Spinal nerves emerge from the spinal cord and are numbered from superior to inferior positions.

The autonomic nervous system senses the internal environment and controls involuntary activities. It is divided into the sympathetic division and parasympathetic division. Both affect most of the same organs and glands, but in opposite ways. The sympathetic division controls the fight-or-flight response and the parasympathetic division returns the body to normal after the fight-or-flight response has occurred.

The PNS does not have the same protections (bones, meninges, CSF, blood-brain barrier) that the CNS has, so it is more prone to injury and disease. If a nerve is transacted, it may regenerate, but this is a very slow process.

4.5.7 Additional Resources

Interested in the effects of meditation on the brain? See Integrative and Contemplative Neuroscience

Mindfulness techniques have been shown to reduce symptoms of depression as well as those of anxiety and stress. They have also been shown to be useful for pain management and performance enhancement. Specific mindfulness programs include Mindfulness-Based Stress Reduction (MBSR) and Mindfulness Mind-Fitness Training (MMFT). You can learn more about MBSR by watching the video below.

4.5.8 Attributions

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4.6: Communication and the Endocrine System

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Explain the difference between chemical signals in the nervous system and chemical signals in the endocrine system
2. Understand the reciprocal interactions between the influence of hormones on behavior and behavior on hormones
3. Identify at least three endocrine glands and describe their primary functions

4.6.1 Overview

Throughout the nervous system, neurons communicate via electrical and chemical signals. Another form of chemical communication is the secretion of hormones into the bloodstream, which is accomplished via endocrine glands located in the endocrine system. This chapter introduces the endocrine system and the major endocrine glands found in the brain and the body.

4.6.2 Communication in the Nervous System versus the Endocrine System

Nerve impulses are covered in depth in the nervous system communication chapter. Briefly, neurons in the nervous system communicate via electrical and chemical signals. When a neuron transmits an electrical signal, called a nerve impulse (or action potential), it travels down the axon and causes neurotransmitters to be released into the synapse. This chemical signal then influences the receiving cell in either an excitatory or inhibitory manner. A cell that receives nerve impulses from a neuron may be excited to perform a function, inhibited from carrying out an action, or otherwise controlled. In this way, the information transmitted by the nervous system is specific to particular cells and is transmitted very rapidly. In fact, the fastest nerve impulses travel at speeds greater than 100 meters per second! Compare this to the chemical messages carried by the hormones that are secreted into the blood by endocrine glands (below). These hormonal messages are “broadcast” to all the cells of the body, and they can travel only as quickly as the blood flows through the cardiovascular system.

4.6.2.1 Neural Transmission versus Hormonal Communication

Hormones are similar in function to neurotransmitters, the chemicals used by the nervous system in coordinating animals’ activities (as mentioned above). However, hormones can operate over a greater distance and over a much greater temporal range than neurotransmitters. Neural and hormonal communication both rely on chemical signals, but several important differences exist. Communication in the nervous system is analogous to traveling on a train. You can use the train in your travel plans as long as tracks exist between your intended origin and destination. Likewise, neural messages can travel only to destinations along existing nerve tracts. Hormonal communication, on the other hand, is like traveling in a car. You can drive to many more destinations than train travel allows because there are many more roads than railroad tracks. Similarly, hormonal messages can travel anywhere in the body via the circulatory system; any cell receiving blood is potentially able to receive a hormonal message.

Not all cells are influenced by each and every hormone. Rather, any given hormone can directly influence only cells that have specific hormone receptors for that particular hormone. Cells that have these specific receptors are called target cells for the hormone. When a hormone engages its receptor, a series of subsequent events either activates enzymes or turns genes on or off to regulate protein synthesis. The newly synthesized proteins may then activate or deactivate other genes, causing additional effects. Importantly, sufficient numbers of appropriate hormone receptors must be available for a specific hormone to produce any effects. For example, testosterone is important for male sexual behavior. If men have too little testosterone, their sexual motivation may be low, which can be restored by testosterone treatment. However, if men have normal or even elevated levels of testosterone yet display low sex drive, then it might be possible for a lack of receptors to be the cause, in which case treatment with additional hormones will not be effective.

Another difference is that neural messages are all-or-none events that have rapid onset and offset: neural signals can take place in milliseconds. For example, the nervous system regulates immediate food intake and directs body movement, changes in the body that are relatively rapid. In contrast, hormonal messages are graded events that may take seconds, minutes, or even hours to occur. Hormones can mediate long-term processes, such as growth, development, reproduction, and metabolism.

4.6.2.2 Interactions Between Hormones and Behavior

The scientific study of the interaction between hormones and behavior is called behavioral endocrinology. This interaction is bidirectional: hormones can influence behavior, and behavior can sometimes influence hormone concentrations. Hormones are chemical messengers produced and released by specialized glands called endocrine glands (see below). Hormones are released from these glands into the blood, where they travel to act on target structures anywhere in the body, influencing the nervous system to regulate an individual's behaviors (such as aggression, mating, and parenting). Examples of hormones that influence behavior include steroid hormones such as testosterone (a common type of androgen), estradiol (a common type of estrogen), progesterone (a common type of progestin), and cortisol (a common type of glucocorticoid). Several types of protein or peptide (small protein) hormones also influence behavior, including oxytocin, vasopressin, prolactin, and leptin.

There are many ways that hormones influence behavior and behavior feeds back to influence hormone secretion. Some examples include hormones in the mediation of food and fluid intake, social interactions, salt balance, learning and memory, stress coping, as well as psychopathology including depression, anxiety disorders, eating disorders, postpartum depression, and seasonal depression. Some other hormone-behavior interactions that are related to reproductive behaviors are described in Chapter 13.1.

4.6.3 Introduction to the Endocrine System

As the endocrine system is not a part of the nervous system, this section may surprise you. However, as textbook author James W. Kalat states, “Hormonal influences resemble synaptic transmission in many ways, including the fact that many chemicals serve both as neurotransmitters and hormones” (Kalat, 2019, page 59). Thus, to understand many of the topics that will be covered in upcoming chapters, you will need a basic understanding of the endocrine system.

The **endocrine system** is a system of glands called **endocrine glands** that release chemical messenger molecules called **hormones** into the bloodstream. Other glands of the body, including sweat glands and salivary glands, also secrete substances but not into the bloodstream. Instead, they secrete them through ducts that carry them to nearby body surfaces. These other glands are called **exocrine glands.**

Endocrine hormones must travel through the bloodstream to the cells they affect, and this takes time. Because endocrine hormones are released into the bloodstream, they travel throughout the body wherever blood flows. As a result, endocrine hormones may affect many cells and have body-wide effects. Endocrine hormones may cause effects that last for days, weeks, or even months.

4.6.3.1 Major Glands of the Endocrine System

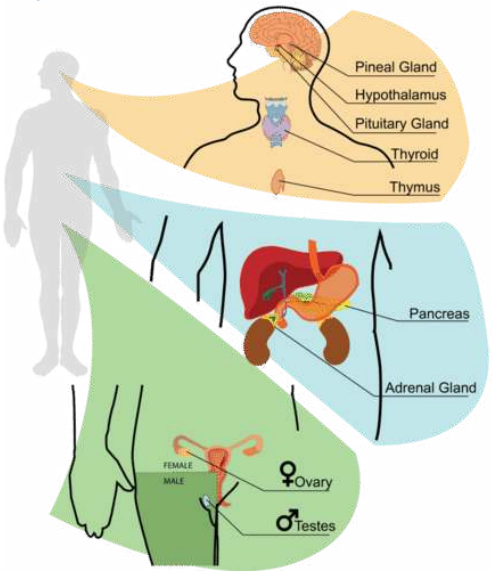


Figure 4.6.1: Endocrine Glands. All of the glands in this figure are part of the endocrine system. Note that the ovary and testis are the only endocrine glands that differ in males and females.

The major glands of the endocrine system are shown in Figure 4.6.1. The glands in the figure are described briefly in the rest of this section. Refer to the figure as you read about the glands in the following text.

4.6.3.1.1 Endocrine Glands in the Brain

The **pituitary gland** is located at the base of the brain. It is controlled by the nervous system via the brain structure called the **hypothalamus**, to which it is connected by a thin stalk (called the **infundibulum**). The pituitary gland consists of two lobes, called the anterior (front) lobe and posterior (back) lobe. The posterior lobe, composed of nervous tissue, stores and secretes hormones synthesized by the hypothalamus, specifically the hormones oxytocin and vasopressin (also called antidiuretic hormone).

The anterior lobe, composed of glandular tissue, synthesizes and secretes many of its own endocrine hormones, also under the influence of the hypothalamus. One endocrine hormone secreted by the anterior pituitary gland is growth hormone, which stimulates cells throughout the body to synthesize proteins and divide. Most of the other endocrine hormones secreted by the anterior pituitary gland are called **tropic hormones** because they control other endocrine glands. Generally, tropic hormones direct other endocrine glands to secrete either more or less of their own hormones, such as adrenocorticotrophic hormone (ACTH) stimulating the adrenal gland to produce the "stress" hormone cortisol. This is why the pituitary gland is often referred to as the “master gland” of the endocrine system. Since the hypothalamus is the structure that controls both the anterior and posterior parts of the pituitary, you can think of it as the "master" of the "master gland".

The **pineal gland** (also called the **epithalamus**) is a tiny gland located near the center of the brain. It secretes the hormone melatonin, which controls the sleep-wake cycle and several other processes. The production of melatonin is stimulated by darkness and inhibited by light. Cells in the retina of the eye detect light and send signals to a structure in the hypothalamus named the **suprachiasmatic nucleus** (SCN). Nerve fibers carry the signals from the SCN to the pineal gland via the autonomic nervous system.

4.6.3.1.2 Endocrine Glands in the Body

Each of the other major glands of the endocrine system is summarized briefly below. Several of these endocrine glands are also discussed in greater detail as they relate to other topics in separate chapters.

- The **thyroid gland** is a large gland in the neck. Thyroid hormones such as **thyroxine** increase the rate of metabolism in cells throughout the body. They control how quickly cells use energy and make proteins.
- The **thymus gland** is located in front of the heart. It is the site where immune system cells called T cells mature. T cells are critical to the adaptive immune system, facilitating the body's adaption to specific pathogens.
- The **pancreas** is located near the stomach. Its endocrine hormones include **insulin** and **glucagon**, which work together to control the level of glucose in the blood. The pancreas also secretes digestive enzymes into the small intestine.
- The two **adrenal glands** are located above the kidneys. Adrenal glands secrete several different endocrine hormones, including the hormone **epinephrine** (also known as adrenaline), which is involved in the fight-or-flight response. Other endocrine hormones secreted by the adrenal glands have a variety of functions. For example, the hormone **aldosterone** helps to regulate the balance of minerals in the body. The "stress" hormone **cortisol** is also an adrenal gland hormone.
- The paired **gonads** include the **ovaries** in females and **testes** in males. They secrete sex hormones, such as **testosterone** (in males) and **estrogen** (in females). These hormones control sexual maturation during puberty and the production of **gametes** (sperm or egg cells) by the gonads after sexual maturation.

4.6.4 Summary

Neurons communicate via electrical and chemical signals. The endocrine system also communicates via chemical signals, using hormones traveling through the bloodstream. Hormones are secreted by endocrine glands, and have similar features to neurotransmitters (which are released at synapses between neurons in the nervous system). Both neural and hormonal communication rely on chemical signals. However, hormones can operate over a greater distance (anywhere in the body via the circulatory system) and over a much greater time length, and can thus mediate long-term processes. A particular hormone can only influence cells that have receptors for that specific hormone. The interaction between hormones and behavior is bidirectional: hormones can influence behavior, and behavior can sometimes influence hormone concentrations.

A basic understanding of the endocrine system is necessary to understand many of the topics covered in other chapters. Endocrine glands in the brain include the pituitary gland (located at the base of the brain), the hypothalamus (immediately above the pituitary gland), and the pineal gland (near the center of the brain). The pituitary gland is controlled by the hypothalamus, to which it is connected by a thin stalk (the infundibulum). The pituitary gland consists of an anterior (front) lobe and a posterior (back) lobe. The posterior lobe (composed of nervous tissue) stores and secretes hormones synthesized by the hypothalamus, specifically oxytocin and vasopressin (also called antidiuretic hormone). The anterior lobe (composed of glandular tissue) synthesizes and secretes many of its own endocrine hormones, one of which is growth hormone, which stimulates cells throughout the body to

synthesize proteins and divide. Most of the anterior pituitary gland hormones control other endocrine glands, such as adrenocorticotrophic hormone (ACTH), which stimulates the adrenal gland to produce cortisol. The pineal gland secretes the hormone melatonin, which controls the sleep-wake cycle.

Some major endocrine glands in the body include the thyroid gland, the thymus gland, the pancreas, the adrenal glands, and the gonads. The thyroid gland is in the neck and secretes hormones that control how quickly cells use energy and make proteins. The thymus gland is located in front of the heart, and is the site where T cells (of the immune system) mature. T cells facilitate the body's adaption to specific pathogens. The pancreas is located near the stomach. Its endocrine hormones (insulin and glucagon) work together to control the level of glucose in the blood. The two adrenal glands (located above the kidneys) secrete several different endocrine hormones, including the hormone epinephrine (adrenaline), involved in the fight-or-flight response, and the "stress" hormone cortisol. The paired gonads include the ovaries in females and testes in males. The gonads secrete sex hormones (such as testosterone in males and estrogen in females), which control sexual maturation during puberty and the production of gametes (sperm or egg cells).

4.6.5 References

Kalat, J.W. (2019). *Biological Psychology* (13th ed.). Cengage.

4.6.6 Additional Resources

Most people want to live a long, healthy life. Geneticist Cynthia Kenyon’s research suggests that endocrine hormones may be a key to human longevity. Watch this fascinating TED talk to learn how.

4.6.7 Attributions

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CHAPTER OVERVIEW

5: Communication within the Nervous System

5.1: Neurons and their Basic Functions

5.2: Within-neuron Communication- Electrical Potentials from Resting to Action

5.3: Between-Neuron Communicaton- Synaptic Transmission

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5.1: Neurons and their Basic Functions

5.1.1 Learning Objectives

1. Describe the anatomy of neurons and the function of each of the three major parts of a neuron
2. Describe neurotransmitters, synapse, synaptic vesicles, resting potential, EPSP, IPSP, and action potential
3. Explain saltatory conduction and why it is important to communication within the nervous system; include description of the myelin sheath and nodes of Ranvier
4. Describe the role of post-synaptic receptor sites in communication between neurons
5. Describe neurons classified by shape and by their functions

5.1.2 **Overview**

In this section, we continue our exploration of neurons, the building blocks of the nervous system. We examine how they generate electrochemical signals, and how the billions of neurons in the nervous system communicate with one another, a process known as synaptic transmission. Before tackling these topics, we review and expand the basic anatomy and functioning of neurons covered in part in Chapter 4. A sound grasp of these facts provides the groundwork for understanding how neuron potentials are generated within neurons and how they combine to trigger synaptic transmission. As you read, remember that the voltages and chemical events we discuss in this section, operating in large populations of brain cells, somehow generate our perceptions, thoughts, emotions, and the entirety of our mental experience. To date, how this happens, how patterns of neuron potentials in brain circuits become conscious minds, remains the greatest mystery of all facing modern science.

5.1.3 Neuron Anatomy and The Synapse

To understand neuron function, it is important to review the neuronal anatomy presented previously.

Although there are some exceptions, neurons have three major structural parts - - the **soma** or cell body, **dendrites** (the "receivers" of the neuron), and the **axon** (the ouput end of the neuron). The entire neuron is bounded by a **cell membrane**, the neuronal membrane. The neuronal membrane of a neuron has **channels or "doors" for ions** (electrically charged atoms) which are able to pass through the membrane when specific channels are opened. Figure 5.1.1 shows this basic neuron anatomy.

The **soma or cell body** contains organelles, such as ribosomes and mitochondria which are common to most types of cells in the body. These are involved in the basic metabolism of the cell. The soma also contains the **nucleus**, where the genes and chromosomes (containing DNA) are located.

The second main part of the neuron are the **dendrites**, the information receivers of the neuron. Dendrites in some neurons can branch profusely (**dendritic trees**), expanding the region of the neuron that can receive inputs from other neurons. The **receptor sites** (or more technically, **postsynaptic receptor sites** because of their location on the receiving or postsynaptic neuron) which receive molecules of **neurotransmitter** are located on the dendrites (and, to a lesser degree, on the soma) of the receiving neuron. On the dendrites are small **dendritic spines** which are associated with the connections between neurons (the **synapses**) and can change shape rapidly when learning occurs. Notice that the spines are not the same thing as dendritic branches. In Figure 5.1.2, a dendritic branch with dendritic spines is shown on the left in microscopic detail, and on the right, are dendritic trees of two types of neuron found in the retina. Spines are not visible in the images of dendritic trees on the right because the dendritic spines are too small, while dendritic branches comprising the dendritic trees can easily be seen (see caption for Figure 5.1.2).

Note: A detailed discussion of the structure of the synapse and synaptic communication will be covered later in this chapter.

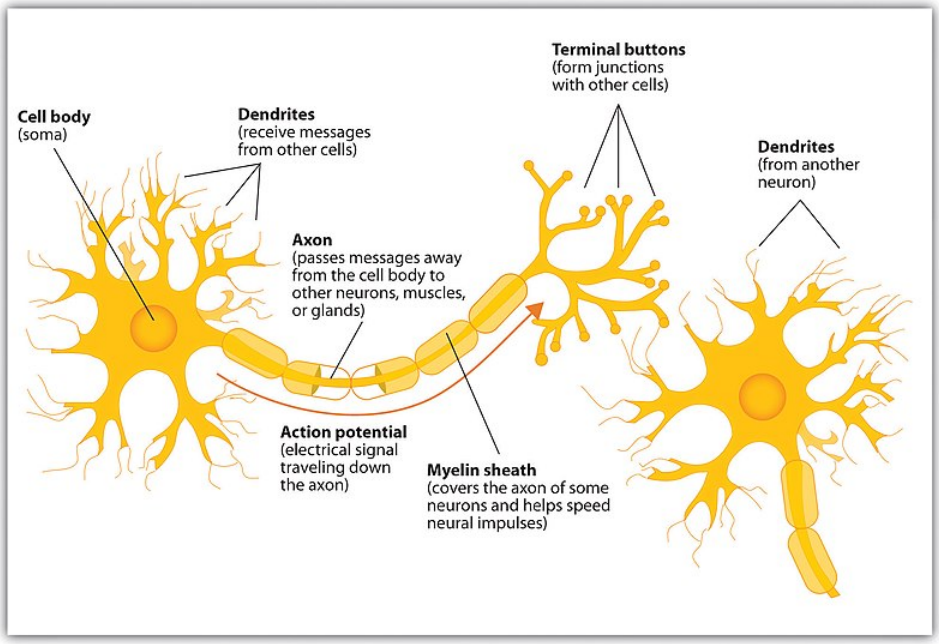


Figure 5.1.1: Basic structure of a neuron (Image from Wikimedia Commons; File:Components of neuron.jpg; https://commons.wikimedia.org/wiki/F..._of_neuron.jpg; by Jennifer Walinga; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

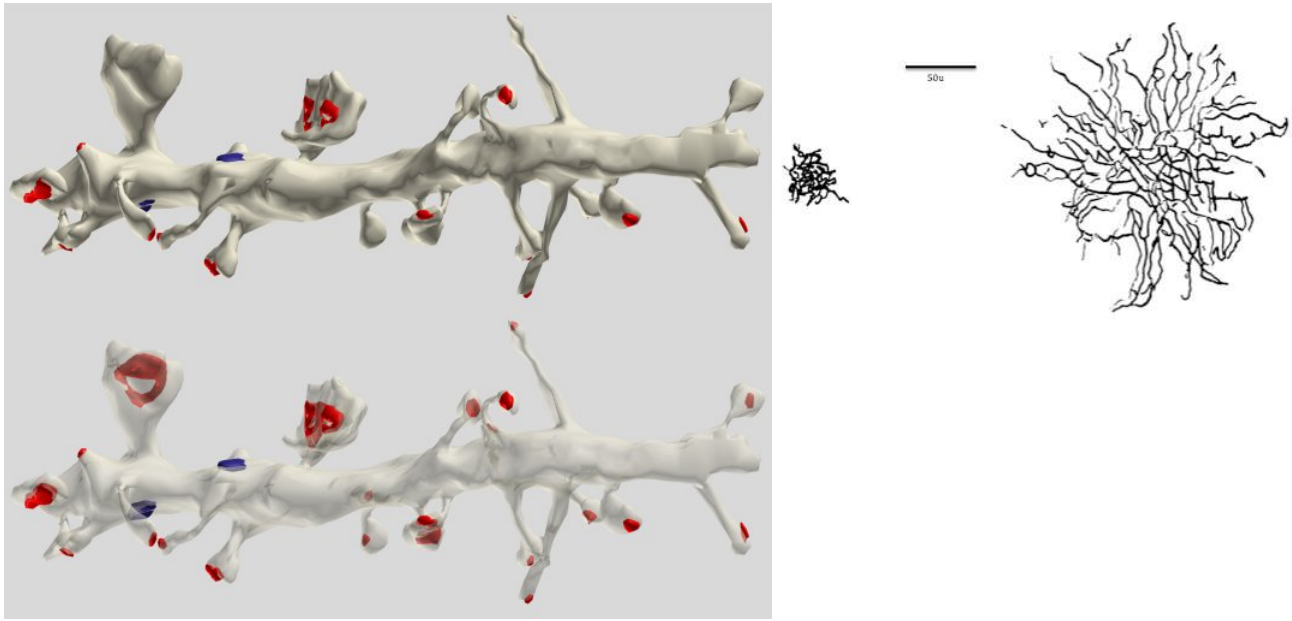


Figure 5.1.2: (Left) A segment of a pyramidal cell dendrite from a brain area known as the hippocampus with thin, stubby, and mushroom-shaped spines. Spine synapses are colored in red, stem (or shaft) synapses are colored in blue. The dendrite was made transparent in the lower image to enable visualization of all synapses. (Right) Dendritic spines in two different neurons are too small to be visible in the two images on the right. (Left Image: Authored by Synapse Web, Kristen M. Harris, PI, https://commons.wikimedia.org/wiki/F...atum_(CA1).jpg licensed under Creative Commons Attribution 2.0 Generic license; Right Image: From Wikimedia Commons; https://commons.wikimedia.org/wiki/F...rasol_cell.png; by Stromdabomb licensed under the Creative Commons Attribution-Share Alike 4.0 International license; Additional explanation by Kenneth A. Koenigshofer, PhD).

The third major part of the neuron is the **axon**, coming out of the soma like a hose. The axon carries the output messages of a neuron (nerve impulses) along its length to its **axon terminals** (axon endings). There is only one axon per neuron, although it can branch into multiple axon terminals. In a typical neuron, the root end of the axon emerges out of the soma at a small swelling called the **axon hillock**. Between the axon hillock and the first segment of the axon is where the nerve impulse is first generated (see discussion of the action potential, the nerve impulse, that follows below).

5.1.3.1 Myelinated and Unmyelinated Axons

Some axons have a glial cell covering known as the **myelin sheath**. The glial cells capable of producing myelin include oligodendrocytes of the CNS and the Schwann cells of the PNS. This fatty, insulating, myelin sheath has gaps in it, revealing the bare axon, at regular intervals along the axon's length. These bare spots along the length of a **myelinated axon** are called nodes, or **nodes of Ranvier**, after their discoverer.

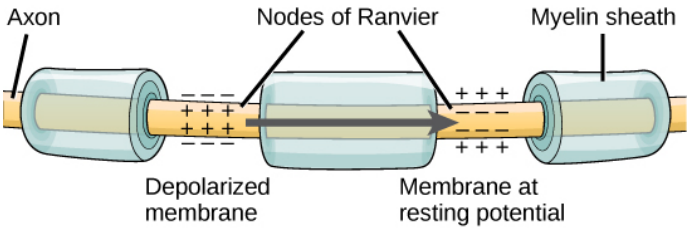


Figure 5.1.3: **Nodes of Ranvier.** Nodes of Ranvier are gaps in the myelin sheath which covers myelinated axons. Nodes contain voltage-gated potassium (K+) and sodium (Na+) channels. Action potentials travel down the axon by "jumping"from one node to the next, speeding conduction of the action potential down the length of the axon toward the axon ending, also known as the axon bouton, axon button, or axon terminal.

The function of the myelin sheath and the nodes is to speed up the rate at which nerve impulses travel down the length of the axon toward their destination, the axon terminal. In myelinated axons, the impulses sort of "jump" from node to node allowing the action potential to move more rapidly down the axon. This leaping of the nerve impulse (action potential) from node to node is called **saltatory conduction,** from the Latin "saltatore" which means to dance. Imagine the romantic image of the impulse dancing from node to node. More details on the electrical nature of this conduction will be addressed in the next section of this chapter.

Not all axons are myelinated. **Unmyelinated axons** tend to be older in evolution and to be the smaller diameter axons (classified as C fibers based on their small diameters; large diameter myelinated axons are called A fibers). In unmyelinated axons, in order to move, the nerve impulse must be regenerated at every successive point along the axon. This takes time and slows the conduction of the nerve impulse (the action potential) down the length of the axon. Therefore, conduction of the action potential down the length of an unmyelinated axon is relatively slow. An example of unmyelinated C fibers are axons that are part of slow pain pathways. These pathways mediate the slower aching pain that follows tissue damage. The quick, sharp pain from an injury is mediated by larger diameter A fibers (axons).

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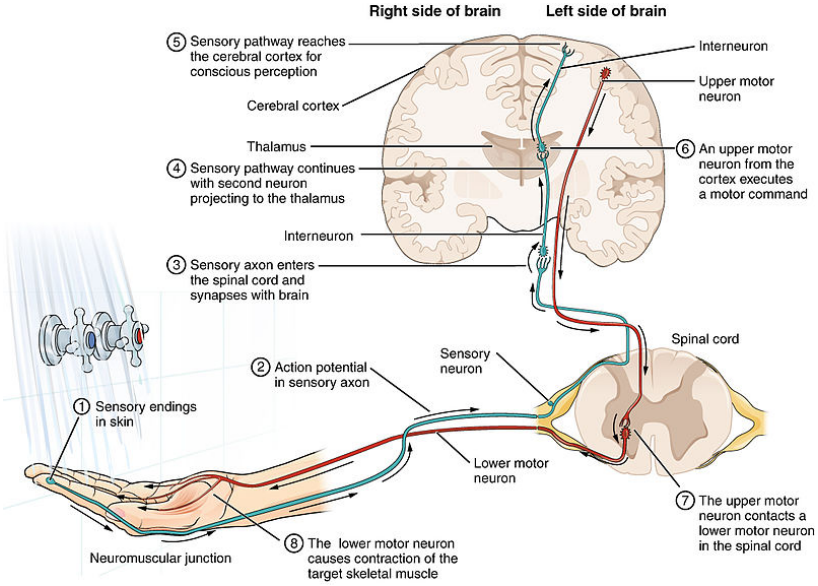


Figure 5.1.4: Sensory neurons carry information towards the CNS. Motor neurons carry information from the CNS. Interneurons carry information between sensory and motor neurons.

"Approximately 95% of the cortical neuronal activity is mediated by fast excitatory (glutamate, 80%) and fast inhibitory (GABA, 15%) neurons. The remaining 5% percent is associated with the slow modulatory action of monoaminergic (dopamine, serotonin, noradrenaline) and non-monoaminergic (acetylcholine, endorphins, etc.) neurons located in small subcortical nuclei of the mesencephalon and projecting to the cerebral cortex" (Marco Catani, in Encyclopedia of Behavioral Neuroscience, 2nd edition, 2022, Science Direct; https://www.sciencedirect.com/topics...pyramidal-cell; retrieved 4/25/22).

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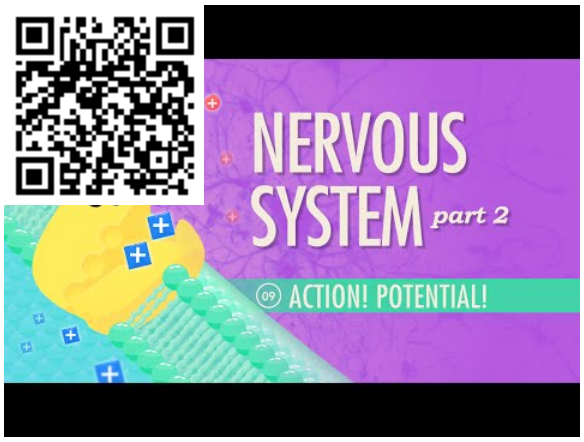
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5.1.5.1 Outside Resources

Video: An animation and an explanation of an action potential

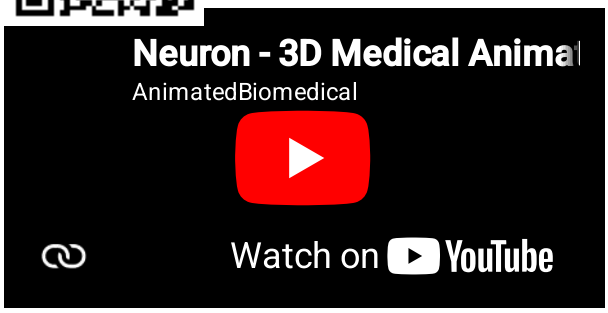




Video: An animation of neurotransmitter actions at the synapse



Vid ation of an action potential





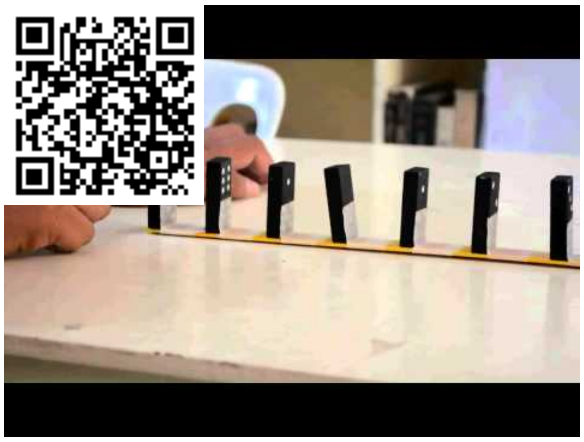
Video: Another animation of neurotransmitter actions at the synapse



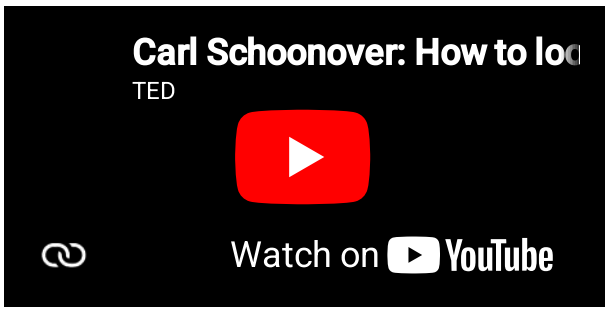


Video: Domino Action Potential: This hands-on activity helps students grasp the complex process of the action potential, as well as become familiar with the characteristics of transmission (e.g., all-or-none response, refractory period).





Video: For perspective on techniques in neuroscience to look inside the brain





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Video: You can grow new brain cells. Here's how. -Can we, as adults, grow new neurons? Neuroscientist Sandrine Thuret says that we can, and she offers research and practical advice on how we can help our brains better perform neurogenesis—improving mood, increasing memory formation and preventing the decline associated with aging along the way.





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5.2: Within-neuron Communication- Electrical Potentials from Resting to Action

5.2.1 Overview

Information processing that contributes to the workings of our minds and control behavior depend upon neurons and their electrical and chemical interactions. Neurons produce electrical potentials (voltages) that act as signals in the information processing activities of the brain. As previously mentioned, neurons communicate with one another across synaptic spaces using chemicals known as neurotransmitters. However, before communication can take place between neurons, there is a series of electrical changes that must occur ***within*** neurons. In this module, we examine how neurons create these electrical changes or potentials including the resting, post-synaptic, and action potential.

5.2.2 Within-Neuron Potentials: How Neurons Produce Electrical Potentials

Before a neuron can send a chemical message to another neuron, muscle, or gland it usually must experience an electrical change within itself. Neurons are capable of producing electrical activity (i.e. voltage potentials) by the unequal distribution and movement of electrically charged atoms called ions across the neuron's cell membrane. These ions come mainly from dissolved salts in the body fluids inside and outside neurons.

The main ions used by neurons to produce their voltages are sodium (Na+), potassium (K+), and chloride (Cl-). Notice that the first two are positive ions and the last, chloride ions, are negatively charged. A fourth ion, organic anions (A-), which are large (on the molecular scale) negatively charged proteins, are manufactured inside the neuron. They are too large to cross the cell membrane, and therefore give the neuron's ***resting voltage*** a **negative** bias. The distribution or concentrations of these ions inside and outside a neuron determine its voltage (voltage is just the physical separation of charged particles, like in a car battery with its positive and negative poles around which are concentrated positively and negatively charged particles floating in battery acid).

By these means, three main types of neuron voltages or neuron potentials are produced by neurons: 1) **the resting potential** (often equal to about negative 70 thousandths of a volt, -70 millivolts) 2) **post-synaptic potentials (PSPs)**-- which can be **excitatory (EPSPs)** or **inhibitory (IPSPs)** and 3) the **action potential** (AP, the nerve impulse). The action potential is the last step of within-neuron communication which then triggers the chemical communication between neurons. Let's examine these potentials in more detail and see how they are generated inside neurons.

5.2.3 The Neuronal Cell Membrane

The **neuronal cell membrane**, which is composed of a lipid bilayer of fat molecules, separates the fluid inside of the cell from the surrounding extracellular fluid. There are proteins that span the membrane, forming **ion channels** that allow, when open, particular ions to pass between the intracellular and extracellular fluid (see Figure 5.2.1). 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 ion concentration and charge, in part enforced by the physical barrier of the cell membrane when ion channels to specific ions are closed, a voltage is produced, the resting potential.

5.2.4 The Resting Membrane Potential

The **resting potential** can be thought of as a baseline voltage from which the other neuron potentials are generated. It is the voltage inside a nerve cell when it is at rest, that is, it is neither receiving inputs at the moment nor generating any outputs. In this state of "rest", the voltage inside the nerve cell is approximately -70 mv. It is negative inside the neuron at "rest" because there are more negative ions inside the neuron (the intracellular fluid) and more positive ions on the outside (the extracellular fluid). Specifically, there are large numbers of Na+ ions (sodium ions) outside the neuron and very few of these on the inside, when the neuron is "at rest". And there are more negatively charged ions inside the cell than on the outside during resting potential. During the resting potential ion channels to Na+ are closed.

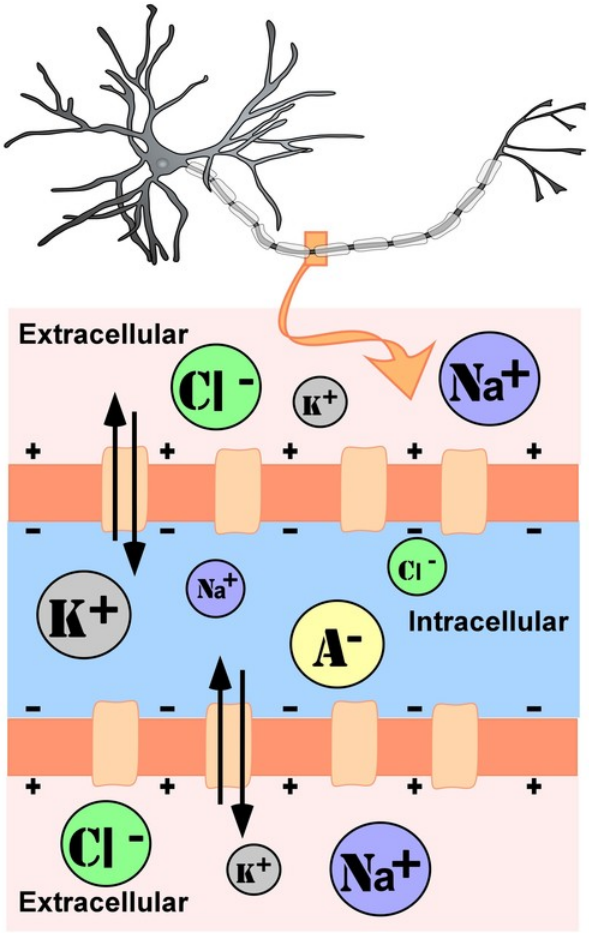
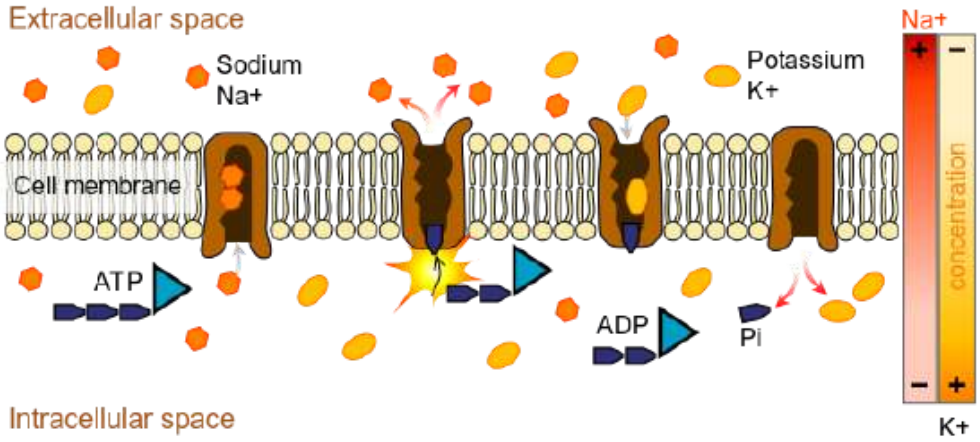


Figure 5.2.1: Representation of ion concentrations inside (intracellular) and outside (extracellular) a neuron at rest in the unmyelinated segment of the axon. Size of the circles represents relative concentrations of each ion inside and outside the neuron; note that when the neuron is "at rest" it has a net negative charge inside, the resting potential, equal to about -70 millivolts in most neurons. Also note the higher concentrations of sodium (Na+) and chloride (Cl-) ions outside the cell. Sodium on the outside of the neuron "would like" to move into the cell along its charge and concentration gradients, but it can't when the cell is at rest, because the ion channels for sodium ions are closed, creating a physical barrier keeping most of the extracellular sodium ions from crossing through the cell membrane. But what happens when the sodium channels open? And, test yourself, what opens the ion channels? (Authored by: R. Biswas-Diener & E. Diener (Eds), *Noba textbook series: Psychology.* Champaign, IL: DEF publishers, Neurons by Sharon Furtak at NOBA is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

5.2.4.1 The Sodium-Potassium Pump

During the resting potential, the **sodium-potassium pump** maintains a difference in charge across the cell membrane of the neuron. The sodium-potassium pump is a mechanism of active transport that moves sodium ions out of cells and potassium ions into cells. The sodium-potassium pump moves both ions from areas of lower to higher concentration, using energy in ATP and carrier proteins in the cell membrane (see Figure 5.2.2).



5.2.4.1.1

Figure 5.2.2: The sodium-potassium pump helps maintain the resting potential of a neuron. During resting potential, there is more negative charge inside than outside the cell creating a resting potential of -70mv. During resting potential, some Na+ leaks into the neuron and some K+ leaks out. ATP (Adenosine triphosphate) provides energy to pump sodium out and potassium into the cell. There is more concentration of sodium outside the membrane and more concentration of potassium inside the cell due in part to the unequal movement of these ions by the pump. The presence of negatively charged organic anions (A-) contributes to the net negative charge (-70mv) inside the neuron at rest. (Image from Wikimedia Commons; File:Scheme sodium-potassium pump-en.svg; https://commons.wikimedia.org/wiki/F...um_pump-en.svg; by LadyofHats Mariana Ruiz Villarreal; released into the **public domain** by its author, **LadyofHats**. This applies worldwide).

5.2.5 Electrical and Concentration Gradients: How Ions Move Across the Neuronal Membrane.

For a neuron to move away from the resting state, other neuron potentials need to be generated. In other words, a redistribution of ions (and their electrical charges) must occur across the cell membrane resulting in a positive or negative voltage change in the neuron. In short, ions must move.

There are two main forces (called gradients) that can cause these ions to move.

First, opposite charges attract one another ("opposites attract"), and like charges repel one another. When ions of opposite charge are unequally distributed across the cell membrane (as is the case during the resting potential), this sets up what is called a **charge or electrical gradient** (an unequal distribution of charged particles).This gradient then creates an **electrostatic force.** If these ions are allowed to move freely, they will move along this electrical gradient with positive charges moving toward negative ones and vice versa.

Secondly, when ions of any particular type (for example, sodium ions) are unequally distributed across the cell membrane (like during the resting potential), this sets up what is called a **concentration gradient** which can cause diffusion. Diffusion is when the net movement of ions from a region of higher concentration to a region of lower concentration occurs. Such concentration gradients for several ions (sodium, potassium, and chloride ions) exist when the neuron is at resting potential (see Figure 5.2.1). Ions, if allowed to move freely, will move along their concentration gradients, such that ions of a particular type (like Na+ ions) will move from a region of high concentration (of Na+) to a region of lower concentration (of Na+).

In short, ions, if allowed to move freely, will move along both their electrical and concentration gradients. Ions "want" to move to equalize their concentrations across the cell membrane and also "want" to move to equalize the charges across the cell membrane.

However, it is important to note that **these two forces created by the electrical and concentration gradients for each ion can oppose one another** in the case of some ions, **or can act together** (as is the case with Na+ ions during the resting potential).

Let us see how these two forces, diffusion (due to concentration gradients) and electrostatic pressure (due to a charge gradient), 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 A- is 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 very permeable to potassium at rest, but potassium remains in high concentrations inside the cell. Diffusion created by the concentration gradient pushes K+ to the outside of the cell because it is in high concentration

inside the cell. However, electrostatic pressure created by the charge gradient pushes K+ into 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+ *with the charge gradient (opposite charges attract) overpowering the concentration gradient so that the net effect is to push and keep K+ inside the neuron in higher concentrations*.

3. ***Chloride (Cl-)****:* The cell membrane is also very permeable to chloride at rest, but chloride remains in high concentration outside the cell. Diffusion created by a concentration gradient for Cl- pushes Cl- toward the inside of the cell because it is in high concentration outside the cell. However, electrostatic pressure created by the charge gradient for Cl- pushes Cl- toward the outside of the cell because the negative charge of Cl- is attracted to the positive charge outside the cell created primarily by the high concentration of Na+ there. Similar to K+, these forces oppose one another with respect to Cl- *and again, in this case, like Na+, the more powerful charge gradient (like charges repel) overcomes the weaker concentration gradient for Cl-.*
4. ***Sodium (Na+)****:* The cell membrane is not very permeable to sodium when the neuron is at rest. Diffusion created by a concentration gradient pushes Na+ toward the inside of the cell because it is in high concentration outside the cell. Electrostatic pressure created by the charge gradient for Na+ also pushes Na+ toward the inside of 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, as discussed above, Na+ cannot permeate the cell membrane because the channels for Na+ are closed and so Na+ remains in high concentration outside the cell. The small amounts of Na+ inside the cell are removed by the **sodium-potassium pump** (Figure 5.2.2), which uses the neuron's energy (adenosine triphosphate, ATP) to pump three Na+ ions out of the cell in exchange for bringing two K+ ions inside the cell.

Though ions "want" to move in these ways dictated by their charge gradients and concentration gradients, Na+ can't move freely when the neuron is at resting membrane potential because Na+ ion channels are closed. Thus, the cell membrane acts as a physical barrier to Na+ ions, preserving the unequal distributions of Na+ ions inside and outside the neuron. To get ion movement, pores or ion channels in the cell membrane of the neuron "at rest" must be opened, overcoming the physical barrier created by the cell membrane when the neuron is "at rest" (not receiving any inputs via its dendrites and not generating any outputs, action potentials, via its axon) and its sodium channels are closed.

What is it that causes the ion channels to open allowing the ions to move along their gradients? What is it that opens the ion channels? In reality, there are several possible triggers for ion channel changes, many of which are related to sensory input (physical stimulation to dendrites, chemical input from taste or smell systems, light or sound energy, etc.) However, the axonal release and subsequent arrival of transmitter molecules onto the postsynaptic neuron is the main trigger for PSPs that is presented here. In short, the "lock and key" interaction between molecules of transmitter and the post-synaptic receptor sites causes "doors" (specific ion channels) to open.

When specific ion channels get opened in this way (Na+ channels, for example), those specific ions move through the cell membrane along their specific concentration and electrical gradients. This will cause a voltage shift away from resting potential. This voltage shift is the post-synaptic potential. n this case it is an excitatory post-synaptic potential (EPSP), a positive shift in voltage away from resting potential because when Na+ channels in the cell membrane are opened by neurotransmitter, then Na+ ions will move along their charge gradient and concentration gradient into the cell, making the inside of the neuron more positively charged.

5.2.6 Excitatory and Inhibitory Post-synaptic Potentials (EPSPs and IPSPs)

As mentioned above, the cell membrane of a neuron has **channels or "doors" for ions** (electrically charged atoms) which can pass through the membrane when specific channels are opened for specific ions. Normally the ion channels on the membrane of a postsynaptic neuron are closed until they experience a sensory input or are acted upon by the attachment of neurotransmitter molecules to receptors sites on the membrane. The attachment of the molecules of transmitter to the receptors sites **(receptor binding)**, like a key into a lock, **opens the "doors" (ion channels) to specific ions** which pass through the cell membrane carrying with them their electrical charge.

This ion channel opening results in a change in the electrical state of the neuron, a post-synaptic potential (i.e. a voltage shift in the post-synaptic neuron). If a positive shift in voltage occurs, it is called an **EPSP**, an **excitatory post-synaptic potential**; if a negative shift in voltage occurs, then it is called an **IPSP**, an **inhibitory post-synaptic potential**. **EPSPs** are triggered when neurotransmitter binds to "excitatory" receptors, and **IPSPs** are produced when transmitter binds to "inhibitory" receptors. Receptors are classified as excitatory if their transmitter binding results in an excitation or increase in voltage of the neuron. They are classified as inhibitory if they result in the decrease of the voltage of the neuron.

These **PSPs**, whether excitatory or inhibitory, are called **graded potentials** because they are **not of a fixed voltage,** but instead vary in voltage depending on the amount of neurotransmitter (and other factors) that has been released into the synapse. This is in contrast to the **action potential** (the nerve impulse) which is of a **fixed voltage and is "all or none,"** The all or none law will be fully detailed in the action potential section below. Think of two types of light switches: a typical on/off switch vs. a dimmer switch. A typical on/off switch only has two options and is similar to the all or none action potential, whereas, the dimmer switch has multiple options along a continuum and is most similar to the graded PSPs.

These post-synaptic potentials occur in a post-synaptic neuron (thus the name), a receiver neuron. When such a neuron receives an input from a pre-synaptic neuron, in the form of transmitter molecules which attach to the **post-synaptic receptor sites (which are proteins that are embedded in the membrane of the post-synaptic cell)**, ion channels then open, ions move across the cell membrane, carrying with them their electrical charges. These events change the voltage inside the post-synaptic neuron. It is this voltage shift away from resting potential that constitutes the post-synaptic potential (PSP).

Note, again, that in both the EPSP and the IPSP, it is the attachment of molecules of transmitter to post-synaptic receptor sites (like keys going into locks of a specific shape) that opens the "doors", the ion channels, allowing ions to move through the cell membrane.

But there is one more key issue here. What is it that determines *which* ion channels open, and therefore, whether an EPSP or an IPSP occurs? The answer was implied above. The answer is: it is the type of neurotransmitter and type of receptor site receiving the transmitter molecules that determines the ultimate effect.

Excitatory transmitters (such as glutamate, acetylcholine--ACh, norepinephrine--NE, dopamine--DA) are those which **open positive ion channels** in the post-synaptic membrane, allowing these ions (i.e. sodium - NA+, Ca++) to flow, carrying their positive charge, into the cell and triggering an EPSP.

Inhibitory transmitters (such as gamma-amino-butyric acid--GABA, serotonin--5-HT, or dopamine--DA) are those which affect specific channels, such as chloride and potassium channels in the post-synaptic membrane, allowing chloride to follow its concentration gradient (overcoming the opposing charge gradient) into the post-synaptic neuron and allowing potassium to follow its concentration gradient (overcoming its opposing charge gradient) and moving out. These ion movements make the inside of the neuron more negative, making an IPSP.

Notice that DA is listed as both excitatory and inhibitory. That's because some post-synaptic DA receptors are inhibitory, leading to IPSPs when activated by DA, and other DA receptors are excitatory, producing EPSPs when they bind with DA. In fact, many neurotransmitters have both excitatory and inhibitory receptors. The particular distribution of these two types of receptors on a postsynaptic cell will ultimately determine whether excitation or inhibition occurs when neurotransmitter travels across the synapse. Thus,we must be careful when referring to a particular transmitter as excitatory or inhibitory, because they probably can be both.

In summary,

1. **Excitatory postsynaptic potentials** (EPSPs): a graded *depolarizing (increasing)* current that causes the membrane potential to become more positive and move closer to the threshold of excitation (approximately -55 millivolts) for action potential production.
2. **Inhibitory postsynaptic potentials** (IPSPs): a *hyperpolarizing* (*decreasing*) current that causes the membrane potential to become more negative and move farther from the threshold of excitation (approximately -55 millivolts) for action potential production.

5.2.6.1 Spatial and Temporal Summation

There is one additional factor in this process. Each neuron connects with numerous other neurons, often receiving multiple impulses from them. Sometimes, a single excitatory postsynaptic potential (EPSP) is strong enough to induce an action potential in the postsynaptic neuron, but often multiple presynaptic inputs must create EPSPs around the same time for the postsynaptic neuron to be sufficiently depolarized to fire an action potential. Summation, either spatial or temporal, is the addition of these impulses at the axon hillock. Together, synaptic summation and the threshold for excitation act as a filter so that random “noise” in the system is not transmitted as important information.

At any moment in time, each neuron can be receiving mixed messages, both EPSPs and IPSPs. Thus, receiver neurons (post-synaptic neurons) can receive multiple inputs--simultaneously or over time or space. The multiple inputs can add up--this is called summation and there are two types. **Spatial summation** refers to two or more PSPs arriving at different locations (i.e. different

spaces on the receiving neuron, thus spatial summation) on the post-synaptic (receiver) neuron simultaneously or close enough in time so that their voltages add together. For example, an IPSP of negative 25 millivolts (thousandths of a volt) might add to an EPSP of 50 millivolts occurring at the same time = 50 millivolts positive - 25 millivolts = net positive 25 millivolts. That would be spatial summation. The other kind of summation is **temporal summation** when the PSPs from a single pre-synaptic source, arriving to the post-synaptic neuron in "rapid fire," add together. For example, three EPSPs of 10 millivolts each occurring in rapid sequence would add together. Spatial and temporal summation are important in determining whether "trigger threshold" will be reached in the receiving neuron, triggering an action potential in that neuron. Summation permits activity from many input neurons to be integrated in the neuron receiving the inputs. If membrane depolarization does not reach the threshold level, an action potential will not happen. See Figure 5.2.3.

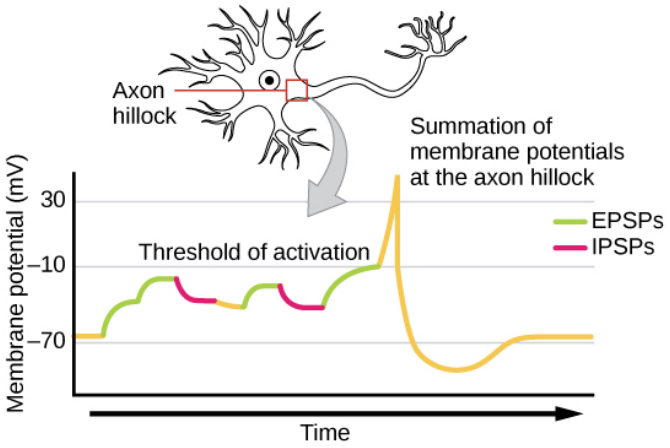


Figure 5.2.3: **Signal summation at the axon hillock**: A single neuron can receive both excitatory and inhibitory inputs from multiple neurons. All these inputs are added together at the axon hillock. If the EPSPs are strong enough to overcome the IPSPs and reach the threshold of excitation, the neuron will fire an action potential. (Image from Biology, Signal Summation; Libretexts; https://bio.libretexts.org/Bookshelv...%20will%20fire. Unless otherwise noted, LibreTexts content is licensed by CC BY-NC-SA 3.0).

One neuron often has input from many presynaptic neurons, whether excitatory or inhibitory; therefore, inhibitory postsynaptic potentials (IPSPs) can cancel out EPSPs and vice versa. The net change in postsynaptic membrane voltage determines whether the postsynaptic cell has reached its threshold of excitation ("trigger threshold") needed to fire an action potential. If the neuron only receives excitatory impulses, it will also generate an action potential. However, if the neuron receives both inhibitory and excitatory inputs, the inhibition may cancel out the excitation and the nerve impulse will stop there. To review, spatial summation means that the effects of impulses received at different places on the neuron add up so that the neuron may fire when such impulses are received simultaneously, even if each input on its own would not be sufficient to cause firing. Temporal summation means that the effects of impulses received at the same place can add up if the impulses are received in close temporal succession. Thus, the neuron may fire when multiple inputs are received, even if each input on its own would not be sufficient to cause firing.

5.2.7 The Action Potential (the "nerve impulse")

The action potential is the main "output" message of the neuron and occurs in the axon where it travels from the beginning segment (**axon hillock**) to the end (**axon terminal**). The action potential is generated in a post-synaptic neuron only if a **"trigger threshold" ("threshold of excitation") of approximately -55 millivolts** is reached. Note that the trigger threshold varies from neuron to neuron and may be anywhere from minus 65 to minus 55, but will always be the same for any particular neuron. When that trigger voltage is attained (for example, as a result of an EPSP of at least 15 millivolts), then **all the *voltage-gated* sodium ion (Na+) channels in the axon hillock suddenly open**, allowing a massive inflow of Na+ into the axon along both concentration and electrical gradients for sodium. This produces a rapid, **large positive shift or "spike"** in the voltage of the post-synaptic neuron. This is the **nerve impulse or action potential**. In most neurons, it is a positive shift of about 100 to 130 millivolts, if we measure from the -70 millivolts of the resting potential, up to about a positive 30 to 60 millivolts, depending on the neuron. This value for any particular neuron is always the same for that neuron. Typically neurons with larger diameters produce the largest action potentials, while the neurons with smaller diameter axons produce action potentials in the lower range.

As fast as the voltage of the action potential rises, it starts to fall just as quickly after reaching its peak (corresponding to peak Na+ concentration inside the neuron). It quickly falls back to the resting potential and even a bit below (the so-called refractory period), as Na+ and K+ ions move out, before the return of the neuron's potential back to -70 mv, the resting potential. This rapid rise to the

action potential's peak and then its rapid fall gives the action potential, when graphed, a spike appearance. For this reason, action potentials are often called "spikes" by neuroscientists. See the diagram of the action potential (Figure 5.2.4 & Figure 5.2.5) to get a clearer picture of these events. Note that an **EPSP**, an excitatory post-synaptic potential, **moves the neuron's voltage closer to "trigger threshold"**, increasing the chances that the neuron will be sufficiently "excited" to generate an action potential. By contrast, the **IPSP**, the inhibitory post-synaptic potential, **moves the neuron's voltage further away from "trigger threshold"** inhibiting the neuron from firing an action potential.

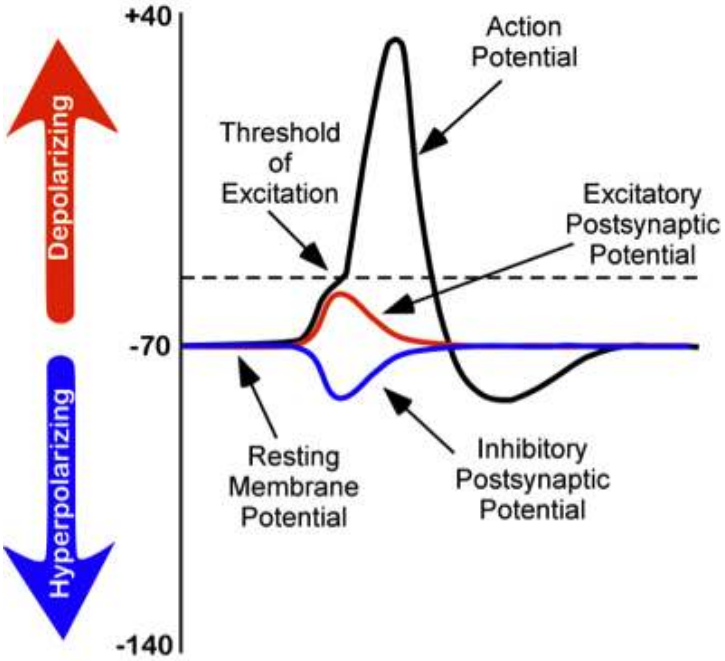


Figure 5.2.4: Changes in membrane potentials of neurons. (left) Dotted line represents trigger threshold ("threshold of excitation"), about -55 millivolts, an action potential is generated once trigger threshold voltage is reached.

Note that an EPSP (depolarization) moves the neuron's voltage more positive and thus closer to trigger threshold, making it more likely that the voltage reaches trigger threshold, "firing" an action potential down the axon of the neuron; thus it is excitatory. An IPSP does the opposite. It moves the voltage in the negative direction, further from trigger threshold, and thus inhibiting the neuron from producing an output (an action potential) in its axon. Also note that the peak of the action potential (top of the black line shaped like a spike) is the peak of its positive voltage and corresponds to the maximum concentration of Na+ ions inside the cell as a result of Na+ ion channels opening after trigger threshold has been reached. After this peak concentration of Na+ making the peak of the voltage of the action potential, positively charged ions (including K+ ions) begin to leave the interior of the cell and as they do so, the positive voltage inside the neuron progressively drops, corresponding to the downward slope of the spike. Note in addition that the spike goes further negative than the resting potential. In this state the neuron is inhibited by this **refractory period** and cannot fire another action potential for a brief time. This keeps the action potential as a discrete digital event. This is important for source coding, an important feature of neural coding, discussed in the chapter on learning and memory in this text. The entire process from the triggering of the action potential (which starts in the root of the axon, called the **axon hillock**, nearest the cell body) to the end of the refractory period takes about 1 millisecond, making the maximum rate at which a neuron can generate and "fire" action potentials (nerve "impulses") about 1,000 per second, although most neurons when active fire at a much lower frequency. Frequency of action potentials is one code that the nervous system uses to represent information. For example, the brighter a light source is, the higher the frequency of action potentials in the optic nerve in response to it.

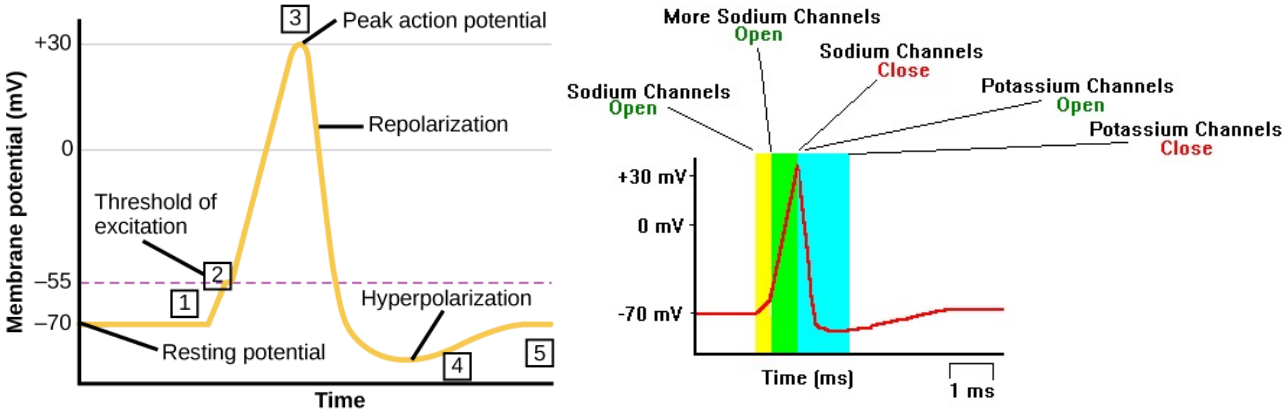


Figure 5.2.5: Formation of an action potential. (left) The formation of an action potential can be divided into five steps. (1) A stimulus from a sensory cell or another neuron causes the target cell to depolarize toward the threshold potential. (2) If the threshold of excitation is reached, all Na+ channels open and the membrane depolarizes. (3) At the peak action potential, K+ channels open and K+ begins to leave the cell. At the same time, Na+ channels close. (4) The membrane becomes hyperpolarized as K+ ions continue to leave the cell. The hyperpolarized membrane is in a refractory period and cannot fire. (5) The K+ channels close and the Na+/K+ transporter (requiring energy expenditure) restores the resting potential. (right) Sequence of opening and closing of Sodium (Na+) and Potassium (K+) ion channels producing the rising and falling phases of the action potential. (Image on left and caption from Lumen Boundless Biology; How Neurons Communicate; https://courses.lumenlearning.com/bo...s-communicate/. Unless otherwise noted, content is licensed under the Creative Commons Attribution 4.0 License. Image on right from Wikimedia Commons; File.مراحل ارسال سیگنال عصبی.jpg; https://commons.wikimedia.org/wiki/F...8%A8%DB%8C.jpg; by Vidakarimnia; licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license).

5.2.8 Neural Conduction in Axons

Once the **trigger threshold ("threshold of excitation")** is reached (dotted line in Figure 5.2.5) and an action potential is generated, it is then conducted down the length of this neuron's axon (See Figure 5.2.6). This conductance is due to the recreation of the full action potential at every sequential segment or patch of axon. This is caused by the opening of the voltage-dependent sodium and potassium channels located along the length of the axon. If the axon is myelinated it will travel more quickly than an unmyelinated one due to saltatory conduction (discussed below).

Once the AP reaches this neuron's axon terminal, its arrival causes the **release of neurotransmitter** molecules located there. Now this neuron is no longer called a post-synaptic neuron, but becomes a pre-synaptic neuron (a sender neuron) with respect to the next cell in line. It's this release of transmitter that leads to Between-Neuron communication, which is discussed in the next section of this chapter..

5.2.8.1 Saltatory Conduction

As discussed previously, many axons in the nervous system are coated in packets of the fatty substance, myelin which is produced by certain glial cells. This wrapping acts similar to insulation on an electrical wire and will speed up the process of action potential movement from the axon hillock to the terminals. These myelin wrappings do not fully ensheath the axon, but leave gaps. A **node of Ranvier** is one of these natural gaps in the myelin sheath along the axon. These unmyelinated spaces are about one micrometer long and contain voltage-gated (i.e., opened by voltage) sodium (Na^+) and potassium (K^+) ion channels (ions are electrically charged atoms). The flow of ions through these channels, particularly the Na^+ channels, regenerates the action potential over and over again along the axon at each successive node of Ranvier. Below the myelinated sections, the positive charges move rapidly down the axon toward the next node to reproduce the action potential. This makes it appear that the action potential “jumps” from one node to the next, giving it the Latin name related to dancing, **saltatory** conduction.

Nodes of Ranvier also save energy for the neuron since the ion channels only need to be present and opened and closed at the nodes and not along the entire axon. It is extraordinary that the nodes are placed along the axon's length at just the right spatial intervals to make impulse conduction down the axon the most efficient and speedy as possible. One can only wonder at the incredible precision with which natural selection operated on this feature of myelinated axons over the long course of animal evolution to create this optimal spacing of the nodes.

Because the action potential in a myelinated axon must be regenerated fewer times to move any particular distance along the length of the axon, it reaches its destination faster, compared to the speed of conduction in an unmyelinated axon.

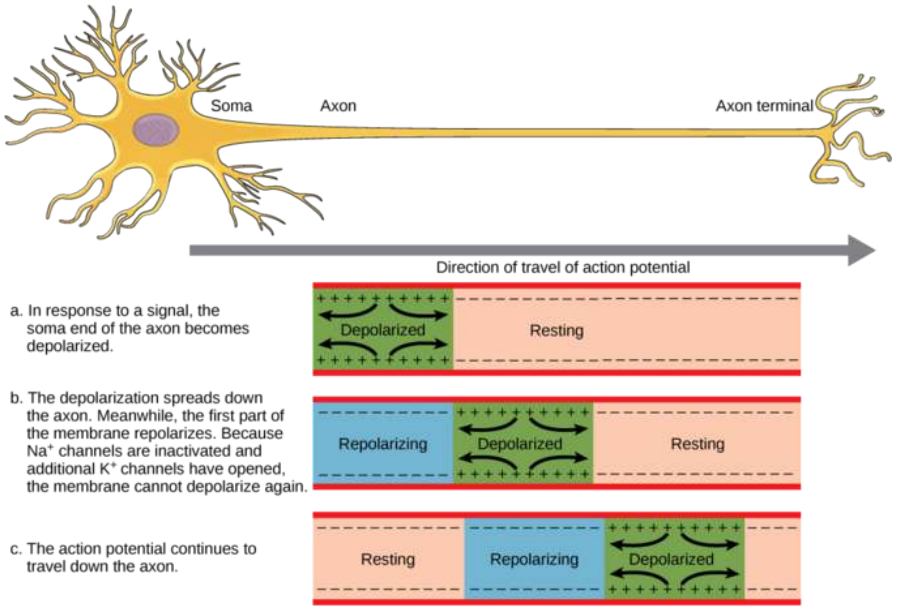


Figure 5.2.6: Action potential traveling along an unmyelinated neuronal axon. The action potential is conducted down the axon as the axon membrane depolarizes, then repolarizes. Because of these dynamics, the action potential can only be conducted in one direction, away from the cell body. Image: figure-35-02-04_NGB_added_resting.png adapted by Naomi Bahm (resting added to part a) from https://s3-us-west-2.amazonaws.com/c...e-35-02-04.png

5.2.9 From Within-Neuron to Between-Neuron Communication and Beyond

A single neuron by itself can't generate psychological states like feelings, perceptions, or thoughts. Neurons must interact with other neurons. The generation of a thought, or other complex psychological/mental experience, requires that enormous numbers of neurons interact with one another. To interact, they must communicate with other neurons.

As described previously, neurons communicate with one another, across spaces between them known as "synaptic gaps" by the release of chemicals (called neurotransmitters or simply transmitters) from one neuron's axon terminals onto receptor sites of the target neuron (a post-synaptic neuron).

There are an enormous number of neurons in the human brain, but the number of *possible* different combinations of synaptic connections among those 80-100 billion neurons is unimaginable--one neuroscientist estimated that the number of possible patterns of interconnect between neurons in a human brain exceeds the number of atoms in the entire universe! This neural complexity appears to be sufficient to code all the information contained in a human brain including all the thoughts, feelings, perceptions and memories of a human lifetime. The foundational process of Between-Neuron (Synaptic) Communication is detailed in the next section.

5.2.10 Attributions

Communication within the Nervous System, "Neurons Generate Voltage Changes to Code Information" by Kenneth A. Koenigshofer, PhD, Chaffey College, is licensed under CC BY 4.0

Figure 5.2.4, and some text adapted from: Furtak, S. (2021). Neurons. In R. Biswas-Diener & E. Diener (Eds), *Noba textbook series: Psychology.* Champaign, IL: DEF publishers. Retrieved from http://noba.to/s678why4; Neurons by Sharon Furtak at NOBA is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License. Figure 5.2.4 caption by Kenneth A. Koenigshofer, PhD, Chaffey College.

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Additional revisions made by Alan Keys, Ph.D., Sacramento City College, Sacramento, CA.

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5.3: Between-Neuron Communicaton- Synaptic Transmission

5.3.0.0.1 Learning Objectives

1. Differentiate the components of a typical electrical and chemical synapse
2. Describe ion channels, and what changes they undergo when neuron potentials are produced; what causes ion channels to change during synaptic transmission?
3. Define ionotropic and metabotropic receptors and discuss in what ways they differ from one another in their effects during synaptic transmission
4. Explain the steps in synaptic transmission from pre-synaptic neuron to post-synaptic neuron
5. Describe how excitatory and inhibitory transmitters differ in their effects on post-synaptic neurons during synaptic transmission
6. Discuss how layers of neurons, simulated by processing units in artificial neural networks, might produce psychological processes such as learning

5.3.1 Overview

Even before the action potential (i.e. "Nerve Impulse") has made it's way down to a neuron's axon terminals, the next form of neural communication has already begun. Thus, as Within-Neuron communication winds down, **Between-Neuron (synaptic)** Communication takes off in order to transmit the message to the next neuron (muscle or gland) in the circuit. In this section, we will explore the overlap of within- and between-neuron communication and examine the specifics of both electrical and chemical communication at the point of contact between neurons (i.e. **synapses**). The key structural elements of the synapse will be covered, including details on the receptors which receive the chemical messages known as neurotransmitters. All the **steps of synaptic communication** and their involvement in successful communication will be addressed.

5.3.2 Synapses

Recall that axons often split into several branches so that they can communicate with several other neurons. At the end of the axon's branches, the **axon** terminals typically form "**synapses**" with the dendritic **spines** or small protrusions on the dendrites of receiving neurons. Synapses form between the axon terminal of the ***presynaptic neuron*** (neuron sending the signal) and the ***postsynaptic*** neuron (neuron receiving the signal). See Figure 5.3.1). Here we will focus specifically on synapses between the axon terminal of an axon and a dendritic spine; however, synapses can also form between the axon terminal of the presynaptic neuron and the postsynaptic neuron's soma, dendritic shaft, or the axon of another neuron.

A very small space called a **synapse** or **synaptic gap/cleft** exists between the pre-synaptic axon's terminal and the post-synaptic neuron's dendritic spine. To give you an idea of the size of the synaptic gap, a dime is 1.35 mm (millimeter) thick. There are 1,350,000 nm (nanometers) in the thickness of a dime. The synaptic gap is only about 5 nm wide. In the pre-synaptic terminal, there are **storage** packets made of fat called **synaptic vesicles** that package together the chemical messengers of neurons known as **neurotransmitters** (see Figure 5.3.1). These vesicles **protect neurotransmitters from breakdown** and aid in their release from the presynaptic axon's terminal. Upon release into the synapse, the transmitters travel across the synapse to communicate a message to the postsynaptic neuron. They accomplish this by **binding** to a protein on the postsynaptic cell known as a **receptor**. More detail on the **steps of synaptic transmission** will be detailed below.

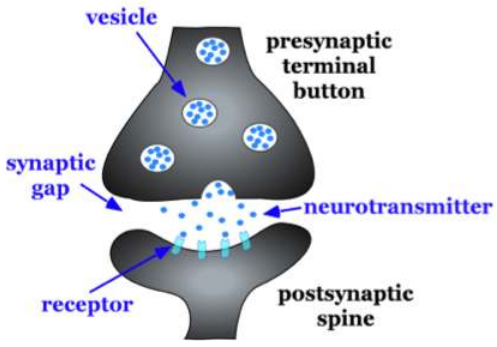


Figure 5.3.1: Basic characteristics of a typical synapse. Enlargement of the synapse between one of the axon terminal buttons (presynaptic terminal button) and one of the dendritic spines of a second neuron (postsynaptic spine).

5.3.3 SYNAPTIC TRANSMISSION

The between-neuron communication of chemical messages across the synaptic gap via neurotransmitters is one type of **synaptic transmission**. Synaptic transmission can also take place electrically without the need for the steps of chemical transmission. Synaptic transmission is central to the brain's capacity to process information, generate mental states, and produce adaptive behavior. Some synapses are purely electrical and make direct electrical connections between neurons, but, most synapses are chemical in nature and utilize neurotransmitters to transmit messages. The transmission of neural signals across **chemical synapses** is more complex than at **electrical synapses** and involves many steps.

5.3.4 Electrical Synapses

Electrical synapses are much less common than chemical synapses, but they are nevertheless distributed throughout the brain. In chemical synapses neurotransmitter is needed for communication between neurons, but for electrical synapses this is not the case. In electrical synapses current, ions, and molecules can flow between two neurons through direct physical connections that allow cytoplasm to flow between them. The physical connection between neurons with electrical synapses is in the form of large pore structures, called connexons, at **gap junctions** between such neurons. Communication between neurons with electrical synapses is faster than at chemical synapses which must go through more steps to transmit signals to another neuron. Therefore, electrical synapses are often found in neural systems that require rapid response such as defensive reflexes. Electrical synapses can communicate signals in both directions between neurons in contrast to chemical synapses which transmit messages in one direction, from pre-synaptic by transmitter release to post-synaptic neuron.

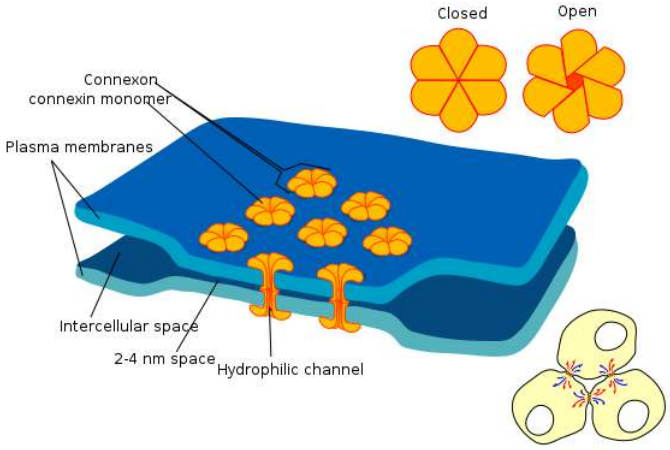


Figure 5.3.2: Gap junction at an electrical synapse. Two adjacent neurons with electrical synapse between them can communicate through hydrophilic channels Note that the gap between cell membranes of pre and post-synaptic neurons at electrical synapses is much smaller than the synaptic gap at chemical synapses which is about 10 times larger. (Image from Wikimedia Commons; File:Gap cell junction-en.svg; by Mariana Ruiz LadyofHats.https://commons.wikimedia.org/wiki/F...unction-en.svg; by Mariana Ruiz LadyofHats; **public domain** by its author, **LadyofHats**).

5.3.5 Chemical Synapses

Recall that in Within-Neuron Communication, several key charged particles (ions) are involved in maintaining the resting membrane potential and creating both post-synaptic and action potentials. At the end of this process, the action potential arrives at the axon terminals due to the exchange of sodium (Na^+) and potassium (K^+) ions that occurred along the length of the axon. Upon it's arrival at the terminal, the action potential triggers the opening of another ion channel which allows Calcium (Ca^{2+}) ions to enter. This entry of Ca^{2+} ions triggers the release of chemical neurotransmitters into the synapse.

The **release** of neurotransmitter is actually the 3rd **step of synaptic transmission**. *Prior* to release, the transmitters have to first be **synthesized** and then **stored**. *After* neurotransmitters are released one of 3 other steps can occur. The transmitter can either **bind** to a receptor protein on the post-synaptic cell, be taken back into the presynaptic cell by a process known as **reuptake**, or **metabolized (i.e. inactivation**) by enzymes in the synapse. Reuptake and inactivation are both termination mechanisms for synaptic communication. In other words, they reduce or stop the between-neuron communication from continuing.

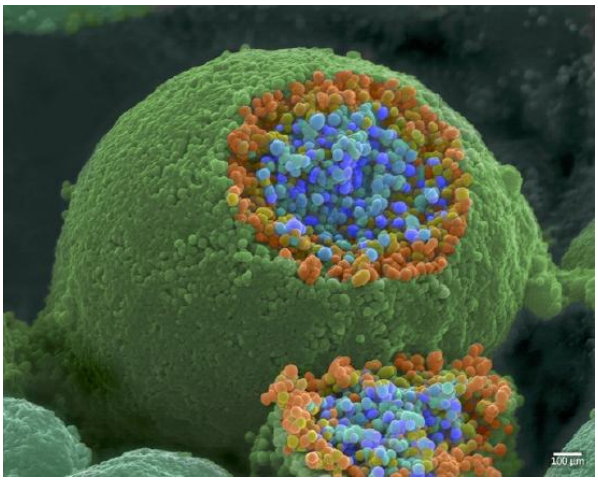


Figure 5.3.3: **Synaptic vesicles inside a neuron**: This pseudocolored image taken with a scanning electron microscope shows an axon terminal that was broken open to reveal synaptic vesicles (blue and orange) inside the neuron. (Image and caption adapted from: General Biology (Boundless), Chapter 35, The Nervous System; https://bio.libretexts.org/Bookshelv...gy_(Boundless); LibreTexts content is licensed by CC BY-NC-SA 3.0. Legal).

5.3.5.1 Steps of Synaptic Transmission

The process detailed in the previous section is known as the **Steps of Synaptic Transmission**. Depending on how you organize them, there are 5-6 of these steps as follows:

5.3.5.2 Synthesis, Storage, Release, Receptor Binding, Termination (Reuptake & Breakdown)

Let's explore these in a bit more detail.

Synthesis: There is a very large variety of neurotransmitters that act in the nervous system. Several of the major neurotransmitters will be described in detail in the Neurotransmitter section below. Of these, several are produced or synthesized by the enzymatic alterations of precursor amino acid molecules. In other words, certain amino acids from our diet are transformed into neurotransmitter molecules with the help of certain enzymes. Also, some neurotransmitters are manufactured in the cell body (**soma**) and transported to the axon terminal, while others (small ones) are synthesized in the axon terminal itself. Some of these synthesis pathways are more complicated than others, but all the resulting neurotransmitters share one thing in common. They are capable of communicating with other neurons and triggering or continuing a message.

Storage: With rare exception, neurotransmitters must be stored quickly after synthesis in order for them to be successfully released into the synapse. Structures made of the same fatty substance as the neuronal membrane are known as **synaptic vesicles** and serve to protect neurotransmitters from enzymatic breakdown and aid in their release to the synapse. As described previously, the the arrival of the action potential at the axon terminal causes the entry of Ca^{2+} ions which trigger the release of neurotransmitters into the synapse. Well, the Ca^{2+} ions actually interact with the synaptic vesicles and, essentially pushes them to the end of the terminal where they merge with the presynaptic membrane. This leads to the next step of neurotransmitter release.

Release: The release of neurotransmitter into the synapse is a critical step in the ultimate transmission of a message to the next neuron, muscle, or gland. As described above, it is the interaction of Ca^{2+} ions with the synaptic vesicles that results in the release of the thousands of neurotransmitter molecules stored within them. Remember that the nerve cell releasing the neurotransmitter, the sender neuron, is known technically as the **presynaptic neuron**. The neuron receiving the neurotransmitter, the receiver cell, is called the **postsynaptic neuron**. The release transmitter must make it to the postsynaptic neuron in order to acheive the next step of message transmission. However, there are two other "termination" steps that often stop it from being successful.

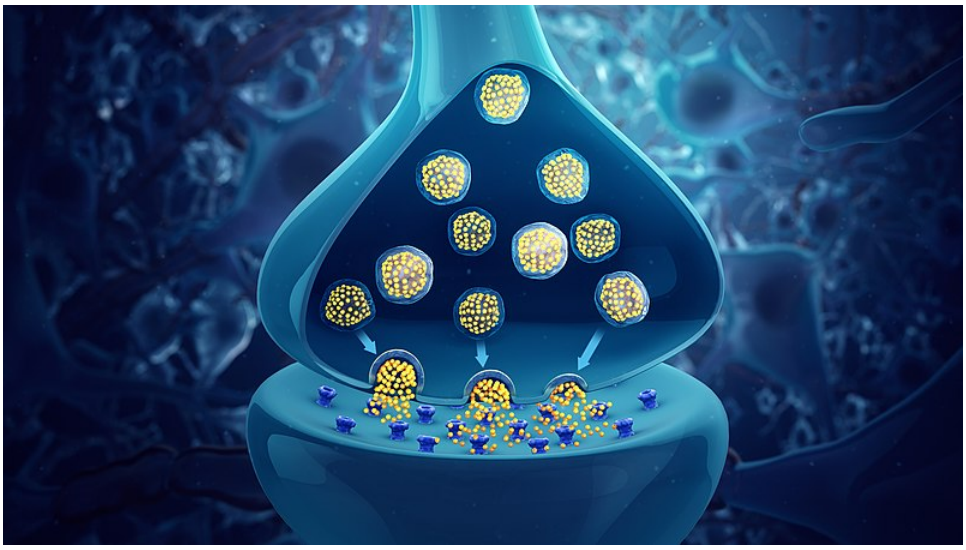


Figure 5.3.9: A synapse. Synaptic vesicles release neurotransmitters (small yellow balls) which bind to the receptors (blue peg-like structures) on the postsynaptic membrane. Synaptic vesicles inside a presynaptic axon terminal button (axon ending) releasing neurotransmitter molecules onto receptors on a dendrite of a receiving (post-synaptic) neuron. (Image from Wikimedia Commons; File:Neurotransmitters.jpg; https://commons.wikimedia.org/wiki/F...ansmitters.jpg; by https://www.scientificanimations.com/; by https://www.scientificanimations.com/; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Binding: If the released neurotransmitter avoids the termination mechanisms (see below), they may be able to **bind** to special sites on the membrane of the postsynaptic neuron. These special sites are proteins embedded in the membrane called **receptors or postsynaptic receptor sites**. They can be located anywhere on the neuron, but many are on the postsynaptic membrane of dendrites or dendritic spines of the receiving neuron. If their molecular shapes match the shapes of the neurotransmitter molecules, a molecular "lock and key" fit occurs which allows them to open (or close) chemically-gated ion channels. This change in the opening of ion channels is essentially the "message" and results in within-neuron electrical changes in voltage called **postsynaptic potentials** (PSPs). If there are enough excitatory post-synaptic potentials (EPSPs) to move the neuron past its activation threshold, an action potential will be produced and the whole communication process will continue.

There are more details on receptor binding in a special section toward the end of this section.

Termination Mechanisms - Inactivation

Special enzymes are present in the synapse and the neuron's themselves which are designed to metabolize and breakdown the neurotransmitter molecules. This enzymatic breakdown is known as **inactivation** and will stop the message in it's tracks. If neurotransmitter is not stored in vesicles and protected, it can be inactivated before it even gets released. If it is released, it can be inactivated by enzymes in the synapse before it has a chance to bind and interact with the post-synaptic neuron.

Termination Mechanisms - Reuptake

The other way the synaptic message can be reduced or terminated is via the process known as **reuptake**. Reuptake involves special proteins embedded in the PREsynaptic membrane which work very efficiently to clear the synapse of neurotransmitter by pulling it back inside the axon terminal. This is a type of recycling mechanism which reduces synaptic transmission and allows those transmitters to potentially be used again.

5.3.6 Summary of Steps of Synaptic Transmission

These steps of synaptic transmission from synthesis to the eventual termination of the neurotransmitter comprise **synaptic transmission**. Most, if not all of our thinking, feeling, and behaving rely on healthy function of this type of communication. Many psychological and physical issues relate to problems or dysregulation of this process. In addition, many **psychoactive drugs** (drugs that alter mind and/or behavior) such as nicotine, LSD, psilocybin, marijuana, etc. produce their effects by **blocking or activating specific receptor sites.** Other psychoactives produce their effects by altering one of the other steps of synaptic transmission, such as release or reuptake.

Here's a somewhat simplified but useful summary of the **steps in synaptic transmission** at synapses:

Generic Neurotransmitter System

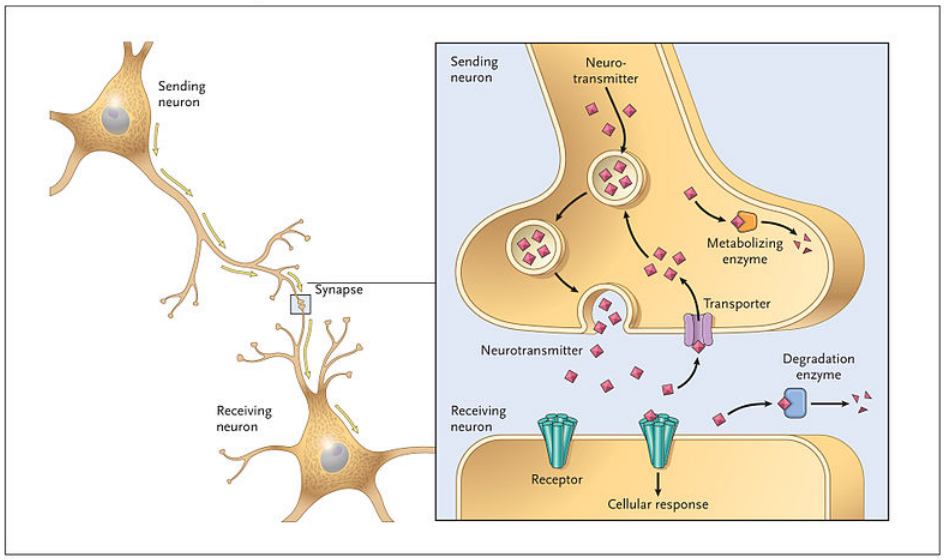
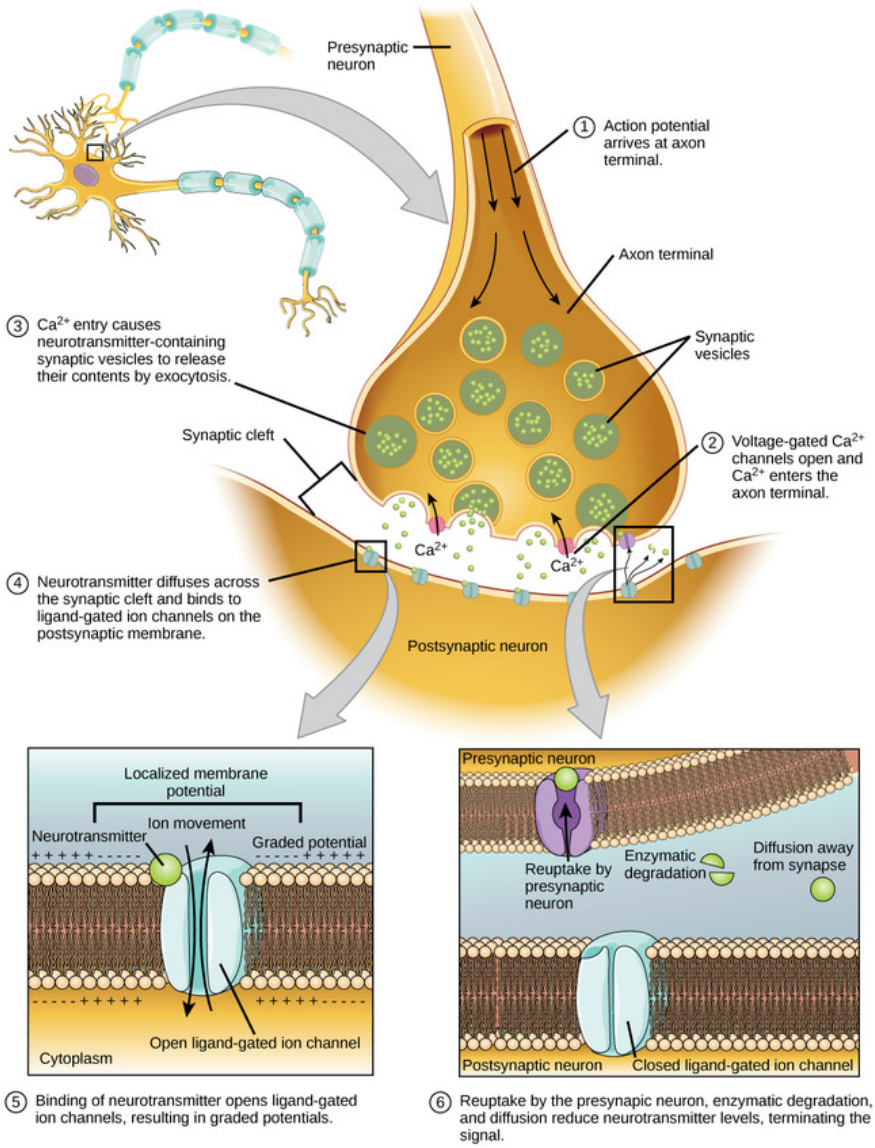


Figure 5.3.4: Image on left shows two neurons communicating with one another (synaptic transmission). The neuron at the top is the sender or pre-synaptic neuron. The neuron on the bottom is the receiver or post-synaptic neuron. In the image on the left of the figure, notice the small box at the synapse. This box is enlarged in the image on the right side of the figure to reveal details of the synapse and events there during synaptic transmission. The axon terminal of the pre-synaptic neuron is located at the top of the image on the right of the figure above. Transmitter molecules (small red squares) are in this axon terminal where they are stored in synaptic vesicles (yellow circles containing small red squares, i.e. transmitter molecules). (Image from Wikimedia Commons; File:Generic Neurotransmitter System.jpg; https://commons.wikimedia.org/wiki/F...ter_System.jpg; by NIDA(NIH); this work is in the **public domain** in the United States. Caption by Kenneth A. Koenigshofer, Ph.D.).

When a nerve impulse (action potential) reaches the axon terminal, calcium ions enter causing synaptic vesicles to move to the terminal membrane and release their transmitter molecules into the synapse. If they don't get inactivated by enzymes or undergo reuptake back into the terminal, the transmitter molecules may bind to post-synaptic receptors (green) causing specific ion channels ("doors") to open to specific ions. Ions (not shown in this figure) would then move through the ion channels causing a change in the voltage inside the post-synaptic neuron (either an EPSP or an IPSP). If trigger threshold (about negative 55 millivolts) is reached, an action potential is generated in the receiver neuron, which now becomes a sender neuron for the next cell in line (not shown in this figure). Inactivation of the used transmitter is the final step and is depicted in this figure by "enzyme degradation" (enzymatic destruction).



5.3.7

Figure 5.3.5: **Communication at a chemical synapse**: This illustrates most of the key steps of between-neuron, chemical communication that occur at the synapse. The initial step of "Synthesis" of neurotransmitter is not indicated, but would have occurred prior to storing the transmitter in the synaptic vesicles. Image adapted from: General Biology (Boundless), Chapter 35, The Nervous System; https://bio.libretexts.org/Bookshelv...gy_(Boundless); LibreTexts content is licensed by CC BY-NC-SA 3.0. Legal).

Communication at chemical synapses requires initial **synthesis, storage**, and then the **release** of neurotransmitters. When the depolarizing action potential arrives at the pre-synaptic axon terminal, voltage-gated Calcium (Ca2+) channels open and allow Ca2+ to enter the cell. The Ca2+ entry causes synaptic vesicles to fuse with the membrane and release neurotransmitter molecules into the synaptic cleft. The neurotransmitter can then do one of three things: It can either **bind** to a receptor, be taken back into the presynaptic terminal (**reuptake**), or be **inactivated** by enzymes in the synapse. If neurotransmitter diffuses across the synaptic cleft and binds to ligand-gated ion channels (channels opened by chemical transmitter) in the post-synaptic membrane, it will result in either a relatively small, localized depolarization or hyperpolarization of the post-synaptic neuron depending upon the type of receptor that it binds to. The local depolarizations are referred to as Excitatory Post Synaptic Potentials (EPSPs) and the local hyperpolarizations are Inhibitory Post Synaptic Potentials (IPSPs).

5.3.7.1 Receptor Binding

The binding of neurotransmitter to post-synaptic receptors is one of the most influential and dynamic steps of synaptic communication. All the other steps (synthesis, storage, release, reuptake, and breakdown) can be functioning, but without neurotransmitter binding, the chemical communication between neurons stops immediately. If the neurotransmitter does make it across the synapse and binds to a receptor, it can then produce one of a variety of effects depending on the type of receptor. Most neurotransmitters have a family of receptors which are able to bind them. Every system or circuitry of the brain contains particular transmitters and a subset of their receptor family.

To simplify, receptors vary based on two main characteristics: ***Type* of post-synaptic effect** that they cause and the ***speed* of that effect**.

The type of post-synaptic effect is determined by whether the receptor produces EPSPs or IPSPs, as described in the previous section. An "**Excitatory**" receptor will produce EPSPs, which will bring a neuron closer to the activation threshold for producing an action potential. An "**Inhibitory**" receptor will produce IPSPs which will make it more difficult for a neuron to reach the activation threshold. The particular type of receptor is determined by its molecular structure and the type of ions it will ultimately allow to flow into or out of the neuron. If the net effect is to cause the inside of the neuron to be less negative than it is at rest, it would be excitatory, and if it were to result in more negative charge inside the neuron it would be inhibitory.

In terms of the speed of effect, there are two major receptor subtypes: **Ionotropic (Fast)** and **Metabotropic (Slow)**. In reality, both receptors produce very fast responses on the order of milliseconds, but metabotropics are slightly slower, as detailed below.

Ionotropic receptors, when activated by transmitter from a pre-synaptic neuron, cause ion channels to open, allowing ions, with their electrical charges, to move across the cell membrane of the receiving (post-synaptic) neuron, causing an EPSP or an IPSP (see above). These are fast acting receptors because the receptors are directly located on ion channels that open or close. In short, the receptor *is* an ion channel.

By contrast, **metabotropic receptors** (usually coupled with G-proteins; i.e. guanine nucleotide-binding proteins), when activated by transmitter from a pre-synaptic neuron, act indirectly and more slowly, using second messengers to produce a variety of metabolic effects to modulate cell activity. These effects include changes in gene transcription, regulation of proteins in the cell, release of Ca+ (calcium ions) within the cell, and effects on ion channels on the neuron's cell membrane (Sterling & Laughlin, 2015). Such modulation of neurons and synapses can be more long-lasting than effects of the activation of ionotropic receptors and may play an important role in cellular level mechanisms of learning and memory (Nadim and Bucher, 2014).

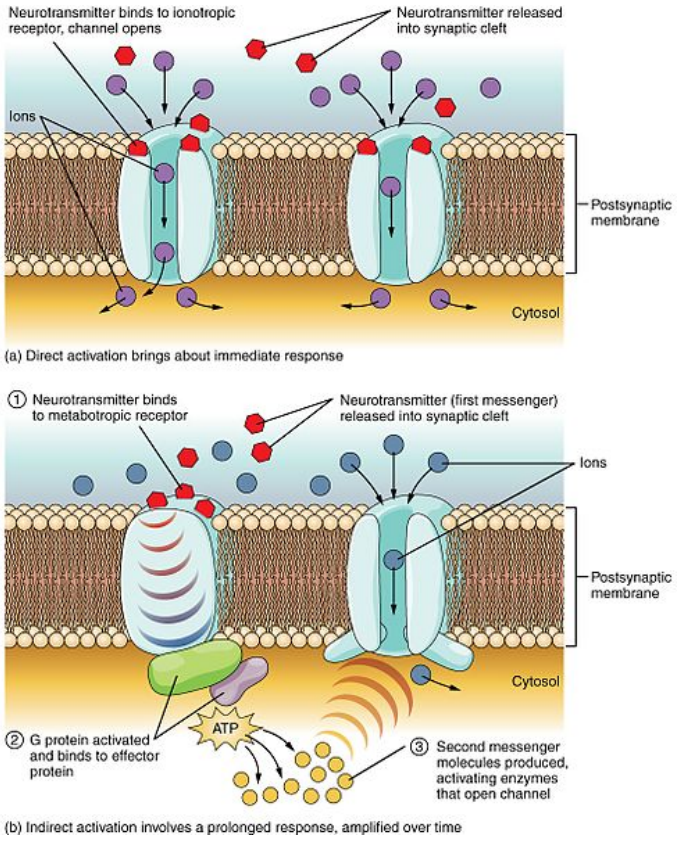


Figure 5.3.6: Comparison of Ionotropic and Metabotropic Post-Synaptic Receptors. The image at the top (a) shows ionotropic receptors which when activated by transmitter open ion channels immediately resulting in ion movement and an immediate response, a post-synaptic potential. The image at the bottom (b) shows metabotropic receptors which when activated by transmitter initiate a second messenger system. Second messengers can have a variety of effects including indirectly opening ion channels (Image from Wikimedia Commons; File:1226 Receptor Types.jpg; https://commons.wikimedia.org/wiki/F...ptor_Types.jpg; by OpenStax; licensed under the Creative Commons Attribution 4.0 International license).

5.3.7.2 After Receptor Binding

The binding of a neurotransmitter to its receptor is reversible, and for good reason. As long as it is bound to a receptor, a neurotransmitter continues to affect membrane potential, so it must eventually be removed from the synapse. The effects of the neurotransmitter generally lasts a few milliseconds before being terminated. If the used transmitter is not removed by the reuptake or inactivated by enzymes, it can cause over-activation of neurons, potentially leading to pathological mental states and behavior if enough synapses are affected. The two main types of neurotransmitter termination are: 1. Reuptake by astrocytes or the presynaptic axon terminal where the used transmitter can either be inactivated by enzymes or stored again, and 2. Inactivation by enzymes in the synaptic cleft. In some situations transmitter can also diffuse away from the synapse, thus stopping it's effects on the post-synaptic cell.

5.3.8 Types of Neurotransmitter

There are at least 60-100 neurotransmitters and probably many others yet to be discovered. The best known can be grouped into types based on their chemical structure.

Today, the majority of neuroscientists will tell you that most neurons release the same neurotransmitter from their axons—which is why you may see some neurons referred to as “dopaminergic” or “serotonergic,” releasing dopamine or serotonin, respectively. But new work in the field has uncovered that neurons are not fixed when it comes to the chemicals they release.

Some cells change the type of neurotransmitters they release depending on the circumstances, sometimes releasing up to five different kinds. Scientists call this phenomenon “neurotransmitter switching.”

Neurotransmitters, at the highest level, can be sorted into two types: small-molecule transmitters and neuropeptides. Small-molecule transmitters, like dopamine and glutamate, typically act directly on neighboring cells. The neuropeptides, small molecules like insulin and oxytocin, work more subtly, modulating, or adjusting, how cells communicate at the synapse. These powerful neurochemicals are at the center of neurotransmission, and, as such, are critical to human cognition and behavior.

Often, neurotransmitters are talked about as if they have a single role or function. Dopamine is a "pleasure chemical" and GABA is a "learning" neurotransmitter, even though glutamate also plays a major role in learning and memory formation. But neuroscientists are discovering they are multi-faceted and complex, working with and against each other to facilitate neural signaling across the cortex. Here is a list of some of the most common neurotransmitters discussed in neuroscience.

5.3.8.1 Amino acids neurotransmitters

- **Glutamate (GLU).** This is the most common and most abundant excitatory neurotransmitter. Glutamate has an important role in cognitive functions like thinking, learning and memory. Too much glutamate results in excitotoxicity, or the death of neurons due to stroke, traumatic brain injury, or amyotrophic lateral sclerosis (ALS), the debilitating neurodegenerative disorder better known Lou Gehrig's disease. GLU is also important to learning and memory: long term potentiation (LTP), occurs in glutamatergic neurons in the hippocampus and cortex.
- **Gamma-aminobutryic acid (GABA).** GABA works to inhibit neural signaling. GABA is the most common inhibitory neurotransmitter in the nervous system, particularly in the brain. New research suggests that GABA helps lay down important brain circuits in early development. GABA also has a nickname: the "learning chemical." Studies have found a link between the levels of GABA in the brain and whether or not learning is successful.
- **Glycine.** Glycine is the most common inhibitory neurotransmitter in the spinal cord and is involved in auditory processing, pain and metabolism.

5.3.8.1.1 Monoamines neurotransmitters

Monoamines neurotransmitters are involved in consciousness, cognition, attention and emotion.

- **Serotonin (5HT).** Serotonin is an inhibitory neurotransmitter. Serotonin helps regulate mood, sleep patterns, sexuality, anxiety, appetite and pain. Diseases associated with serotonin imbalance include seasonal affective disorder, anxiety, depression, fibromyalgia and chronic pain. Medications that regulate serotonin and treat these disorders include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which increase the levels of transmitter by inhibiting their reuptake after they have done their work at the postsynaptic receptor sites. Serotonin (5HT), sometimes called the "calming chemical," is best known for its mood modulating effects. A lack of 5HT has been linked to depression and related neuropsychiatric disorders. 5HT has also been implicated in facilitating memory, and, most recently, in decision-making behavior
- **Histamine.** Histamine regulates body functions including wakefulness, feeding behavior and motivation.
- **Dopamine (DA).** Dopamine is involved in the brain's reward system, feelings of pleasure, cognitive arousal, learning, focus of attention, concentration, memory, sleep, mood and motivation. Dopamine is often referred to as the "pleasure chemical" because it is released when mammals receive a reward in response to their behavior; that reward could be food, drugs, or sex. Diseases associated with dysfunctions of the dopamine system include Parkinson's disease, schizophrenia, bipolar disease, and attention deficit hyperactivity disorder (ADHD). Many highly addictive drugs (cocaine, methamphetamines, amphetamines) act directly on the brain's dopamine circuits.
- **Epinephrine.** Epinephrine (also called adrenaline) and norepinephrine (see below) are responsible for the "fight-or-flight response" to fear and stress, activating the sympathetic nervous system (see Chapter 4).
- **Norepinephrine (NE).** Norepinephrine is both a hormone and a neurotransmitter. Some refer to it as noradrenalin. It has been linked to mood, arousal, vigilance, memory, and stress. Newer research has focused on its role in both post-traumatic stress disorder (PTSD) and Parkinson's disease. Norepinephrine (noradrenaline) increases blood pressure, heart rate, alertness, arousal, attention and focus. Many medications (stimulants and depression medications) increase norepinephrine to improve focus or concentration to treat ADHD or to reduce symptoms of depression.

5.3.8.1.2 Peptide neurotransmitters

Peptides are short chains of amino acids.

- **Endorphins.** Endorphins are natural pain killers. They are natural opiate-like substances, similar in molecular properties to morphine. Release of endorphins reduces pain, and elevates mood. They are endogenous opiates released by the hypothalamus and pituitary gland during stress or pain.

5.3.8.1.3 Acetylcholine (ACh)

This excitatory neurotransmitter is found in both the central and peripheral nervous systems, specifically in the autonomic nervous system and in spinal motor neurons releasing acetylcholine onto skeletal muscles producing movements. It is also involved in memory, motivation, sexual desire, sleep and learning. Abnormalities in acetylcholine levels are associated with Alzheimer's disease. But it also has other roles in the brain, including helping direct attention and playing a key role in facilitating neuroplasticity across the cortex.

5.3.8.1.4 **Other Neurotransmitters**

Neurochemicals like oxytocin and vasopressin are also classified as neurotransmitters. Made and released from the hypothalamus, they act directly on neurons and have been linked to pair-bond formation, monogamous behaviors, and drug addiction. Hormones like estrogen and testosterone can also work as neurotransmitters and influence synaptic activity.

Other neurotransmitter types include corticotropin-releasing factor (CRF), galanin, enkephalin, dynorphin, and neuropeptide Y. CRF, dynorphin, and neuropeptide Y have been implicated in the brain's response to stress. Galanin, enkephalin, and neuropeptide Y are often referred to as "co-transmitters," because they are released and then work in partnership with other neurotransmitters. Enkephalin, for example, is released with glutamate to signal the desire to eat and process rewards.

As neuroscientists are learning more about the complexity of neurotransmission, it's clear that the brain needs these different molecules so it can have a greater range of flexibility and function.

5.3.8.1.5 **Glia Release Neurotransmitters, Too**

It was once believed that only neurons released neurotransmitters. New research, however, has demonstrated glia, the cells that make up the "glue" that fills the space between neurons to help support and maintain those cells, also have the power to release neurotransmitters into synapses. In 2004, researchers found that glial cells release glutamate into synapses in the hippocampus, helping synchronize signaling activity.

Astrocytes, a star-shaped glial cell, are known to release a variety of different neurotransmitters into the synapse to help foster synaptic plasticity, when required. Researchers are working diligently to understand the contributions of these different cell types–and the neurotransmitter molecules they release—on how humans think, feel, and behave.

5.3.8.2 Different Types of Receptors Activated by the Same Transmitter

There are different types of receptor for transmitters of a specific type. For example, for dopamine there are at least 5 types, D1 through D5 receptors, all for dopamine transmitter. Different receptor types for a specific transmitter may be localized in different parts of the brain and therefore may produce different effects and have different functions.

The function of each dopamine receptor type (Mishra, et al., 2018):

- D1: memory, attention, impulse control, regulation of renal (kidney) function, locomotion (movement)
- D2: locomotion, attention, sleep, memory, learning
- D3: cognition, impulse control, attention, sleep
- D4: cognition, impulse control, attention, sleep
- D5: decision making, cognition, attention, renin secretion (by the kidney)

Of particular interest, the mental disorder schizophrenia, characterized by disordered thought, hallucinations, and delusions, is associated with excess dopamine neuron activity in the brain. Some drug treatments for schizophrenia decrease activity primarily at D2 receptors.

Another example is acetylcholine transmitter. There are two distinct types of acetylcholine receptors affected by two different substances, either muscarine or nicotine. Those postsynaptic acetylcholine receptors that respond to muscarine are called muscarinic receptors. Those that respond to nicotine (in tobacco products, for example) are called nicotinic. Nicotinic receptors cause sympathetic postganglionic neurons and parasympathetic postganglionic neurons to fire and release their chemicals and cause skeletal muscle to contract. Muscarinic receptors are associated mainly with parasympathetic functions and stimulate receptors located in peripheral tissues (e.g., glands, smooth muscle). Acetylcholine transmitter activates all of these sites.

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5.3.9 Attributions

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CHAPTER OVERVIEW

6: The Effects of Psychoactive Drugs

6.1: Psychopharmacology and Psychoactive Drug Classification
6.2: Mechanisms of Psychoactive Drug Action
6.3: Substance Use and Addiction - Theories, Brain Mechanisms, and Treatment
6.4: Specific Drug Effects, Misuse, and Risks
6.5: Psychotherapeutics

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6.1: Psychopharmacology and Psychoactive Drug Classification

Learning Objectives

1. Describe the general principles of psychopharmacology.
2. Explain the criteria for psychoactive drugs and the various types of classification systems.
3. Differentiate drug types based on their neurochemical effects on neurotransmission and behavioral impacts.

6.1.1 Overview

Psychopharmacology is the study of how drugs affect how we think, feel, or behave most often through their actions on the nervous system. Understanding some of the basics about psychopharmacology can help us better explain a wide range of issues that interest psychologists and others. For example, the pharmacological treatment of certain neurodegenerative diseases such as Parkinson's and Alzheimer's disease tells us something about the disease itself. The pharmacological treatments used to treat psychiatric conditions such as schizophrenia or depression have undergone amazing development since the 1950s, and the drugs used to treat these disorders provide clues to what is happening in the brain of individuals with these conditions. Finally, understanding something about the actions of drugs of abuse on the nervous system and the way they are processed by the body can help us understand why some psychoactive drugs are so likely to be abused. In this chapter, we will provide an overview of some of these topics as well as discuss some current controversial areas in the field of psychopharmacology.

6.1.2 Psychopharmacology

Psychopharmacology, the study of how drugs affect the brain and behavior, is a relatively new science, although people have probably been taking drugs to change how they feel from early in human history (consider the eating of fermented fruit, ancient beer recipes, chewing on the leaves of the cocaine plant for stimulant properties as just some examples). The word *psychopharmacology* itself tells us that this is a field that bridges our understanding of behavior, brain function, and pharmacology. Additionally, the topics included within this field are extremely broad including the influence of expectations of drug effects, how the drug is processed by the body, and ultimately, to how the drug impacts various systems, particularly the central nervous system.

6.1.2.1 Psychoactive Drugs

If a drug changes the way you feel, think, or behave it is often doing so by acting on your brain and other parts of your nervous system. We call these ***psychoactive* drugs,** and almost everyone has used them at some point (yes, caffeine counts). Virtually all psychoactive drugs cause psychological or behavioral changes by altering how neurons communicate with each other. It is important to recall that neurons communicate with each other by releasing **neurotransmitters** across the **synapse**. When the neurotransmitter crosses the synapse, it binds to a postsynaptic receptor (protein) 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** alter how neurons communicate with each other in one way or another. While some drugs, such as most antidepressants and many stimulants, have well-defined effects at the level of the neuron, others, like alcohol, have more widespread and less-clear effects.

Some of the most important in terms of psychopharmacological treatment and drugs of abuse are outlined in Table 1. The neurons that release these neurotransmitters, for the most part, are localized within specific circuits of the brain that mediate specific types of behaviors.

Table 1: Key Neurotransmitters and Highlights of Their Neural, Behavioral, and Psychological Effects

Neurotransmitter	Abbreviation	Behaviors or Diseases Related to These Neurotransmitters
Acetylcholine	ACh	Learning and memory; Alzheimer's disease; Voluntary muscle movement in the peripheral nervous system
Dopamine	DA	Reward circuits; Motor control; Parkinson's disease; Schizophrenia
Norepinephrine	NE	Arousal; Depression

Neurotransmitter	Abbreviation	Behaviors or Diseases Related to These Neurotransmitters
Serotonin	5-HT	Depression; Aggression; Schizophrenia
Glutamate	GLU	Learning; Major excitatory neurotransmitter in the brain
GABA	GABA	Anxiety disorders; Epilepsy; Major inhibitory neurotransmitter in the bran
Endogenous Opioids	Endorphins, Enkephalins	Pain; Analgesia; Reward

Psychoactive drugs can either increase the typical effect of neurotransmitters at the synapse (these are called **agonists**) or decrease it (**antagonists**). It is important to remember that the "typical" effect of a neurotransmitter can be either excitatory or inhibitory depending on the type of receptor it binds to. For example, stimulant drugs, such as amphetamine, methamphetamine, or ADHD medications like Adderall are agonists for dopamine and norepinephrine systems and can increase the "typical" *excitation* that occurs at certain dopamine or norepinephrine receptors. Other agonistic drugs, such as morphine and fentanyl will increase the typical *inhibitory* effect at many of our endogenous opioid (endorphin) synapses. In other words, acting as an agonist at an inhibitory receptor will cause even more inhibition than without the drug present. Antagonists for these same systems will have the opposite effects, such as the effect of the opioid receptor blocker, naloxone (Narcan) which results in less inhibition at endogenous opioid synapses. Yes, this is complicated, but you just need to remember that agonist drugs increase and antagonist drugs decrease whatever the typical effect is at a particular synapse, be it excitatory or inhibitory.

There are various ways that drugs can effect the steps of synaptic communication and, thus produce their agonistic and antagonistic effects. Some of these are more intuitive than others. For example, antidepressants such as Prozac or Celexa are selective serotonin reuptake inhibitors (commonly referred to as SSRIs) are agonists for the serotonin system. However, they achieve increased serotonin activity at the synapse by *blocking* the reuptake of serotonin back into the presynaptic axon terminal from which it was released. In other words, they increase serotonin activity by interfering with the mechanism that normally turns its activity off (i.e., reuptake). As you can see, the basic distinction of whether a drug is an agonist or antagonist can get quite complicated very quickly. More examples of agonists and antagonists for various neurotransmitter systems are presented in Table 2. For each example, the drug's trade name, which is the name of the drug provided by the drug company, and generic name (in parentheses) are provided.

Table 2 provides examples of drugs and their primary mechanism of action, but it is very important to realize that drugs can also have effects on other neurotransmitters or even hormones. Sometimes these varied effects can change the potency and/or effectiveness of a drug. This could prove useful when trying to find just the right combination of transmitter action to treat an individual's psychological disorder. Or it could be problematic if it leads to unwanted side effects. The reality is that most drugs currently available work only where we would like them to in the brain or only on a specific neurotransmitter. In many cases, individuals are sometimes prescribed one drug but then may also have to take additional drugs to reduce the side effects. Sometimes individuals stop taking medication because the side effects are so profound.

Table 2: Drug function and mechanism

Drug	Mechanism	Use	Agonist/Antagonist
Seroquel (quetiapine)	Blocks DA and 5-HT receptors	Schizophrenia, bipolar disorder	Antagonist for DA, 5-HT
L-dopa	Increase synthesis of DA	Parkinson's disease	Agonist for DA
Prozac (fluoxetine)	Blocks removal of 5-HT from synapse (prevents reuptake)	Depression, obsessive compulsive disorder	Agonist 5-HT
Aricept (donepezil)	Blocks removal of ACh from synapse	Alzheimer's disease	Agonist for ACh
Revia (naltrexone)	Blocks opioid post-synaptic receptors	Alcoholism, opioid addiction	Antagonist (for opioids)

Drug	Mechanism	Use	Agonist/Antagonist
Adderall (mixed salts amphetamine)	Increase release of DA, NE	ADHD	Agonist for DA, NE
Ritalin (methylphenidate)	Blocks removal of DA, NE, and lesser (5-HT) from synapse	ADHD	Agonist for DA, NE mostly

6.1.3 Drug Classifications

Art in a Cup

Who knew that a cup of coffee could also be a work of art? A talented barista can make coffee look as good as it tastes. If you are a coffee drinker, you probably know that coffee can also affect your mental state. It can make you more alert and may improve your concentration. That's because the caffeine in coffee is a psychoactive drug. In fact, caffeine is the most widely consumed psychoactive substance in the world. In North America, for example, 90 percent of adults consume caffeine daily.

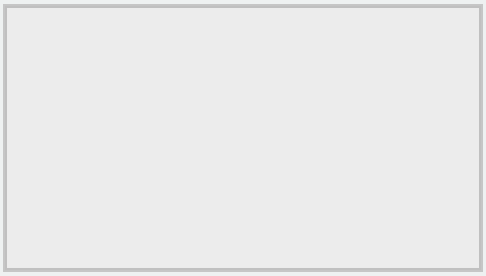


Figure 6.1.1: Murano Coffee with decoration on the surface.

Besides caffeine, other examples of psychoactive drugs include anti-anxiety medications (Xanax, Valium), antidepressants (Prozac, Celexa), alcohol, tobacco, marijuana, cocaine, psilocybin, oxycodone, and morphine. Organizing the wide range of different drugs into distinct categories is no easy task. One of the challenges is their various and, sometimes overlapping, pharmacological effects and mechanisms of action. Another challenge is that psychoactive drugs may be used for a variety of purposes, including therapeutic, ritual, and/or recreational.

In addition, many of these drugs may be legal prescription medications (e.g., oxycodone and morphine), legal nonprescription drugs (e.g., alcohol and tobacco), or illegal drugs (cocaine and psilocybin). To further complicate matters, some of these drugs, legal or not can be both therapeutic and abused. The status of cannabis (or marijuana), for example, is in flux, at least in the United States. Depending on where you are, cannabis may be used recreationally and/or medically, and it may be either legal or illegal. Legal prescription medications, such as opioids are also used illegally by alarmingly large numbers of people, resulting in a tragically high number of overdose deaths.

Although classification of psychoactive drugs is clearly complicated, there are some general categorizations that can prove useful.

6.1.3.1 Classification Based on Psychopharmacological Effects

Psychoactive drugs can be divided into different classes according to their psychopharmacological effects. Several classes are listed below, along with examples of commonly used drugs in each class.

- ***Stimulants**:* Stimulate the brain and increase alertness and wakefulness. Examples of stimulants include caffeine, nicotine, cocaine, and amphetamines.
- ***Depressants**:* Calm the brain, reduce anxious feelings, and induce sleepiness. Examples of depressants include ethanol (in alcoholic beverages) and opioids such as oxycodone and heroin.
- ***Anxiolytics**:* Have a tranquilizing (calming) effect and inhibit anxiety. Examples of anxiolytic drugs include benzodiazepines such as diazepam (Valium), barbiturates such as phenobarbital, opioids, cannabis, and antidepressant drugs such as sertraline (Zoloft).
- ***Euphoriants**:* Cause a state of euphoria, or intense feelings of well-being and happiness. Examples of euphoriants include the so-called club drug MDMA (ecstasy), amphetamines, ethanol, and opioids such as morphine.

- ***Hallucinogens**:* Cause hallucinations and other perceptual anomalies. They also cause subjective changes in thoughts, emotions, and consciousness. Examples of hallucinogens include LSD, mescaline, nitrous oxide, and psilocybin.
- ***Empathogens**:* Produce feelings of empathy, or sympathy with other people. Examples of empathogens include MDMA (Ectasy).



Figure 6.1.2: Ecstasy (MDMA) is most commonly taken in tablet form, like the colorful and decorated tablets shown

Many psychoactive drugs have multiple effects so they may be placed in more than one class. For example, many stimulants also have euphoriant properties, such as MDMA (Ectasy). Furthermore, MDMA may also act as an empathogen or hallucinogen. As of 2016, MDMA had no accepted medical uses, but is undergoing testing for use in the treatment of post-traumatic stress disorder and certain other types of anxiety disorders (Mitchell et al., 2021). As you can tell, drug classification can get a bit complicated.

6.1.3.2 Classification Based on Synaptic Mechanisms of Action

As previously stated, psychoactive drugs generally produce their effects by affecting brain chemistry, which in turn may cause changes in a person's mood, thinking, perception, and/or behavior. Each drug tends to have a specific action on one or more neurotransmitters or neurotransmitter receptors in the brain. Generally, they act as either agonists or antagonists.

- **Agonists** are drugs that mimic or increase the activity of particular neurotransmitters. They might act by promoting the synthesis of the neurotransmitters, reducing their reuptake from synapses, or mimicking their action by binding to receptors for the neurotransmitters.
- **Antagonists** are drugs that decrease the activity of particular neurotransmitters. They might act by interfering with the synthesis of the neurotransmitters or by blocking their receptors so the neurotransmitters cannot bind to them.

Consider the example of the neurotransmitter GABA. This is one of the most common neurotransmitters in the brain, and it normally has an inhibitory effect on cells. GABA *agonists*, which increase its effect at the synapse, include ethanol, depakote (anti-convulsant/bipolar medication), benzodiazepines (anti-anxiety medication), and other psychoactive drugs. All of these drugs work in different ways at the synapse, but ultimately increase the postsynaptic effect of GABA in the brain.

6.1.3.3 Classification Based on Type of Use

You may have been prescribed psychoactive drugs by your doctor. For example, you may have been prescribed a drug to treat anxiety or depression or an opioid, drug such as codeine for pain (most likely in the form of Tylenol with added codeine). You may also use nonprescription psychoactive drugs, such as caffeine for mental alertness or cannabis (CBD or Marijuana) to treat pain or anxiety. These are just some of the many possible uses of psychoactive drugs.

6.1.3.4 Medical Uses



Figure 6.1.3: This child is being prepared to receive a general anesthetic prior to surgery

Medical uses of psychoactive drugs include general anesthesia, in which pain is blocked and unconsciousness is induced. General anesthetics are most often used during surgical procedures and may be administered in gaseous form. General anesthetics include the drugs halothane and ketamine. Other psychoactive drugs are used to manage pain without affecting consciousness. They may be prescribed either for acute pain in cases of trauma such as broken bones; or for chronic pain such as pain caused by arthritis, cancer, or fibromyalgia. Most often, the drugs used for pain control are opioids, such as morphine and codeine. Their pain inhibitory actions rest with their ability to enhance our endogenous opioid activity in the brain, which ultimately will lead to a reduction of incoming pain signals from the body.

Many psychiatric disorders are also managed with psychoactive drugs. For example, antidepressants such as Sertraline or Celexa are used to treat depression, anxiety, and eating disorders. These drugs act as agonists for serotonin systems in key circuits of the brain which play an important role in mood regulation. Anxiety disorders may also be treated with anxiolytic drugs, such as buspirone and diazepam. Diazepam is from the benzodiazepine class of drugs which are agonists of the GABA system and can inhibit limbic areas of the brain involved with the anxiety and fear response.

Stimulants such as amphetamines are agonists for monamine transmitters and can be effective treatments for attention deficit disorder and certain sleep disorders. Antipsychotics such as clozapine and risperidone, as well as mood stabilizers such as lithium, are used to treat schizophrenia and bipolar disorder. These drugs act on a variety of transmitter systems in order to treat a variety of symptoms. Although controversial, relatively recent studies on the therapeutic, controlled use of hallucinogens such as MDMA and Psilocybin to treat disorders such as PTSD have been conducted.

6.1.3.5 Ritual Uses

Certain psychoactive drugs, particularly hallucinogens, have been used for ritual purposes since prehistoric times. For example, Native Americans have used the mescaline-containing peyote cactus (pictured below) for religious ceremonies for as long as 5,700 years. In prehistoric Europe, the mushroom *Amanita muscaria*, which contains a hallucinogenic drug called muscimol, was used for similar purposes. Various other psychoactive drugs — including jimsonweed, psilocybin mushrooms, and cannabis — have also been used by various peoples for ritual purposes for millennia.



Figure 6.1.4: The peyote cactus contains a hallucinogenic drug that is still used by some Native Americans for religious rituals.

6.1.3.6 Recreational Uses

The most typical recreational uses of psychoactive drugs have the purpose of altering one's consciousness and creating a feeling of euphoria commonly called a "high." Some of the drugs used most commonly for these purposes include cannabis, ethanol, opioids, and stimulants such as nicotine, amphetamine, or cocaine. Hallucinogens are also used recreationally, primarily for the alterations in thinking and perception that they cause.

Some investigators have suggested that the urge to alter one's state of consciousness is a universal human drive, similar to the drive to satiate thirst, hunger, or sexual desire. They think that the drive to alter one's state of mind is even present in children, who may attain an altered state by repetitive motions such as spinning or swinging. Some nonhuman animals also exhibit a drive to experience altered states. For example, they may consume fermented berries or fruit and become intoxicated. The way cats respond to catnip (Figure 6.1.6) is another example.

A variety of information on specific drugs used for recreational purposes is provided in section 6.3: Drugs of Abuse.



Figure 6.1.5: This cat is holding a catnip toy and apparently enjoying its psychoactive effects.

6.1.4 Summary

It is probably clear now that psychoactive drugs can have profound and quite varied effects on how we think, feel, perceive the world, and behave. This range of effects depends on a multitude of factors including the particular neurotransmitter systems affected, the general pharmacology of the drug, and it's specific synaptic effects. As described, the ability for drugs to act as either agonists or antagonists at synapses and the role of receptor subtypes (i.e. excitatory or inhibitory) have a major impact on the ultimate outcome to the individual. These synaptic effects and the influence of physiological effects that occur prior to drugs reaching the brain will be explored further in the next section of this chapter.

6.1.5 Supplemental Resources

Learn more about psychiatric drugs that are being researched to treat mental health disorders. In this inspiring TED talk, neurobiologist David Anderson explains how modern psychiatric drugs treat the chemistry of the whole brain and why a more nuanced view of how the brain functions could lead to targeted psychiatric drugs that work better and avoid side effects.

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6.1.7 Attribution

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6.2: Mechanisms of Psychoactive Drug Action

Learning Objectives

1. Describe the key elements of pharmacokinetics and their relationship to drug action.
2. Compare and contrast the various drug administration methods in terms of potency, latency of action, and abuse potential.
3. Describe the key elements of pharmacodynamics, particularly drug effects on steps of synaptic transmission and major neural circuitry
4. Differentiate the major structures of the mesolimbic, "reward" pathway and the role of dopamine in its function.

6.2.1 Overview

Do drugs affect the body or does the body affect drugs? This may seem like either a very easy or a very odd question. Of course, the answer is drugs affect the body, right? For example, you take a certain drug and then your heart rate changes or you feel energized to move around a lot. In terms of psychoactive drugs, the brain, which is part of the body, is definitely affected by drugs. As we will see, neurotransmitters can be become more active and the receptors that these neurotransmitters bind to may trigger either increased or decreased communication with other neurons, glands, or muscles. These examples should make it clear that drugs definitely affect the body. However, even before these effects on the body occur, the *body* is able to affect incoming drugs in profound ways. Thus, the answer to the earlier question is that the body affects drugs and drugs affect the body.

This section will review the basics on how both of these processes occur with a general review of the concepts of **pharmacokinetics** (how the body affects drugs) and **pharmacodynamics** (how drugs affect the body, or more specifically the brain). In covering these topics we will address various physiological processes, such as drug metabolism and elimination and the influence of drug administration methods on a drug's impact. In addition, we will go into the specifics of how drugs interact with the process of synaptic communication and then zoom out to see how they alter the activity of major circuits and structures of the brain, such as the so-called, "reward pathway."

6.2.2 Pharmacokinetics: What Is It – Why Is It Important?

Pharmacokinetics refers to how the body processes drugs as they enter the body. While this section may sound more like pharmacology, it is important to realize how important pharmacokinetics can be when considering the ultimate effects of psychoactive drugs. As mentioned previously, 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 to specify the processes of**:**

- **A - A**dministration **and A**bsorption (how the drug gets into the blood),
- **D - D**istribution (how the drug gets to the organ of interest – in this case, the brain),
- **M - M**etabolism (how the drug is broken down so it no longer exerts its psychoactive effects), and
- **E - E**limination (how the drug leaves the body).

We will focus on some of these processes to show their importance in determining the effects of psychoactive drugs.

6.2.2.1 Drug Administration and Absorption



Figure 6.2.1: 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. (CC BY-SA 3.0; Calleamanecer via Wikimedia Commons)

Before a drug can be absorbed by the body it needs to be administered in some way (i.e., the drug has to get into the body). There are many ways to take drugs, and these routes of drug administration can have a significant impact on how quickly that drug reaches brain.

The most common route of administration is **oral administration,** which begins in the mouth and continues in the digestive system. This route is relatively **slow** and – perhaps surprisingly – often the most variable and complex route of administration. Drugs enter the stomach and then get absorbed by the blood supply and capillaries that line the small intestine. The rate of absorption can be affected by a variety of factors including the quantity and the type of food in the stomach (e.g., fats vs. proteins). This is why the medicine label 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 rate of absorption.

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 brain in less than 10 seconds. IV administration also has the distinction of being the most dangerous because if there is an adverse drug reaction, there is very little time to administer any antidote, as in the case of an IV heroin overdose.

Key Elements of Drug Routes of Administration (Keys)

Route of Administration	Typical Methods Used	Speed of Absorption in Blood	Advantages / Disadvantages
Oral (PO)	Pill, Liquid, Edibles	**SLOWEST**	Convenient, Gradual onset, Relatively safe / Variable blood levels due to individual differences in absorption and metabolism
Subcutaneous	Injection into skin	↓	Gradual onset, Avoids 1st pass metabolism / Only small volumes can be given, Possible localized irritation, tissue damage, infection

Route of Administration	Typical Methods Used	Speed of Absorption in Blood	Advantages / Disadvantages
Intramuscular (IM)	Injection into muscle		Steady absorption rates, Avoids 1st pass metabolism, Extended release possible / Only small volumes can be given, Possible localized irritation, tissue damage, infection
Rectal	Rectal Suppository		Useful in those with digestive issues or unconscious, Mostly avoids 1st pass metabolism, Relatively high blood levels / Invasive, Unpredictable absorption rates
Sublingual	Under tongue		Direct & fast absorption, Avoids 1st pass metabolism, Quick termination possible
Inhalation	Smoke, Vape, Huff, Inhaler, Intranasal		Rapid absorption, Useful for emergency applications or localized effect (i.e. asthma), Reaches brain quickly / Variable dose & absorption, Relatively high abuse potential w/ certain drugs
Intravenous	Injected into vein	**FASTEST**	Very rapid absorption (~instantly), Avoids 1st pass metabolism, Useful for emergency applications, Accurate dosing / High abuse potential and risk for overdose with certain drugs

Why might knowing how quickly a drug gets to the brain be important? If we are considering therapeutic drugs, such as those used to treat anxiety, depression, or psychotic disorders, the time it takes to begin to relieve symptoms and how long this lasts can be critical information. For example, if treating an acute panic attack you would want a drug to act fast, whereas, if you want to prevent non-specific anxiety from occurring on a daily basis, you may use a different drug that acts more gradually but sticks around longer.

When considering potential drugs of abuse, administration and absorption rates are important for other reasons. Although there are multiple non-pharmacological risk factors for drug craving and substance use disorders, the phamacokinetics of a drug can play a significant role. For example, if a drug activates the reward circuits in the brain and reaches these areas quickly, the drug may have a relatively high risk for abuse and psychological dependence. Psychostimulants like amphetamine or cocaine are examples of drugs that have high risk for abuse in part because they are agonists at dopamine 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 hardest addictions to quit, and although part of the reason for this may be that smoking gets the nicotine into the brain very quickly (and indirectly acts on dopamine neurons), it is a more complicated story.

For drugs that reach the brain very quickly, not only is the drug potentially very addictive, but so are the cues associated with the drug (see Rohsenow, Niaura, Childress, Abrams, and Monti, 1990). A learned connection between drug use and the environmental elements that accompany it can complicate quitting by triggering symptoms of withdrawal and/or cravings. For an IV opioid user, this could be the sight of a container in which the drug and syringes are typically stored or other aspects of their typical drug-taking environment. For a cigarette smoker, it could be the smell of another person's smoke or even something as typical as finishing

dinner or waking up in the morning (if that is when the smoker usually has a cigarette). For both the opioid user and the cigarette smoker, the cues associated with the drug may actually cause craving that is alleviated by (you guessed it) – lighting a cigarette or injecting the opioid (i.e., relapse). This is one of the reasons individuals that 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 "environments", including friends and situations associated with drug use. But this is much *more* difficult for a cigarette smoker. How can someone avoid 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.

6.2.2.2 **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 super family. Usually, 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 of an 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 (e.g., fentanyl, codeine). *Metabolic tolerance* is one kind of tolerance and it takes place primarily in the liver. Some drugs, such as 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 the alcoholic needs to drink more to get the same effect – of course, until so much alcohol is consumed that it damages the liver (i.e. fatty liver or cirrhosis).

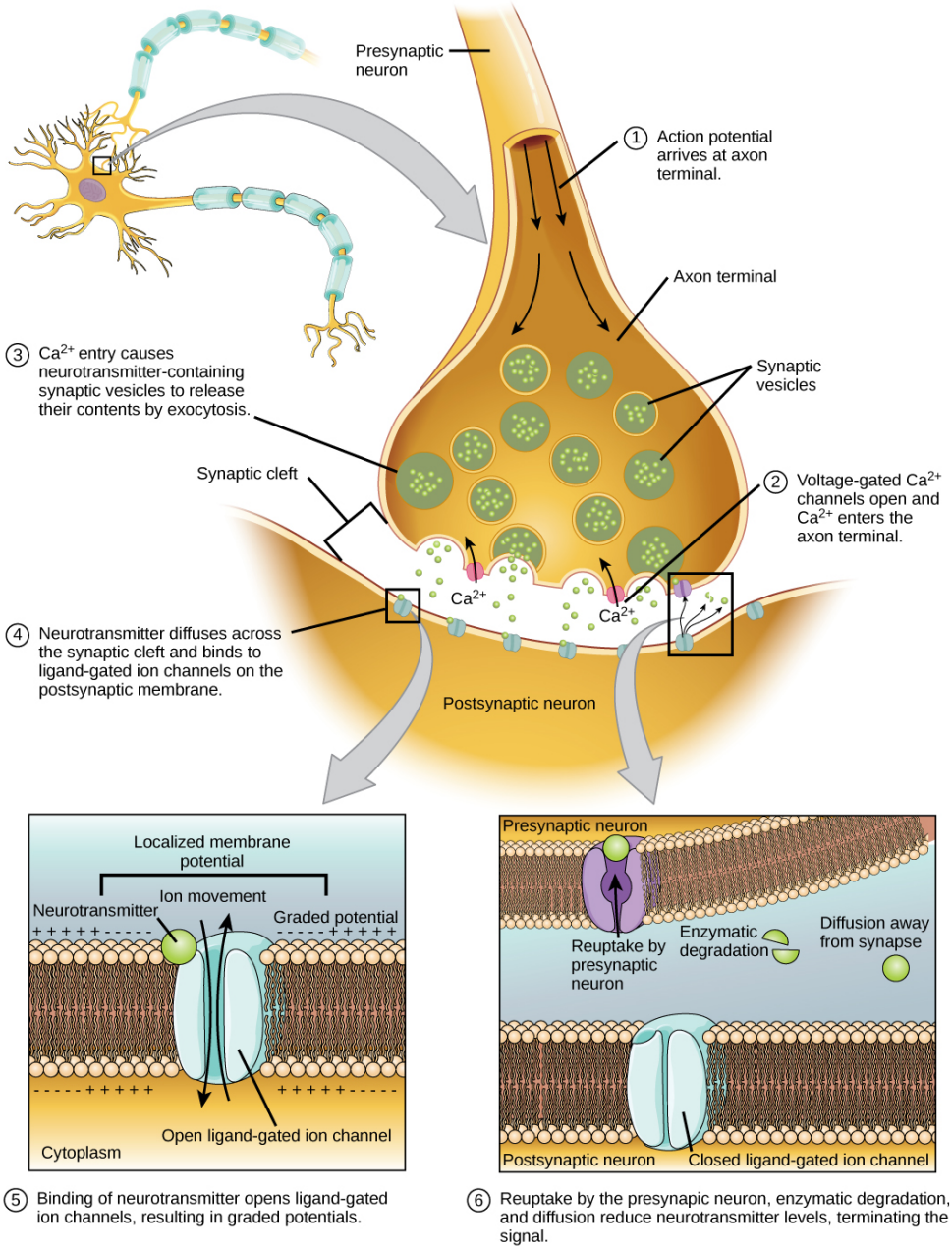
There are a variety of other ways that enzyme action can be altered by both physiological and environmental aspects of drug taking. For example, just the expectation of drug taking or the cues from the environment where drug taking regularly occurs can trigger either enzyme induction or inhibition and, thus altering the ultimate physical and/or psychological effects of the drug. These differences in response can be particularly dangerous if they involve an unexpected increase in life-threatening side effects, such as the respiratory depression seen in response to opioids.

After "surviving" the processes of absorption and initial metabolism but before being eliminated, drugs are distributed throughout the body until they reach their target. In the case of psychoactive drugs, the main target is the brain. At this point, the process shifts to *pharmacodynamics* where the roles reverse and drugs are now able to affect the body.

6.2.3 Pharmacodynamics

If you have a headache or muscle pain, you might take a drug like ibuprofen (Advil, Motrin) or acetaminophen (Tylenol). Part of how these drugs work is to block the production of chemicals that cause the inflammation that is responsible for the pain. Thus, their target is the location of action is where the inflammation or pain is occurring. For psychoactive drugs, including those which treat pain the target of action for their effects is the brain or nervous system. The pharmacodynamics of their effects can be divided into two general categories: Their influence on specific steps of communication at the level of the synapse and the more holistic effect on the activity of certain circuits or major structures of the nervous system.

Just about all psychoactive drugs have their initial effects on one or more of the **steps of synaptic communication: neurotransmitter synthesis, storage, release, binding, reuptake, and breakdown (See Figure 6.2.2)**. Remember, drugs can act as either agonists or antagonists of a neurotransmitter's typical effects. The drug L-dopa, for example acts as an agonist to increase the synthesis of dopamine and treat the dopamine dysfunction present in Parkinson's disease. Other agonist drugs like amphetamine and some other stimulants can increase the amount of dopamine activity by enhancing the release step. And yet others, such as cocaine can increase the synaptic activity of dopamine by blocking its reuptake. All these drugs are dopamine agonists (increase dopamine synaptic activity), but they can have very different psychological and behavioral effects due to the difference in the synaptic step targeted.



5 Binding of neurotransmitter opens ligand-gated ion channels, resulting in graded potentials.

6 Reuptake by the presynapic neuron, enzymatic degradation, and diffusion reduce neurotransmitter levels, terminating the signal.

Figure 6.2.2: Steps in Synaptic Transmission starting with the arrival of the action potential and culminating in transmitter release into the synapse. Details of neurotransmitter binding and termination mechanisms in the synapse are included in insets. Psychoactive drugs can affect one or more of these steps, depending on the drug. (CC BY 4.0 by OpenStax)

Knowing these initial actions of drugs at the level of the synapse is important in order to understand how they ultimately affect our thinking, feeling, and behavior. However, the thousands or even millions of synaptic changes that occur every split second due to

drug action first need to be integrated in order to have noticeable effects. This integration is reflected in alterations of the activity of key structures and circuits of the nervous system.

6.2.4 Drug effects on Neural Structures and Circuits

Every distinct brain area or neural circuit can be affected in some way by the action of psychoactive drugs due to the integration process discussed above. For example, drugs that increase endorphin activity (i.e. Opioids) in certain areas of the brain can trigger changes in a major pain-inhibition pathway. Circuits involved with attention are affected by drugs that enhance norepinephrine systems and can be effective treatments for ADHD. Still other drugs, such as anti-anxiety medications (i.e. Xanax, Valium) are GABA agonists and can enhance the action of GABA throughout the brain, including the amygdala, which plays a significant role in fear and anxiety responses.

6.2.4.1 Mesolimbic "Reward" Circuitry

One of the most interesting and significant circuits that has been studied for its role in drug taking and substance use disorder is the "reward circuit" or "pleasure pathway" of the brain. This circuitry is technically called the mesolimbic circuitry and contains major dopamine pathways in addition to other transmitters which play a role in the positive feelings associated with both natural and drug rewards (See Figure 6.2.3).

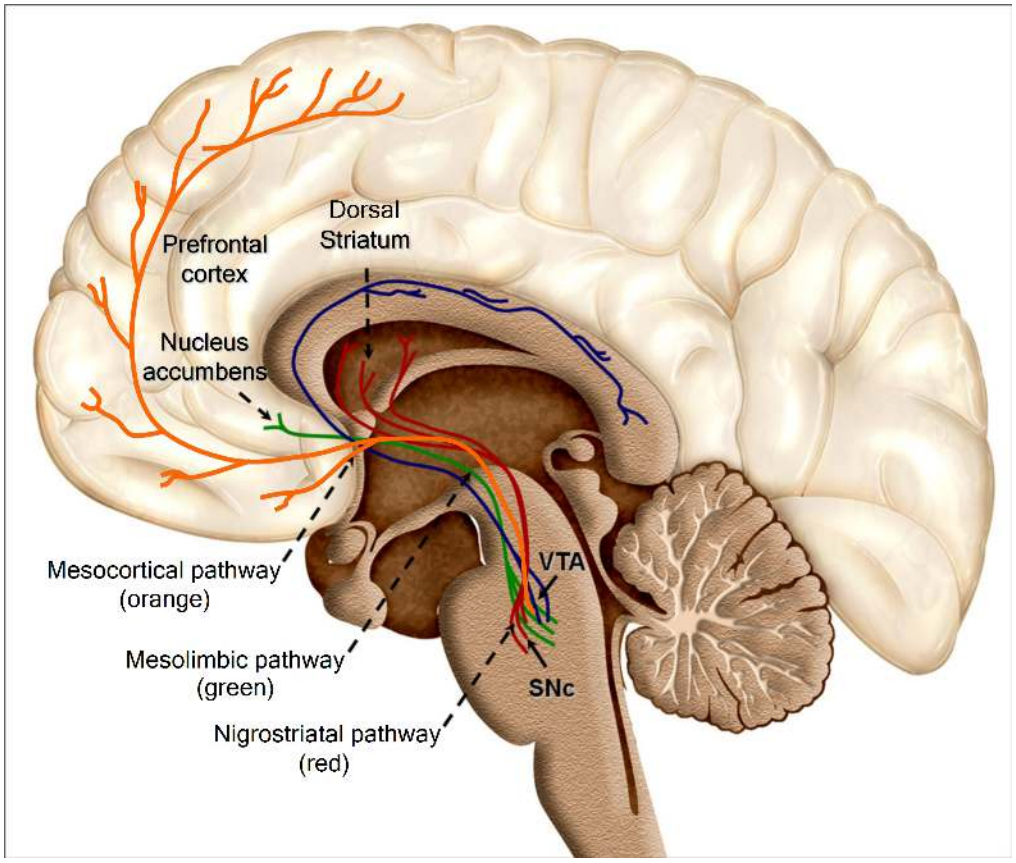


Figure 6.2.3: Mesolimbic, "Reward" Circuit and other Dopamine Pathways. These include pathways from both the Substantia Nigra (SNc) and Ventral Tegmental Area (VTA) to forebrain targets such as the Nucleus Accumbens and Prefrontal Cortex. From: Oscar Arias-Carrión1, Maria Stamelou, Eric Murillo-Rodríguez, Manuel Menéndez-González and Ernst Pöppel.Substantially modified by Seppi333, CC BY 2.0 , via Wikimedia Commons

The nucleus accumbens definitely plays a central role in the **reward circuit.** Its operation is based chiefly on two essential neurotransmitters: dopamine, which promotes desire, and serotonin, whose effects include satiety and inhibition. Many animal studies have shown that many psychoactive drugs and natural rewards increase the production of dopamine in the nucleus accumbens, while reducing that of serotonin.

But the nucleus accumbens does not work in isolation. It maintains close relations with other areas involved in pleasure and reward. One area in particular is the **ventral tegmental area (VTA)**. Located in the midbrain, at the top of the brainstem, the VTA is one of the most primitive parts of the brain. Neurons of the VTA synthesize dopamine and then send it via their axons primarily to the

nucleus accumbens. The VTA is also influenced by endorphins whose receptors are targeted by opiate drugs such as heroin and morphine.

Another structure involved in pleasure mechanisms is the **prefrontal cortex**, whose role in planning and motivating action is well established. The prefrontal cortex is a significant relay in the reward circuit and also is modulated by dopamine.

The locus coeruleus, an alarm area of the brain and packed with norepinephrine, is another brain structure that plays an important role in drug abuse. When stimulated by a lack of the drug in question, the locus coeruleus drives the user to do anything necessary to obtain more drug.

Three other structures in the limbic system also play an active part in the pleasure circuit and, consequently, in drug dependency. The first is the **amygdala**, which can provide affective or mood information in response to drugs or environmental stimuli.

The second is the **hippocampus**, which preserves the agreeable memories associated with drug taking or other non-drug behaviors and, by association, all of the details of the environment in which these behaviors occur. The memory of these details may trigger positive feelings and, in the case of drugs reawaken the desire to take the drug again contributing to the possibility of relapse.

The third structure, the most anterior portion of the **insular cortex**, or insula, is regarded as part of the limbic system that is thought to play a role in the active pleasure-seeking associated both with food and with psychoactive substances. It has been proposed that this part of the cortex tells us about the bodily states associated with our emotional experiences and then relates these feeling states to cognitive processes such as decision-making (Damasio et al., 2013).

6.2.5 Summary

Psychoactive drugs clearly undergo quite a journey through the body and, ultimately the brain prior to causing changes in how we think, feel, perceive the world, and behave. The pharmacokinetic steps of administration, distribution, metabolism, and elimination have a major impact on the timing and amount of drug action prior to their arrival at their targets in the nervous system. Upon arrival, pharmacodynamic actions primarily at the synapse contribute to the diverse and dynamic action of drugs on neural communication and subsequent psychological and behavioral changes. Psychoactive drugs have the potential to affect structures in all parts of the nervous system as long as the appropriate receptors are there to receive the. The structures of the Mesolimbic Reward Circuitry play a particularly critical role in the action of many psychoactive drugs, both therapeutic and recreational.

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6.2.7 Attributions

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6.3: Substance Use and Addiction - Theories, Brain Mechanisms, and Treatment

Learning Objectives

1. Define addiction (substance use disorder) in terms of changes in behavior, emotion, and cognition.
2. Describe the neural mechanisms of addiction, including the role of key neurotransmitters (dopamine & endorphins), brain structures & circuits, and genetics.
3. Differentiate the actions of drugs of abuse in terms of their neurotransmitter effects, neuroanatomy of action, and abuse potential

6.3.1 Overview

Many people don't understand why or how other people become addicted to drugs. They may mistakenly think that those who use drugs lack moral principles or willpower and that they could stop their drug use simply by choosing to. In reality, drug addiction is a complex disease, and quitting usually takes more than good intentions or a strong will. Drugs change the brain in ways that make quitting very difficult, even for those who want to. Fortunately, researchers know more than ever about how drugs affect the brain and have found treatments that can help people recover from drug addiction and lead productive lives.

6.3.2 What Is Addiction?

According to the National Institute of Drug Abuse (NIDA), drug addiction is defined as the continued compulsive use of drugs despite adverse health or social consequences. People addicted to drugs have lost control of their drug use. Because of this they can become isolated from family or friends, have difficulty at work or school, engage in unhealthy behaviors, and may become involved with the criminal justice system. For a person addicted to drugs, continuing to take them becomes the primary focus in life.

The Diagnostic and Statistical Manual, 5th edition (DSM V) from the American Psychological Association has reframed addiction as **substance use disorder** (Hasin, et al., 2013). This diagnostic category views substance use on a continuum with a range of severity from mild to severe based on the presence of 11 criteria. These criteria include some of the same factors noted by the NIDA definition stated above in addition to others, such as physiological effects (i.e. withdrawal & tolerance) and psychological problems related to drug use.

Disagreements about the nature of addiction remain: namely, whether it reflects voluntary or involuntary behavior and whether it should be punished or treated as a health issue. Even though the first time a person takes a drug, it is often by choice—to achieve a pleasurable sensation or desired emotional state—we now know from a large body of research that this ability to choose can be affected by drugs. And when addiction takes hold in the brain, it disrupts a person's ability to exert control over behavior—reflecting the compulsive nature of this disease.

The human brain is an extraordinarily complex and fine-tuned communications network made up of billions of cells that govern our thoughts, emotions, perceptions, and drives. Our brains reward certain behaviors such as eating or procreating—registering these as pleasurable activities that we want to repeat. Drug addiction taps into these vital mechanisms geared for our survival. And although not a life necessity, to an addicted person, drugs become life itself, driving the compulsive use of drugs—even in the face of dire life consequences—*that is the essence of addiction*.

6.3.3 How Does Addiction Take Hold in the Brain?

Decades of research supported by NIDA has proven that addiction is a complex brain disease characterized by compulsive, at times uncontrollable, drug craving, seeking, and use that persist despite potentially devastating consequences. Although not the only factor, the powerful rewarding effects of most drugs of abuse play a major role in their continued use despite negative effects.

The **rewarding effects** of most drugs of abuse come mainly from large and rapid upsurges in **dopamine**, a neurochemical critical to stimulating feelings of pleasure and to motivating behavior. Increased activity of **endorphins**, our natural opiate system can also play a role in these effects. The rapid dopamine "rush" from drugs of abuse mimics but greatly exceeds in intensity and duration the feelings that occur in response to such pleasurable stimuli as the sight or smell of food, for example. Repeated exposure to large, drug-induced dopamine surges has the insidious consequence of ultimately blunting the response of the dopamine system to everyday stimuli. Thus the drug disturbs a person's normal hierarchy of needs and desires and substitutes new priorities concerned with procuring and using the drug.

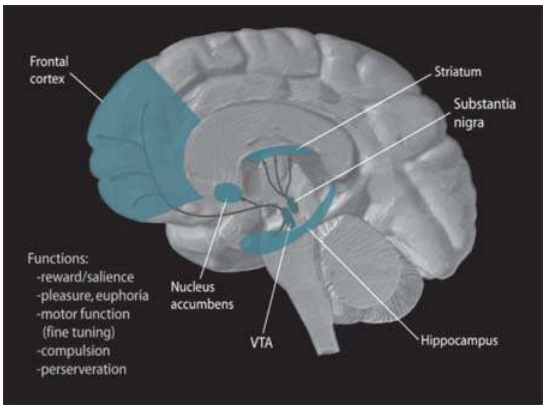


Figure 6.3.1: Dopamine Pathways. In the brain, dopamine plays an important role in the regulation of reward and movement. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex. Its motor functions are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the striatum. From: NIDA Research Report Series - Methamphetamine Abuse and Addiction (2006), PD US NIH, via Wikimedia Commons

Drug abuse also disrupts the brain circuits involved in memory and control over behavior. Memories of the drug experience can trigger craving as can exposure to people, places, or things associated with former drug use. Stress is also a powerful trigger for craving. Control over behavior is compromised because the affected frontal brain regions are what a person needs to exert inhibitory control over desires and emotions. That is why addiction is a brain disease.

As a person's **reward circuitry** becomes increasingly dulled and **desensitized** by drugs, nothing else can compete with them—food, family, and friends lose their relative value, while the ability to curb the need to seek and use drugs evaporates. Ironically and cruelly, eventually even the drug loses its ability to reward, but the compromised brain leads addicted people to pursue it, anyway; the memory of the drug has become more powerful than the drug itself.

Certain drugs, including **opioids and alcohol**, cause **strong physical reactions** in the body when drug use stops. When a person addicted to heroin stops taking heroin, they can experience a variety of symptoms ranging from watery eyes and a runny nose to irritability and loss of appetite and then diarrhea, shivering, sweating, abdominal cramps, increased sensitivity to pain, and sleep problems. In general, **withdrawal** from heroin makes people feel miserable. Withdrawal from alcohol can cause serious effects such as seizures and even death. Withdrawal from other drugs, such as cocaine and amphetamines, does not typically lead to strong physical reactions, but it may make the person feel depressed or lethargic. For most drugs, physical withdrawal symptoms can usually be controlled effectively with medications.

Even though withdrawal from some drugs does not cause the person abusing them to have physical reactions, stopping drug use is difficult because of the changes the drugs have caused in the brain. Once the drugs stop, the person will have **cravings**, or intense desire for the drugs that may lead to **relapse** of drug taking. Craving arises from the brain's need to maintain a state of homeostasis (balance) that now relies on the presence of the drug. A person may experience cravings at any stage of drug abuse or addiction, even early in the experimentation phase of drug abuse. Cravings have been shown to have a physical basis in the brain. Using PET imaging, scientists have shown that just seeing images of drug paraphernalia can stimulate the **amygdala** (part of the brain involved in emotional memory) in an addicted person.

Drugs of abuse do not merely cause short-term changes in an individual's cognitive skill and behavior. A drug "**high**" (i.e. euphoric state) typically lasts a short time, ranging from less than an hour to 12 hours, depending on the drug, dose, and route of administration. The changes in the brain that result from continued drug use, however, can last a long time. Scientists believe that some of these changes disappear when drug use stops; some disappear within a short time after drug use stops, and other changes are potentially permanent.

One of the first changes in the brain that may occur in response to repeated drug abuse is **tolerance**. Tolerance develops when a person needs increasing doses of a drug to achieve the same high or "rush" that previously resulted from a lower dose of the drug. Two primary mechanisms underlie the development of tolerance. First, the body may become more efficient at metabolizing the drug, thereby reducing the amount that enters the brain. Second, the cells of the body and brain may become more resistant to the effect of the drug. For example, after continued cocaine use, neurons decrease the number of dopamine receptors, which results in decreasing cocaine's stimulatory effect. Opioids, on the other hand, do not typically cause a change in the number of receptors.

Instead the opioid receptors become less efficient in activating associated cellular processes, thus reducing the effects of the opioids.

6.3.4 Why do some people become addicted to drugs while others don't?

No one factor can predict if a person will become addicted to drugs. A combination of factors influences risk for addiction. The more risk factors a person has, the greater the chance that taking drugs can lead to addiction. For example:

- **Biology**. The genes that people are born with account for about half of a person's risk for addiction. Gender, ethnicity, and the presence of other mental disorders may also influence risk for drug use and addiction.
- **Environment**. A person's environment includes many different influences, from family and friends to economic status and general quality of life. Factors such as peer pressure, physical and sexual abuse, early exposure to drugs, stress, and socioeconomic pressures can greatly affect a person's likelihood of drug use and addiction.
- **Development**. Genetic and environmental factors interact with critical developmental stages in a person's life to affect addiction risk. Although taking drugs at any age can lead to addiction, the earlier that drug use begins, the more likely it will progress to addiction. This is particularly problematic for teens. Because areas in their brains that control decision-making, judgment, and self-control are still developing, teens may be especially prone to risky behaviors, including trying drugs.

6.3.5 Can drug addiction be treated?

As with most other chronic diseases, such as diabetes, asthma, or heart disease, treatment for drug addiction generally isn't a cure. However, addiction is treatable and can be successfully managed. People who are recovering from an addiction will most likely be at risk for relapse for years and possibly their whole lives. Research shows that combining addiction treatment medicines with behavioral therapy ensures the best chance of success for most patients. Treatment approaches tailored to each patient's drug use patterns and any co-occurring medical, mental, and social problems can lead to continued recovery.

More good news is that drug use and addiction are preventable. Results from NIDA-funded research have shown that prevention programs involving families, schools, communities, and the media are effective for preventing or reducing drug use and addiction. Although personal events and cultural factors affect drug use trends, when young people view drug use as harmful, they tend to decrease their drug taking. Therefore, education and outreach are key in helping people understand the possible risks of drug use. Teachers, parents, and health care providers have crucial roles in educating young people and preventing drug use and addiction.

6.3.5.1 Medications and Devices used in Drug Addiction Treatment

Medications and devices can be used to manage withdrawal symptoms, prevent relapse, and treat co-occurring conditions.

Withdrawal. Medications and devices can help suppress withdrawal symptoms during detoxification. Detoxification is not in itself "treatment," but only the first step in the process. Patients who do not receive any further treatment after detoxification usually resume their drug use. One study of treatment facilities found that medications were used in almost 80 percent of detoxifications (SAMHSA, 2014). In November 2017, the Food and Drug Administration (FDA) granted a new indication to an electronic stimulation device, NSS-2 Bridge, for use in helping reduce opioid withdrawal symptoms. This device is placed behind the ear and sends electrical pulses to stimulate certain brain nerves. Also, in May 2018, the FDA approved lofexidine, a non-opioid medicine designed to reduce opioid withdrawal symptoms.

Relapse prevention. Patients can use medications to help re-establish normal brain function and decrease cravings. Medications are available for treatment of opioid (heroin, prescription pain relievers), tobacco (nicotine), and alcohol addiction. Scientists are developing other medications to treat stimulant (cocaine, methamphetamine) and cannabis (marijuana) addiction. People who use more than one drug, which is very common, need treatment for all of the substances they use.

- ***Opioids:*** Methadone (Dolophine®, Methadose®), buprenorphine (Suboxone®, Subutex®, Probuphine® , Sublocade™), and naltrexone (Vivitrol®) are used to treat opioid addiction. Acting on the same targets in the brain as heroin and morphine, methadone and buprenorphine suppress withdrawal symptoms and relieve cravings. Naltrexone blocks the effects of opioids at their receptor sites in the brain and should be used only in patients who have already been detoxified. All medications help patients reduce drug seeking and related criminal behavior and help them become more open to behavioral treatments. A NIDA study found that once treatment is initiated, both a buprenorphine/naloxone combination and an extended release naltrexone formulation are similarly effective in treating opioid addiction. Because full detoxification is necessary for treatment with naloxone, initiating treatment among active users was difficult, but once detoxification was complete, both medications had similar effectiveness.

- ***Tobacco:*** Nicotine replacement therapies have several forms, including the patch, spray, gum, and lozenges. These products are available over the counter. The U.S. Food and Drug Administration (FDA) has approved two prescription medications for nicotine addiction: bupropion (Zyban®) and varenicline (Chantix®). They work differently in the brain, but both help prevent relapse in people trying to quit. The medications are more effective when combined with behavioral treatments, such as group and individual therapy as well as telephone quitlines.
- ***Alcohol:*** Three medications have been FDA-approved for treating alcohol addiction and a fourth, topiramate, has shown promise in clinical trials (large-scale studies with people). The three approved medications are as follows:
  - **Naltrexone** blocks opioid receptors that are involved in the rewarding effects of drinking and in the craving for alcohol. It reduces relapse to heavy drinking and is highly effective in some patients. Genetic differences may affect how well the drug works in certain patients.
  - **Acamprosate (Campral®)** may reduce symptoms of long-lasting withdrawal, such as insomnia, anxiety, restlessness, and dysphoria (generally feeling unwell or unhappy). It may be more effective in patients with severe addiction.
  - **Disulfiram (Antabuse®)** interferes with the breakdown of alcohol. Acetaldehyde builds up in the body, leading to unpleasant reactions that include flushing (warmth and redness in the face), nausea, and irregular heartbeat if the patient drinks alcohol. Compliance (taking the drug as prescribed) can be a problem, but it may help patients who are highly motivated to quit drinking.
- ***Co-occuring conditions:*** Other medications are available to treat possible mental health conditions, such as depression or anxiety, that may be contributing to the person's addiction.

More details on the addictive potential for some of the specific drugs mentioned above and others are included in the next section.

6.3.6 Summary

Drug addiction (i.e. Substance Use Disorder) is clearly a chronic disease characterized by drug seeking and use that is compulsive, or difficult to control, despite harmful consequences. Brain changes that occur over time with drug use challenge an individual's self-control and interfere with their ability to resist intense urges to take drugs, thus relapse is common. Most drugs affect the brain's reward circuit by flooding it with the chemical messenger dopamine. This causes the "high" that leads people to take a drug again. Over time, the brain adjusts to excess dopamine activity, which ultimately results in the effect known as tolerance, leading the user to take more of the drug in order to achieve the same high. Typically, a combination of genetic, environmental, and developmental factors influences risk for drug misuse. The more risk factors a person has, the greater the chance that taking drugs can lead to a substance use disorder. However, there is hope in that substance use disorder is both preventable and treatable.

6.3.7 References

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6.3.8 Attributions

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6.4: Specific Drug Effects, Misuse, and Risks

Learning Objectives

- Identify the specific types of drugs which are commonly misused and abused
- Describe the desired and adverse effects of commonly abused drugs
- Differentiate the potential contributing factors for drug misuse and abuse of commonly abused drugs.

6.4.1 Overview

A wide variety of drugs both legal and illegal can lead to misuse and addiction due to several possible causal factors. As noted previously, not everyone who takes these drugs will ultimately end up with a substance use disorder. Some, in fact are used therapeutically with success or recreationally without negative consequences. However, it is also true that some pose an unusually high risk for developing abusive patterns and significant adverse physical, psychological, and behavioral effects. This section will highlight some of the most prevalent and risky drugs in terms of their potential for being abused. This selection of potential drugs of abuse and their associated effects is just a sample of the wide array of chemical substances that can result in abusive patterns of intake. More information on the effects of the drugs presented here along with several other potential drugs of abuse can be found in the links to the National Institute of Drug Abuse sites provided at the end of this section.

6.4.2 Prescription Drugs

Prescription drugs are often strong medications, which is why they require a prescription from a doctor or dentist. Listed below are three common types of prescription drugs along with their primary neural mechanisms of action and clinical uses.

- **Opioids**— Acts on the **endorphin** neurotransmitter system and is used to relieve pain
- **Depressants**—Acts primarily on **inhibitory** mechanisms, such as the **GABA** system and is used to relieve anxiety or help a person sleep
- **Stimulants**— Acts primarily on **excitatory** mechanisms, such as **dopamine and norepinephrine** and is used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy, and other disorders.

6.4.2.1 How Prescription Drugs are Misused

Along with their clinical uses, all three of the drug types stated above are commonly abused. In the initial stages of drug misuse, people tend to take these drugs to either get “high” or achieve a state of altered consciousness. Prescription drug misuse has become a very significant public health problem primarily due to the risks and adverse effects of prescription opioids which has contributed to a recent dramatic increase in overdose deaths.

Some of the most common ways that prescription drugs are misused include the following:

- Taking someone else’s prescription medication, even if it is for a medical reason (such as to relieve pain, to stay awake, or to fall asleep).
- Taking a prescription medication (yours or someone else's) in a way other than prescribed—for instance, taking more than the prescribed dose or taking it more often, or crushing pills into powder to snort or inject the drug.
- Mixing it with alcohol or certain other drugs.

All three of these methods have an inherent set of both psychological and physiological risks which contribute to their likelihood of being abused and adverse reactions.

6.4.2.2 What Makes Prescription Drug Misuse Unsafe

Every medication has some risk for harmful effects, sometimes serious ones. Doctors and dentists consider the potential benefits and risks to each patient before prescribing medications and take into account a lot of different factors, as described below:

- **Personal information.** Before prescribing a drug, health providers consider a person's weight, how long they've been prescribed the medication, other medical conditions, and what other medications they are taking. Someone misusing prescription drugs may overload their system or put themselves at risk for dangerous drug interactions.
- **Form and dose.** Doctors know how long it takes for a pill or capsule to dissolve in the stomach, release drugs to the blood, and reach the brain. When misused, prescription drugs are sometimes taken in larger amounts or in ways that change the way the drug works in the body and brain, putting the person at greater risk for an overdose. For example, when people who misuse

OxyContin® crush and inhale the pills, a dose that normally works over the course of 12 hours hits the central nervous system all at once. This effect increases the risk for addiction and overdose.

- **Side effects.** Prescription drugs are designed to treat a specific illness or condition, but they often affect the body in other ways, some of which can be uncomfortable, and in some cases, dangerous. These are called side effects. Side effects can be worse when prescription drugs are not taken as prescribed or are used in combination with other substances. Side effects for the most commonly abused prescription drugs include the following:
  - Using **opioids** like oxycodone and codeine can cause you to feel sleepy, sick to your stomach, and constipated. At higher doses, opioids can make it hard to breathe properly and can cause overdose and death.
  - Using **stimulants** like Adderall or Ritalin can make you feel paranoid. It also can cause your body temperature to get dangerously high and make your heart beat too fast. This is especially likely if stimulants are taken in large doses or in ways other than swallowing a pill.
  - Using **depressants** like barbiturates can cause slurred speech, shallow breathing, sleepiness, disorientation, and lack of coordination. People who misuse depressants regularly and then stop suddenly may experience seizures. At higher doses depressants can also cause overdose and death, especially when combined with alcohol.

6.4.2.3 Overdose Risk

More than half of the drug overdose deaths in the United States each year are caused by prescription drug misuse. Overdose deaths involving prescription drugs—including pain relievers, benzodiazepines and antidepressants—increased steadily throughout the 1990s, peaked in 2017 and then decreased steadily in 2018 and 2019, and then increased again in 2020. Increases were linked to a rise in the misuse of prescription opioid pain relievers, as well as the presence of fentanyl in the drug supply. In 2013, only 9% of deaths (1,630 deaths) involving prescription drugs also involved fentanyl. In 2019, more than 46% of deaths (10,400 deaths) involving prescription drugs also involved fentanyl.

Mixing different types of prescription drugs can be particularly dangerous. For example, benzodiazepines interact with opioids (pain relievers) and increase the risk of overdose. Also, combining opioids with alcohol can make breathing problems worse and can lead to death.

6.4.3 **Alcohol**

Alcohol is among the most used drugs, plays a large role in many societies and cultures around the world, and greatly impacts public health. More people over age 12 in the United States have used alcohol in the past year than any other drug or tobacco product, and alcohol use disorder is the most common type of substance use disorder in the United States.

6.4.3.1 Alcohol Effects on the Brain and Behavior

Alcohol is a potent depressant whose main mechanism of action is to increase inhibitory action throughout the nervous system. It's primary mode of action to accomplish this is by acting as an agonist in the GABA neurotransmitter system. This can then act to release people from inhibitions, which gives the initial appearance of alcohol being excitatory.

When people drink alcohol, they may temporarily feel elated and happy, but they should not be fooled. As blood alcohol level rises, the effects on the body—and the potential risks—multiply.

- Inhibitions and memory become affected, so people may say and do things that they will regret later and possibly not remember doing at all.
- Decision-making skills are affected, so people may be at greater risk for driving under the influence or making unwise decisions.
- Aggression can increase, potentially leading to everything from verbal abuse to physical fights.
- Coordination and physical control are also impacted. When drinking leads to loss of balance, slurred speech, and blurred vision, even normal activities can become more dangerous.

Research also suggests that drinking during the teen years could interfere with normal brain development and change the brain in various ways, including negative effects on information processing and learning and increased risk of developing alcohol use disorder later in life.

6.4.3.2 Adverse Effects and Overdose Risk

Alcohol use disorder (AUD) is a chronic relapsing brain disorder characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. AUD ranges from mild to severe.

Consuming a dangerously high amount of alcohol can also lead to alcohol overdose and death. When people drink too much, they may eventually pass out (lose consciousness). Reflexes like gagging and breathing can be suppressed. That means people who have had too much alcohol could vomit and choke, or just stop breathing completely. Vulnerability to overdose increases if the person is already on a sedative-hypnotic (such as Valium, Xanax, or Benadryl) or pain medication.

An alcohol overdose occurs when there is so much alcohol in the bloodstream that areas of the brain controlling basic life-support functions—such as breathing, heart rate, and temperature control—begin to shut down. Alcohol overdose can lead to permanent brain damage or death.

Symptoms of alcohol overdose may include, mental confusion, difficulty remaining conscious, vomiting, seizures, slow (fewer than 8 breaths per minute) or irregular breathing (10 seconds or more between breaths), slow heart rate, clammy skin, dulled responses, such as no gag reflex (which prevents choking).

Know the danger signals and, if you suspect that someone has an alcohol overdose, call 911 for help immediately. Do not wait for the person to have all the symptoms, and be aware that a person who has passed out can die. Don't play doctor—cold showers, hot coffee, and walking do not reverse the effects of alcohol overdose and could actually make things worse.

6.4.4 **Marijuana**

Marijuana is the dried leaves and flowers of the *Cannabis sativa* or *Cannabis indica* plant. Stronger forms of the drug include high potency strains - known as sinsemilla (sin-seh-me-yah), hashish (hash for short), and extracts.

Of the more than 500 chemicals in marijuana, *delta-9-tetrahydrocannabinol*, known as THC, is responsible for many of the drug's psychotropic (mind-altering) effects. It's this chemical that distorts how the mind perceives the world. In other words, it's what makes a person high.

The amount of THC in marijuana has increased over the past few decades. In the early 1990s, the average THC content in marijuana was less than 4 percent. It is now about 15 percent and much higher in some products such as oils and other extracts (see below). Some people adjust how they consume marijuana (by smoking or eating less) to compensate for the greater potency. There have been reports of people seeking help in emergency rooms with symptoms, including nervousness, shaking, and psychosis after consuming high concentrations of THC.

Smoking extracts and resins from the marijuana plant with high levels of THC is on the rise. These resins have 3 to 5 times more THC than the plant itself. Smoking or vaping it (also called **dabbing**) can deliver dangerous amounts of THC and has led some people to seek treatment in the emergency room. There have also been reports of people injured in fires and explosions caused by attempts to extract hash oil from marijuana leaves using butane (lighter fluid).

6.4.4.1 Marijuana Effects on the Brain and Behavior

When marijuana is smoked or vaporized, THC quickly passes from the lungs into the bloodstream, which carries it to organs throughout the body, including the brain. Its effects begin almost immediately and can last from 1 to 3 hours. This can affect decision making, concentration, and memory for days after use, especially in people who use marijuana regularly. If marijuana is consumed in "edibles," foods, or beverages the effects of THC appear later—usually in 30 minutes to 1 hour—and may last for many hours. Some people consume more and more waiting for the "high" and end up in the emergency room with uncomfortable symptoms from too much THC.

As it enters the brain, THC attaches to cells, or neurons, with specific kinds of receptors called *cannabinoid receptors*. Normally, these receptors are activated by chemicals similar to THC that occur naturally in the body. They are part of a communication network in the brain called the *endocannabinoid system*. This system is important in normal brain development and function.

Most of the cannabinoid receptors are found in parts of the brain that influence pleasure, memory, thinking, concentration, sensory and time perception, and coordinated movement. Marijuana activates the endocannabinoid system, which causes the "high" and stimulates the release of **dopamine** in the brain's reward centers, reinforcing the behavior. Other effects include changes in perceptions and mood, lack of coordination, difficulty with thinking and problem solving, and disrupted learning and memory.

6.4.4.2 Potential Risks of Marijuana Use and Addiction

Regular marijuana use has been associated with the following risks:

- **Reduced school performance.** Students who smoke marijuana tend to get lower grades and are more likely to drop out of high school than their peers who do not use. The effects of marijuana on attention, memory, and learning can last for days or weeks.

- **Reduced life satisfaction.** Research suggests that people who use marijuana regularly for a long time are less satisfied with their lives and have more problems with friends and family compared to people who do not use marijuana.
- **Impaired driving.** Marijuana affects a number of skills required for safe driving—alertness, concentration, coordination, and reaction time—so it's not safe to drive high or to ride with someone using marijuana. Marijuana makes it hard to judge distances and react to signals and sounds on the road. Combining marijuana with drinking even a small amount of alcohol greatly increases driving danger, more than either drug alone. Learn more about what happens when you mix **marijuana and driving**.
- **Use of other drugs.** Most young people who use marijuana do not go on to use other drugs. However, those who use are more likely to use other illegal drugs. It isn't clear why some people go on to try other drugs, but researchers have a few theories. The human brain continues to develop into the early 20s. Exposure to addictive substances, including marijuana, may cause changes to the developing brain that make other drugs more appealing.
- **Severe nausea and vomiting.** Studies have shown that in rare cases, regular, long-term marijuana use can lead some people to have cycles of severe nausea, vomiting, and dehydration, sometimes requiring visits to the emergency room.

Marijuana can also be addictive---meaning users continue to use it despite negative consequences. Approximately 10 percent of people who use marijuana may develop what is called a **marijuana use disorder**—problems with their health, school, friendships, family or other conflicts in their life. The person can't stop using marijuana even though it gets in the way of daily life. People who begin using marijuana before the age of 18 are 4–7 times more likely than adults to develop a marijuana use disorder.

What causes one person to become addicted to marijuana while another does not depends on many factors—including their family history (genetics), the age they start using, if they also use other drugs, their family and friend relationships, and if they take part in positive activities like school, clubs, or sports. More research needs to be done to determine if people who use marijuana for medical reasons are at the same risk for addiction as those who use it just to get high.

People who use marijuana may feel a mild **withdrawal** when they stop using the drug, but might not recognize their symptoms as drug withdrawal. These symptoms may include, irritability, sleeplessness, lack of appetite, anxiety, and drug cravings.

These effects can last for several days to a few weeks after drug use is stopped. Relapse (returning to the drug after you've quit) is common during this period because people may crave the drug to relieve these symptoms.

6.4.4.3 Potential Therapeutic Effects

The marijuana plant itself has not been approved as a medicine by the federal government, yet several states have made it legal for recreational and/or medical use. The plant contains chemicals—called cannabinoids—that may be useful for treating a range of illnesses or symptoms. Here are some samples of cannabinoids that have been approved or are being tested as medicines:

- **THC:** The cannabinoid that can make you "high"—THC—has some medicinal properties. Two laboratory-made versions of THC, nabilone and dronabinol, have been approved by the federal government to treat nausea, prevent sickness and vomiting from chemotherapy in cancer patients, and increase appetite in some patients with AIDS.
- **CBD:** Another chemical in marijuana with potential therapeutic effects is called cannabidiol, or CBD. CBD doesn't have mind-altering effects and is being studied for its possible uses as medicine. For example, CBD oil has been approved as a possible treatment for seizures in children with some severe forms of epilepsy.
- **THC and CBD:** A medication with a combination of THC and CBD is available in several countries outside the United States as a mouth spray for treating pain or the symptoms of multiple sclerosis.

It is important to remember that smoking marijuana can have side effects, making it difficult to develop as a medicine. Side effects might outweigh its value as a medical treatment, especially for people who are not very sick. Another problem with smoking or eating marijuana plant material is that the ingredients can vary a lot from plant to plant, so it is difficult to get an exact dose. Until a medicine can be proven safe and effective, it will not be approved by the federal government.

6.4.5 Tobacco, Nicotine, & Vaping (E-Cigarettes)

Tobacco is a leafy plant grown around the world, including in parts of the United States. There are many chemicals found in tobacco leaves but **nicotine** is the one that can lead to addiction. Other chemicals produced by smoking tobacco, such as tar, carbon monoxide, acetaldehyde, and nitrosamines, also can cause serious harm to the body. For example, tar causes lung cancer and other serious diseases that affect breathing, and carbon monoxide can cause heart problems.

6.4.5.1 How Tobacco and Nicotine Products Are Used

Tobacco and nicotine products come in many forms. People can smoke, chew, sniff them, or inhale their vapors.

- **Smoked tobacco products.**
  - *Cigarettes:* These are labeled as regular, light, or menthol, but no evidence exists that “lite” or menthol cigarettes are safer than regular cigarettes.
  - *Cigars and pipes:* Some small cigars are hollowed out to make room for marijuana, known as "blunts," often done to hide the fact that they are smoking marijuana.
  - *Hookahs or water pipes*: Hookah tobacco comes in many flavors, and the pipe is typically passed around in groups. A typical hookah session delivers approximately 125 times the smoke, 25 times the tar, 2.5 times the nicotine, and 10 times the carbon monoxide as smoking a cigarette.
- **Smokeless tobacco products.** The tobacco is not burned with these products:
  - *Chewing tobacco.* It is typically placed between the cheek and gums.
  - *Snuff:* Ground tobacco that can be sniffed if dried or placed between the cheek and gums.
  - *Dissolvable products:* These include lozenges, orbs, sticks, and strip.
- **Vaping/electronic cigarettes** (also called e-cigarettes, electronic nicotine delivery systems, vaping devices, e-cigs, or JUULing). Vaping products are battery-operated devices that deliver nicotine and flavorings without burning tobacco. In most products, puffing activates the battery-powered heating device, which vaporizes the liquid in the cartridge. The resulting vapor is then inhaled (called “vaping”).

6.4.5.3 Tobacco Effects on the Brain

Like many other drugs, nicotine increases levels of a neurotransmitter called **dopamine**. Dopamine is released naturally when you experience something pleasurable like good food, your favorite activity, or spending time with people you care about. When a person uses tobacco products, the release of dopamine causes similar “feel-good” effects. This effect wears off quickly, causing people who smoke to get the urge to light up again for more of that good feeling, which can lead to addiction.

A typical smoker will take 10 puffs on a cigarette over the period of about 5 minutes that the cigarette is lit. So, a person who smokes about a pack of 25 cigarettes a day gets 250 “hits” of nicotine.

When smokeless tobacco is used, nicotine is absorbed through the mouth tissues directly into the blood, where it goes to the brain. Even after the tobacco is removed from the mouth, nicotine continues to be absorbed into the bloodstream. Also, the nicotine stays in the blood longer for users of smokeless tobacco than for smokers.

6.4.5.4 Is Vaping Worse Than Smoking?

Regardless of how vaping compares to cigarette smoking, it is important to recognize that nicotine vaping has its own risks, which include addiction and other potentially harmful health effects. Research so far suggests that nicotine vaping might be less harmful than cigarettes when people who regularly smoke switch to them completely and no longer use tobacco cigarettes.

However, nicotine in any form is a highly addictive drug, and health experts have raised many questions about the safety of vaping devices, particularly for teens:

- Testing of some vaping products found the aerosol (vapor) to contain known cancer-causing and toxic chemicals. The health effects of repeated exposure to these chemicals are not yet clear.
- Some research suggests that nicotine vaping may increase the likelihood that teens will try other tobacco products, including cigarettes. A study showed that students who have vaped nicotine by the time they start 9th grade are more likely than others to start smoking traditional cigarettes and other smoked tobacco within the next year.
- Some research suggests that certain vaping products contain metals like nickel and chromium, possibly coming from the heating of coils, that may be harmful when inhaled.

6.4.5.5 Potential Risks and Addiction

It is clear that the nicotine in tobacco is addictive. Each cigarette contains about 10 milligrams of nicotine. A person inhales only some of the smoke from a cigarette, and not all of each puff is absorbed in the lungs. The average person gets about 1 to 2 milligrams of nicotine from each cigarette.

Studies of widely used brands of smokeless tobacco showed that the amount of nicotine per gram of tobacco ranges from 4.4 milligrams to 25.0 milligrams. Holding an average-size dip in your mouth for 30 minutes gives you as much nicotine as smoking 3 cigarettes. A 2-can-a-week snuff dipper gets as much nicotine as a person who smokes 1½ packs a day.

Whether a person smokes tobacco products or uses smokeless tobacco, the amount of nicotine absorbed in the body is enough to make someone addicted. When this happens, the person continues to seek out the tobacco even though he or she understands the harm it causes. Nicotine addiction can cause:

- *Tolerance:* Over the course of a day, someone who uses tobacco products develops tolerance—more nicotine is required to produce the same initial effects. In fact, people who smoke often report that the first cigarette of the day is the strongest or the "best."
- *Withdrawal:* When people quit using tobacco products, they usually experience uncomfortable **withdrawal** symptoms, which often drive them back to tobacco use. Nicotine withdrawal symptoms include irritability, problems with thinking and paying attention, sleep problems, increased appetite, and craving, which may last 6 months or longer, and can be a major stumbling block to quitting.

6.4.6 Methamphetamine

Methamphetamine is a powerful, highly addictive stimulant that affects the central nervous system. Crystal methamphetamine is a form of the drug that looks like glass fragments or shiny, bluish-white rocks. It is chemically similar to amphetamine, a drug used to treat attention-deficit hyperactivity disorder (ADHD) and narcolepsy, a sleep disorder.

People can take methamphetamine by, smoking, swallowing (pill), snorting, or injecting the powder that has been dissolved.

Because the "high" from the drug both starts and fades quickly, people often take repeated doses in a "binge and crash" pattern. In some cases, people take methamphetamine in a form of binging known as a "run," giving up food and sleep while continuing to take the drug every few hours for up to several days.

6.4.6.1 Methamphetamine Effects on the Brain and Behavior

Methamphetamine increases the amount of the natural chemical **dopamine** in the brain. Dopamine is involved in body movement, motivation, and reinforcement of rewarding behaviors. The drug's ability to rapidly release high levels of dopamine in reward areas of the brain strongly reinforces drug-taking behavior, making the user want to repeat the experience.

6.4.6.1.1 *Short-Term Effects*

Taking even small amounts of methamphetamine can result in many of the same health effects as those of other stimulants, such as cocaine or amphetamines. These include, increased wakefulness and physical activity, decreased appetite, faster breathing, rapid and/or irregular heartbeat, and increased blood pressure and body temperature.

6.4.6.1.2 *Long-Term Effects*

Long-term methamphetamine use has many other negative consequences, including addiction, extreme weight loss, severe dental problems, anxiety, altered judgement and decision making, confusion, memory loss, sleeping problems, violent behavior, ***paranoia, and hallucinations***.

In addition, continued methamphetamine use can cause changes in brain structure and function. In particular, the brain's dopamine system is often affected, resulting in reduced coordination and impaired verbal learning. In studies of people who used methamphetamine over the long term, severe changes also affected areas of the brain involved with emotion and memory.

Although some of these brain changes may reverse after being off the drug for a year or more, other changes may not recover even after a long period of time. A recent study even suggests that people who once used methamphetamine have an increased the risk of developing Parkinson's disease, a disorder of the nerves that affects movement.

People who inject methamphetamine are at increased risk of contracting infectious diseases such as HIV and hepatitis B and C. In addition, methamphetamine use may worsen the progression of HIV/AIDS and its consequences. Studies indicate that HIV causes more injury to nerve cells and more cognitive problems in people who use methamphetamine than it does in people who have HIV and don't use the drug.

6.4.7 MDMA (i.e. Ecstasy or Molly)

3,4-methylenedioxy-methamphetamine (**MDMA**) is a synthetic, emphatogenic drug that alters mood and perception (awareness of surrounding objects and conditions). It is chemically similar to both stimulants and hallucinogens, producing feelings of increased energy, pleasure, emotional warmth, and distorted sensory and time perception.

MDMA was initially popular in the nightclub scene and at all-night dance parties ("raves"), but the drug now affects a broader range of people who more commonly call the drug Ecstasy or Molly.

6.4.7.1 How do people use MDMA?

People who use MDMA usually take it as a capsule or tablet, though some swallow it in liquid form or snort the powder. The popular nickname Molly (slang for "molecular") often refers to the supposedly "pure" crystalline powder form of MDMA, usually sold in capsules. However, people who purchase powder or capsules sold as Molly often actually get other drugs such as synthetic cathinones ("bath salts") instead. In addition, some people take MDMA in combination with other drugs such as alcohol or marijuana.

6.4.7.2 MDMA Effects on the Brain and Behavior

MDMA increases the activity of three brain chemicals:

- Dopamine—produces increased energy/activity and acts in the reward system to reinforce behaviors
- Norepinephrine—increases heart rate and blood pressure, which are particularly risky for people with heart and blood vessel problems
- Serotonin—affects mood, appetite, sleep, and other functions. It also triggers hormones that affect sexual arousal and trust. The release of large amounts of serotonin likely causes the emotional closeness, elevated mood, and empathy felt by those who use MDMA.

6.4.7.3 Adverse Effects

MDMA's effects last about 3 to 6 hours, although many users take a second dose as the effects of the first dose begin to fade. Negative health effects include nausea, muscle cramping, blurred vision, chills, sweating, and others. Over the course of the week following moderate use of the drug, a person may experience:

- irritability, impulsiveness and/or aggression
- depression
- sleep problems
- anxiety
- memory and attention problems
- decreased appetite
- decreased interest in and pleasure from sex

It's possible that some of these effects may be due to the combined use of MDMA with other drugs, especially marijuana.

6.4.7.4 Addictive Potential

Research results vary on whether MDMA is addictive. Experiments have shown that animals will self-administer MDMA—an important indicator of a drug’s abuse potential—although to a lesser degree than some other drugs such as cocaine.

Some people report signs of addiction, including withdrawal symptoms, such as fatigue, loss of appetite, depression, and trouble concentrating.

6.4.7.5 Therapeutic Potential

MDMA was first used in the 1970s as an aid in psychotherapy (mental disorder treatment using "talk therapy"). The drug did not have the support of clinical trials (studies using humans) or approval from the U.S. Food and Drug Administration (FDA). In 1985, The U.S. Drug Enforcement Administration (DEA) labeled MDMA as an illegal drug with no recognized medicinal use. However, some researchers remain interested in its value in psychotherapy when given to patients under carefully controlled conditions. MDMA is currently in clinical trials as a possible treatment aid for post-traumatic stress disorder (PTSD); for anxiety in terminally ill patients; and for social anxiety in autistic adults. Recently, the FDA gave MDMA-assisted psychotherapy for PTSD a Breakthrough Therapy designation.

6.4.8 **Heroin**

Heroin is a very addictive drug made from morphine, a psychoactive (mind-altering) substance taken from the resin of the seed pod of the opium poppy plant. Heroin is part of a class of drugs called *opioids*. Other opioids include some prescription pain relievers, such as codeine, oxycodone, and hydrocodone.

Heroin use and overdose deaths have dramatically increased recently. This increase is related to the growing number of people misusing prescription opioid pain relievers like OxyContin and Vicodin. Some people who become addicted to those drugs switch to heroin because it produces similar effects but is cheaper and may be easier to get.

In fact, most people who use heroin report they first misused prescription opioids, but it is a small percentage of people who switch to heroin. The numbers of people misusing prescription drugs is so high, that even a small percentage translates to hundreds of thousands of heroin users.

Heroin is mixed with water and injected with a needle. It can also be sniffed, smoked, or snorted. People who use heroin sometimes combine it with other drugs, such as alcohol or cocaine (a “speedball”), which can be particularly dangerous and raise the risk of overdose.

6.4.8.1 Heroin Effects on the Brain and Behavior

When heroin enters the brain, it attaches to molecules on cells known as opioid receptors. These receptors are located in many areas of the brain and body, especially areas involved in the perception of pain and pleasure, as well as a part of the brain that regulates breathing.

Short-term effects of heroin include a rush of good feelings and clouded thinking. These effects can last for a few hours, and during this time people feel drowsy, and their heart rate and breathing slow down. When the drug wears off, people experience a depressed mood and often crave the drug to regain the good feelings.

Regular heroin use changes the functioning of the brain and can result in the following:

- *tolerance*: more of the drug is needed to achieve the same “high”
- *dependence*: the need to continue use of the drug to avoid withdrawal symptoms
- *addiction (i.e. substance use disorder):* a devastating brain disease where, without proper treatment, people have trouble stopping using drugs even when they really want to and even after it causes terrible consequences to their health and other parts of their lives.

6.4.8.2 Adverse Effects of Heroin

Opioid receptors are located in the brain, the brain stem, down the spinal cord, and in the lungs and intestines. Thus, using heroin can result in a wide variety of physical problems related to breathing and other basic life functions, some of which may be very serious. A sample of these effects are given below.

6.4.8.2.1 Short-Term Effects

- dry mouth
- warm flushing skin
- feeling sick to the stomach and throwing up
- severe itching
- clouded thinking
- going "on the nod," switching back and forth between being conscious and semi-conscious
- increased risk of HIV and hepatitis (a liver disease) through shared needles and poor judgment while “high” leading to other risky behaviors.

When mixed with alcohol, short-term effects can include:

- coma—a deep state of unconsciousness
- dangerously slowed (or even stopped) breathing that can lead to overdose death

6.4.8.2.2 Long-Term Effects

- problems sleeping
- damage to the tissues inside the nose for people who sniff or snort it
- infection of the heart

- constipation and stomach cramping
- liver and kidney disease
- lung problems
- mental health problems, such as depression
- sexual problems for men & changes in menstrual cycles for women

In addition to the effects of the drug itself, heroin bought on the street often contains a mix of substances, including the dangerous opioid called **fentanyl** (see section below). Drug dealers add fentanyl because it is cheap, and they can save money. Some of these substances can be toxic and can clog the blood vessels leading to the lungs, liver, kidney, or brain. This can cause permanent damage to those organs.

6.4.9 Fentanyl

Fentanyl is a powerful synthetic opioid that is similar to morphine but is 50 to 100 times more potent. It is a prescription drug that is also made and used illegally. Like morphine, it is a medicine that is typically used to treat patients with severe pain, especially after surgery. It is also sometimes used to treat patients with chronic pain who are physically tolerant to other opioids. Tolerance occurs when you need a higher and/or more frequent amount of a drug to get the desired effects.

Synthetic opioids, including fentanyl, are now the most common drugs involved in drug overdose deaths in the United States. In 2017, 59 percent of opioid-related deaths involved fentanyl compared to 14.3 percent in 2010.

When prescribed by a doctor, fentanyl can be given as a shot, a patch that is put on a person’s skin, or as lozenges that are sucked like cough drops. The illegally used fentanyl most often associated with recent overdoses is made in labs. This synthetic fentanyl is sold illegally as a powder, dropped onto blotter paper, put in eye droppers and nasal sprays, or made into pills that look like other prescription opioids.

Some drug dealers are mixing fentanyl with other drugs, such as heroin, cocaine, methamphetamine, and MDMA (Ectasy). This is because it takes very little to produce a high with fentanyl, making it a cheaper option. This is especially risky when people taking drugs don’t realize they might contain fentanyl as a cheap but dangerous additive. They might be taking stronger opioids than their bodies are used to and can be more likely to overdose.

6.4.9.1 Fentanyl Effects on the Brain and Behavior

Like heroin, morphine, and other opioid drugs, fentanyl works by binding to the body's opioid receptors, which are found in areas of the brain that control pain and emotions. After taking opioids many times, the brain adapts to the drug, diminishing its sensitivity, making it hard to feel pleasure from anything besides the drug.

Fentanyl's effects include

- extreme happiness
- drowsiness
- nausea
- confusion
- constipation
- sedation
- problems breathing
- unconsciousness

Fentanyl is addictive because of its potency. A person taking prescription fentanyl as instructed by a doctor can experience dependence, which is characterized by withdrawal symptoms when the drug is stopped. A person can be dependent on a substance without being addicted, but dependence can sometimes lead to addiction.

People addicted to fentanyl who stop using it can have severe withdrawal symptoms that begin as early as a few hours after the drug was last taken. These symptoms include:

- muscle and bone pain
- sleep problems
- diarrhea and vomiting
- cold flashes with goose bumps
- uncontrollable leg movements

- severe cravings

These symptoms can be extremely uncomfortable and are the reason many people find it so difficult to stop taking fentanyl. There are medicines being developed to help with the withdrawal process for fentanyl and other opioids. The FDA has approved lofexidine, a non-opioid medicine designed to reduce opioid withdrawal symptoms. Also, the NSS-2 Bridge device is a small electrical nerve stimulator placed behind the person's ear, that can be used to try to ease symptoms for up to five days during the acute withdrawal phase. In December 2018, the FDA cleared a mobile medical application, reSET®, to help treat opioid use disorders. This application is a prescription cognitive behavioral therapy and should be used in conjunction with treatment that includes buprenorphine and contingency management.

6.4.9.2 Overdose Risk

The rise of fentanyl misuse has coincided with an unprecedented rise in opioid-related overdose deaths. An overdose occurs when a drug produces serious adverse effects and life-threatening symptoms. When people overdose on fentanyl or other drugs mixed with fentanyl, their breathing can slow or stop. This can decrease the amount of oxygen that reaches the brain, a condition called *hypoxia*. Hypoxia can lead to a coma and permanent brain damage, and even death.

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6.4.9.4

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6.5: Psychotherapeutics

Learning Objectives

- Differentiate the various classifications of Psychotherapeutic drugs based on their therapeutic action, effects on steps of neurotransmission, and neurotransmitter specificity
- Compare and contrast the effectiveness and side effects of Psychotherapeutics

6.5.1 **Overview**

Psychotherapeutic medications can play a role in treating several mental disorders and conditions. Treatment may also include psychotherapy (also called “talk therapy”) and a variety of other medical and non-medical interventions. In some cases, psychotherapy alone may be the best treatment option. Choosing the right treatment plan should be based on a person's individual needs and medical situation, and under a mental health professional’s care.

The National Institute of Mental Health (NIMH) also does not endorse or recommend any particular drug, herb, or supplement. Results from NIMH-supported clinical trials that examine the effectiveness of treatments, including medications, are reported in the medical literature. This section is intended to provide basic information about mental health medications. It is not a complete source for all medications available and should not be used as a guide for making medical decisions.

Information about medications changes frequently. Check the U.S. Food and Drug Administration (FDA) website for the latest warnings, patient medication guides, or newly approved medications. Brand names are not referenced on this page, but you can search by brand name on MedlinePlus Drugs, Herbs and Supplements Drugs website. The MedlinePlus website also provides additional information about each medication, including side effects and FDA warnings.

6.5.2 Psychotherapeutic Classification

Much like the general classification of psychoactive drugs, there are multiple schemes of categorization that can be used. The most clear and useful system is based on the therapeutic purpose of the drugs rather than their synaptic mechanism of action or physiological effects (i.e. stimulant, depressant, etc.). Comprehensive information on various psychotherapeutic medications is available from the National Institute of Mental Health.

6.5.3 **Antidepressants**

Antidepressants are medications commonly used to treat depression. Antidepressants are also used for other health conditions, such as anxiety, pain and insomnia. Although antidepressants are not FDA-approved specifically to treat ADHD, antidepressants are sometimes used to treat ADHD in adults.

The most popular types of antidepressants are called selective serotonin reuptake inhibitors (**SSRIs**). Examples of SSRIs include, Fluoxetine (Prozac), Citalopram (Celexa), and Escitalopram (Lexapro). Other types of antidepressants are serotonin and norepinephrine reuptake inhibitors (SNRIs). SNRIs are similar to SSRIs and include venlafaxine (Effexor) and duloxetine (Cymbalta). By inhibiting the reuptake of either serotonin or norepinephrine, these drugs enhance the activity of these systems by allowing these transmitters to stay in the synapse longer.

Another antidepressant that is commonly used is bupropion. **Bupropion** is a third type of antidepressant which **inhibits the reuptake** of **both norepinephrine and dopamine**. Bupropion is also used to treat seasonal affective disorder and to help people stop smoking.

SSRIs, SNRIs, and bupropion are popular because they do not cause as many side effects as older classes of antidepressants, and seem to help a broader group of depressive and anxiety disorders. Older antidepressant medications include tricyclics, tetracyclics, and monoamine oxidase inhibitors (MAOIs). For some people, these may be the best medications.

6.5.3.1 *How do people respond to antidepressants?*

According to a research review by the Agency for Healthcare Research and Quality, all antidepressant medications work about as well as each other to improve symptoms of depression and to keep depression symptoms from coming back. For reasons not yet well understood, some people respond better to some antidepressant medications than to others.

Therefore, it is important to know that some people may not feel better with the first medicine they try and may need to try several medicines to find the one that works for them. Others may find that a medicine helped for a while, but their symptoms came back. It is important to carefully follow your doctor's directions for taking your medicine at an adequate dose and over an extended period of time (often 4 to 6 weeks) for it to work.

Once a person begins taking antidepressants, it is important to not stop taking them without the help of a doctor. Sometimes people taking antidepressants feel better and stop taking the medication too soon, and the depression may return. When it is time to stop the medication, the doctor will help the person slowly and safely decrease the dose. It's important to give the body time to adjust to the change. People don't get addicted (or "hooked") on these medications, but stopping them abruptly may also cause withdrawal symptoms

6.5.3.2 *Side Effects of Antidepressants*

Some antidepressants may cause more side effects than others. You may need to try several different antidepressant medications before finding the one that improves your symptoms and that causes side effects that you can manage.

The most common side effects listed by the FDA include:

- Nausea and vomiting
- Weight gain
- Diarrhea
- Sleepiness
- Sexual problems

Combining the newer SSRI or SNRI antidepressants with one of the commonly-used "triptan" medications used to treat migraine headaches could cause a life-threatening illness called "serotonin syndrome." A person with serotonin syndrome may be agitated, have hallucinations (see or hear things that are not real), have a high temperature, or have unusual blood pressure changes. Serotonin syndrome is usually associated with the older antidepressants called MAOIs, but it can happen with the newer antidepressants as well, if they are mixed with the wrong medications.

6.5.4 Anti-Anxiety Medications

Anti-anxiety medications help reduce the symptoms of anxiety, such as panic attacks, or extreme fear and worry. The most common anti-anxiety medications are called **benzodiazepines** which act to increase GABA function. Benzodiazepines can be effective in treating generalized anxiety disorder, but in the case of panic disorder or social phobia (social anxiety disorder), benzodiazepines are usually second-line treatments, behind SSRIs or other antidepressants.

Benzodiazepines used to treat anxiety disorders include, Clonazepam (Klonopin), Alprazolam (Xanax), and Lorazepam (Ativan).

Short half-life (or short-acting) benzodiazepines (such as Lorazepam) and beta-blockers (adrenaline inhibitors) are used to treat the short-term symptoms of anxiety. Beta-blockers help manage physical symptoms of anxiety, such as trembling, rapid heartbeat, and sweating that people with phobias (an overwhelming and unreasonable fear of an object or situation, such as public speaking) experience in difficult situations. Taking these medications for a short period of time can help the person keep physical symptoms under control and can be used "as needed" to reduce acute anxiety.

Buspirone (which is unrelated to the benzodiazepines) is sometimes used for the long-term treatment of chronic anxiety. In contrast to the benzodiazepines, buspirone has both agonist and antagonist properties and effects serotonin and dopamine systems in complex ways. This drug must be taken every day for a few weeks to reach its full effect, thus, it is not useful for immediate treatment of anxiety symptoms.

MDMA is an empathogen with both stimulant and hallucinogenic properties. As mentioned in Section 6.4, it was first used in the 1970s as an aid in psychotherapy but faced many legal and regulatory challenges in subsequent years that stalled both the research and clinical tests of its effectiveness. However, some researchers remained interested in its value in psychotherapy when given to patients under carefully controlled conditions. MDMA is currently in clinical trials as a possible treatment aid for post-traumatic stress disorder (PTSD); for anxiety in terminally ill patients; and for social anxiety in autistic adults. Recently, the FDA gave MDMA-assisted psychotherapy for PTSD a "Breakthrough Therapy" designation.

6.5.4.1 **How do people respond to anti-anxiety medications?**

Anti-anxiety medications such as benzodiazepines are effective in relieving anxiety and take effect more quickly than the antidepressant medications (or buspirone) often prescribed for anxiety. However, people can build up a tolerance to

benzodiazepines if they are taken over a long period of time and may need higher and higher doses to get the same effect. Some people may even become dependent on them. To avoid these problems, doctors usually prescribe benzodiazepines for short periods, a practice that is especially helpful for older adults, people who have substance abuse problems and people who become dependent on medication easily. If people suddenly stop taking benzodiazepines, they may have withdrawal symptoms or their anxiety may return. Therefore, benzodiazepines should be tapered off slowly.

6.5.4.2 *Side Effects of* Anti-Anxiety Medications

Like other medications, anti-anxiety medications may cause side effects. Some of these side effects and risks are serious. The most common side effects for benzodiazepines are drowsiness and dizziness. For beta-blockers the common side effects include, fatigue, cold hands, dizziness or light-headedness, and weakness. Beta-blockers generally are not recommended for people with asthma or diabetes because they may worsen symptoms related to both. Possible side effects from buspirone include, dizziness, headaches, nausea, nervousness, lightheadedness, excitement, and trouble sleeping

6.5.5 Stimulants

As the name suggests, stimulants increase alertness, attention, and energy, as well as elevate blood pressure, heart rate, and respiration (National Institute on Drug Abuse, 2014). Stimulant medications are often prescribed to treat children, adolescents, or adults diagnosed with Attention Deficit, Hyperactivity Disorder (ADHD).

Two of the most common stimulants used to treat ADHD are Methylphenidate (Ritalin), and Amphetamine/Dextroamphetamine (Adderall)

Stimulants are also prescribed to treat other health conditions, including narcolepsy, and occasionally depression (especially in older or chronically medically ill people and in those who have not responded to other treatments).

6.5.5.1 *How do people respond to stimulants?*

Stimulants have the potential to cause excessive activity and physiological activation, however, for individuals with ADHD the opposite is true in that it can have a calming and “focusing” effect. Stimulant medications are safe when given under a doctor's supervision. Some children taking them may feel slightly different or "funny."

Some parents worry that stimulant medications may lead to drug abuse or dependence, but there is little evidence of this when they are used properly as prescribed. Additionally, research shows that teens with ADHD who took stimulant medications were less likely to abuse drugs than those who did not take stimulant medications. Despite the findings noted above, there is also research indicating the risk of "diversion" of prescribed stimulants for nonmedical uses between students at educational institutions. This diversion could put individuals at a higher risk for stimulant abuse.

6.5.5.2 *Side Effects of* Stimulants

Most side effects are minor and disappear when dosage levels are lowered. The most common side effects include:

- Difficulty falling asleep or staying asleep
- Loss of appetite
- Stomach pain
- Headache

Less common side effects include:

- Motor tics or verbal tics (sudden, repetitive movements or sounds)
- Personality changes, such as appearing “flat” or without emotion

6.5.6 **Antipsychotics**

Antipsychotic medicines are primarily used to manage psychosis. The word “psychosis” is used to describe conditions that affect the mind, and in which there has been some loss of contact with reality, often including delusions (false, fixed beliefs) or hallucinations (hearing or seeing things that are not really there). It can be a symptom of a physical condition such as drug abuse or a mental disorder such as schizophrenia, bipolar disorder, or very severe depression (also known as “psychotic depression”).

Antipsychotic medicines do not cure these conditions. They are used to help relieve symptoms and improve quality of life.

Older or first-generation antipsychotic medications are also called conventional "typical" antipsychotics or “neuroleptics”. Most of the drugs in this class act as potent dopamine antagonists primarily effecting the dopamine D2 receptor. This antagonistic effect reduces the dopamine overactivity found in psychotic disorders, such as Schizophrenia. Some of the common first-generation antipsychotics include:

- Chlorpromazine
- Haloperidol
- Fluphenazine

Newer or second generation medications are also called "atypical" antipsychotics. These drugs act on various neurotransmitters systems in addition to dopamine and, as such are not as potent in their dopamine antagonism. Some of the common atypical antipsychotics include:

- Risperidone
- Olanzapine
- Quetiapine

Both typical and atypical antipsychotics have been shown to work to treat symptoms of schizophrenia and the manic phase of bipolar disorder. In addtion, several atypical antipsychotics have a “broader spectrum” of action than the older medications, and are used for treating bipolar depression or depression that has not responded to an antidepressant medication alone.

6.5.6.3 *How do people respond to antipsychotics?*

Certain symptoms, such as feeling agitated and having hallucinations, usually go away within days of starting an antipsychotic medication. Symptoms like delusions usually go away within a few weeks, but the full effects of the medication may not be seen for up to six weeks. Every patient responds differently, so it may take several trials of different antipsychotic medications to find the one that works best.

Some people may have a relapse—meaning their symptoms come back or get worse. Usually relapses happen when people stop taking their medication, or when they only take it sometimes. Some people stop taking the medication because they feel better or they may feel that they don't need it anymore, but no one should stop taking an antipsychotic medication without talking to his or her doctor.When a doctor says it is okay to stop taking a medication, it should be gradually tapered off— never stopped suddenly. Many people must stay on an antipsychotic continuously for months or years in order to stay well; treatment should be personalized for each individual.

6.5.6.4 *Side Effects of* A**ntipsychotics?**

Antipsychotics have many side effects (or adverse events) and risks. The FDA lists the following side effects of antipsychotic medicines:

- Drowsiness
- Dizziness
- Restlessness
- Weight gain (the risk is higher with some atypical antipsychotic medicines)
- Dry mouth
- Constipation
- Nausea
- Vomiting
- Blurred vision
- Low blood pressure
- Uncontrollable movements, such as tics and tremors (the risk is higher with typical antipsychotic medicines)
- Seizures
- A low number of white blood cells, which fight infections

The older, typical antipsychotic medications can also cause additional side effects related to physical movement, such as:

- Rigidity
- Persistent muscle spasms
- Tremors
- Restlessness

Long-term use of typical antipsychotic medications may lead to a condition called tardive dyskinesia (TD). TD causes muscle movements, commonly around the mouth, that a person can't control. TD can range from mild to severe, and in some people, the problem cannot be cured. Sometimes people with TD recover partially or fully after they stop taking typical antipsychotic medication. People who think that they might have TD should check with their doctor before stopping their medication. TD rarely occurs while taking atypical antipsychotics.

6.5.7 Mood Stabilizers

Mood stabilizers are used primarily to treat bipolar disorder, mood swings associated with other mental disorders, and in some cases, to augment the effect of other medications used to treat depression. **Lithium**, which is an effective mood stabilizer, has a broad spectrum of action including the inhibition of dopamine and glutamate systems and increased GABA action (Malhi, et al., 2013). Lithium is approved for the treatment of mania and the maintenance treatment of bipolar disorder. Additionally, a number of cohort studies describe anti-suicide benefits of lithium for individuals on long-term maintenance. Because mood stabilizers work primarily by decreasing abnormal activity in the brain they are also sometimes used to treat:

- Depression (usually along with an antidepressant)
- Schizoaffective Disorder
- Disorders of impulse control
- Certain mental illnesses in children

Anticonvulsant medications that primarily act as agonists to GABA neurotransmitter systems are also used as mood stabilizers. They were originally developed to treat seizures, but they were found to help control unstable moods as well. One anticonvulsant commonly used as a mood stabilizer is valproic acid (also called divalproex sodium). For some people, especially those with "mixed" symptoms of mania and depression or those with rapid-cycling bipolar disorder, valproic acid may work better than lithium. Other anticonvulsants used as mood stabilizers include:

- Carbamazepine
- Lamotrigine
- Oxcarbazepine

6.5.7.1 *Side Effects of M*ood Stabilizers

Mood stabilizers can cause several side effects, and some of them may become serious, especially at excessively high blood levels. These side effects include:

- Itching, rash
- Excessive thirst
- Frequent urination
- Tremor (shakiness) of the hands
- Nausea and vomiting
- Slurred speech
- Fast, slow, irregular, or pounding heartbeat
- Blackouts
- Changes in vision
- Seizures
- Hallucinations (seeing things or hearing voices that do not exist)
- Loss of coordination
- Swelling of the eyes, face, lips, tongue, throat, hands, feet, ankles, or lower legs.

Some possible side effects linked to anticonvulsants (such as valproic acid) include:

- Drowsiness
- Dizziness
- Headache
- Diarrhea
- Constipation
- Changes in appetite and/or weight
- Agitation

- Mood swings
- Abnormal thinking
- Uncontrollable shaking or movement of a part of the body
- Loss of coordination
- Blurred or double vision
- Ringing in the ears
- Hair loss

6.5.8 Summary

It should be clear that psychotherapeutic medications have been proven effective at treating a wide variety of psychological disorders, with only a few major types reviewed here. The drugs that treat depression, anxiety, psychosis, and various other disorders of mood and cognition do so by a variety of means. Each category of psychotherapeutic drug can include various different drugs with different actions at the synaptic and neurotransmitter levels. Many other drugs not referenced here, such as hallucinogens and marijuana have also been studied for their potential effectiveness in treating disorders, such as Post Traumatic Stress Disorder, Anxiety, and depression. Some positive outcomes have been found, but more definitive research is needed in order to validate these findings.

6.5.9 Attributions

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6.5.10 References

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CHAPTER OVERVIEW

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7.1: Sensation and Perception

Learning Objectives

- Distinguish between sensation and perception
- Distinguish between top-down and bottom-up contributions to perception
- Describe key principles, such as transduction and sensory adaptation

7.1.1 Overview

This chapter will cover foundational principles and processes of sensation and perception, including common aspects of all sensory systems, basic psychophysical processes, and fundamental properties of perception. In addition, the neuroanatomy and specific processes for the five main senses of vision (sight), audition (hearing), somatosensation (i.e. touch, pain, etc.), gustation (taste), and olfaction (smell) will be examined. The collection of these sensory systems allow us to navigate through our world and influences our ways of thinking, feeling, and behaving on a second by second basis. If the function of any of these systems is significantly degraded, it may have profound effects on our quality of life and many aspects of both our physical and psychological states. This chapter first addresses the commonalities of these sensory systems and then details each in terms of their neuroanatomy, neurochemistry, and function.

7.1.2 Sensation and Perception: A Brief Introduction

The topics of sensation and perception are among the oldest and most important in all of psychology. People are equipped with senses such as sight, hearing and taste that help us to take in the world around us. Amazingly, our senses have the ability to convert real-world information into electrical information that can be processed by the brain. The way we interpret this information-- our perceptions-- is what leads to our experiences of the world. In this module, you will learn about the biological processes of sensation and perception as well as key differences between these two processes.

Sensation and perception are often intertwined, however, there are important distinctions between the two. The *physical* process during which our sensory organs—those involved with vision and hearing, for example—respond to external stimuli is called **sensation**. Sensation is the first neural effect that happens when you taste a flavorful chipotle sauce or ultimately, feel the wind on your face or hear a car horn honking in the distance. During sensation, our sense organs are engaging in **transduction**, the conversion of one form of energy into another. Physical energy such as light or sound is converted into a form of energy the brain can understand: electrical stimulation (i.e. action potentials in neurons). Note, sensation is not the same as being *aware* of that sauce's flavor or the force of the wind. After our brain receives the electrical signals, we make sense of all this stimulation and begin to appreciate the complex world around us. This *psychological* process—making sense of the stimuli—is called **perception**. It is during this process that you are aware of and possibly able to *identify* a particular flavor, feel on your skin, smell, or sound.

While our sensory neurons are constantly collecting information from the environment, it is ultimately how we interpret that information that affects how we interact with the world. Perception involves both **bottom-up** and **top-down processing**. Bottom-up processing refers to the fact that perceptions are built from sensory input. Imagine you are in the forest walking and you are admiring the trees and nature around. As you continue to walk you hear crackling noises and you begin to smell burning wood. As you continue walking you hear people talking and the crackling and smell of burning wood becomes stronger, at some point you may realize you are entering campgrounds, you can't see the campgrounds but bottom-up processing with the help of your other senses tells you what is going on.

On the other hand, how we interpret those sensations is influenced by our available knowledge, our experiences, and our thoughts. This is called top-down processing. One way to illustrate these two concepts is with our ability to read. Read the following quote pictured in Figure 7.1.1: out loud:



Figure 7.1.1: An example of Sensory Processing

Did you notice anything odd while you were reading the text above? Did you notice the second “the”? If not, it’s likely because you were reading this from a top-down approach. Having a second “the” doesn’t make sense. We know this. Our brain knows this and doesn’t *expect* there to be a second one, so we have a tendency to skip right over it. In other words, your past experience has changed the way you perceive the writing in the triangle! A beginning reader—one who is using a bottom-up approach by carefully attending to each piece—would be less likely to make this error. The above demonstration illustrates how our experiences can influence the way our brain processes sensory information.

Another way to distinguish between perception and sensation is that sensation is a physical process, whereas perception is psychological. For example, upon walking into a kitchen and smelling the scent of baking cinnamon rolls, the sensation is the scent receptors detecting the odor of cinnamon, but the perception may be “Mmm, this smells like the bread Grandma used to bake when the family gathered for holidays.” Although our perceptions are built from sensations, not all sensations result in perception. In fact, we often don’t perceive stimuli that remain relatively constant over prolonged periods of time, which is known as **sensory adaptation.** Imagine entering a classroom with an old analog clock. Upon first entering the room, you can hear the ticking of the clock; as you begin to engage in conversation with classmates or listen to your professor greet the class, you are no longer aware of the ticking. The clock is still ticking, and that information is still affecting sensory receptors of the auditory system. The fact that you no longer perceive the sound demonstrates sensory adaptation and shows that while closely associated, sensation and perception are different.

When we experience a sensory stimulus that doesn’t change, we stop paying attention to it. This is why we don’t feel the weight of our clothing, hear the hum of a projector in a lecture hall, or see all the tiny scratches on the lenses of our glasses. Thus, when a stimulus is constant and unchanging, we experience sensory adaptation. This occurs because if a stimulus does not change, our brain quits responding to it. A great example of this occurs when we leave the radio on in our car after we park it at home for the night. When we listen to the radio on our way home, the volume seems reasonable. However, the next morning when we start the car, we might be startled by how loud the radio is. We don’t remember it being that loud last night. What happened? We adapted to the constant stimulus (the radio volume) over the course of the previous day and increased the volume at various times.

7.1.3 Attribution

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7.2: General Principles of Sensory Systems

GENERAL PRINCIPLES OF SENSORY SYSTEMS

Although each of our senses are quite different in the type of stimulation that they respond to, there are many principles that can be generalized across most, if not all sensory systems.

The table below displays the main aspects of the sensation and perception process that takes place across all sensory systems in some way. Some of the steps of the process are more involved for certain systems compared to others, but they all include the four main steps of stimulus input, sensation, perception, and action. There are a number of specific terms for structures and processes included in this table and the terminology list following it. Much more detail on all of these terms and processes will be presented in the sections for each individual sensory system that follows.

Common Aspects of all Sensory Systems

	Stimulus Input →	**Sensation →**	**Perception →**	**Action**
General process	*Sensory systems attend to & translate specific stimuli*	*Stimuli are converted (transduced) into neural messages*	*Sensations are integrated to produce perceptions*	*Perceptions lead to changes in behavior*
Specific mechanisms of action	***Accessory structures*** *and* ***selective attention*** *are involved with initial stimulus processing*	*Specialized* ***Sensory Receptor Neurons*** *are utilized for sensory transduction*	***Initial Perception*** *of stimulus properties occurs in "primary" sensory cortical areas;* ***Holistic Perception*** *occurs in higher cortical areas*	*Behavioral changes include physical behaviors, "mental" or psychological changes, and physiological changes*
Sensory Systems ***Vision***	**Stimulus:** *Light waves - Photons* **Accessory Structure:** *Structures of the Eyeball*	***Sensory Receptor Neurons*****:** *Rods* *Cones*	**Initial Perception:** *Lines of contrast* **Holistic Perception**: *Combination of visual stimulus characteristics (depth, color, movement, etc.)*	
Audition	**Stimulus:** *Sound Waves – Air vibrations* **Accessory Structure:** *Structures of the outer and middle ear*	***Sensory Receptor Neurons*****:** *Auditory Hair Cells*	**Initial Perception:** *Distinct tones (i.e. pitches)* **Holistic Perception**: *Combination of auditory stimulus characteristics (loudness, pitch, timbre)*	
Somatosensory	**Stimulus:** *Varied – Touch, Pressure, Temperature, Pain, etc.* **Accessory Structure:** *Varied – Pacinian Corpuscles, Merkel Discs, Free Nerve Endings, etc.*	***Sensory Receptor Neurons*****:** *Somatosensory Neurons*	**Initial Perception:** *Varied – Touch, Pressure, Temperature, Pain, etc.* **Holistic Perception**: *Combination of somatosensory stimulus characteristics (touch, pressure, pain, etc.)*	

Sensation and Perception Terminology

The following terms are used in most sensory systems and describe key neural elements of the sensation and perception of stimuli.

Sensory transduction

Our sensory systems work by converting different types of stimuli in the environment (i.e. visible light, sound waves, chemical molecules) into action potentials in the nervous system. This conversion is called sensory transduction and occurs in all sensory systems.

Sensory receptors

Sensory transduction begins at the sensory receptors. Each sensory system has specialized cells that are able to detect the environmental stimuli. Photoreceptors detect light, chemical receptors in the tongue and nose detect odors and taste, mechanoreceptors detect touch, and hair cells detect sound.

Receptor Potentials

We have learned about postsynaptic potentials in neurons, receptor potentials are similar membrane potential changes that happen in sensory receptors in response to a stimulus.

Receptive fields

Receptive fields are easiest to understand in the visual and somatosensory systems. The receptive field for a neuron is the region of the retina or skin where a stimulus (light or touch) will evoke a response in the neuron. Receptive fields in the auditory system can consist of a certain frequency of sound and/or the location of sound in space.

Receptive fields can vary in size and shape depending on the characteristics of neuron (i.e. type, location in body, location in pathway). Receptive fields become more complex as information travels to the brain.

Lateral Inhibition

Lateral inhibition is a process used by sensory systems to enhance the perception of signals, particularly at edges, points, or other changes in the stimulus. It occurs because overlapping receptive fields can inhibit each other. This inhibition enhances the perceived differences between the stimulus and the area not stimulated.

Neural Coding

There are a number of different ways in which the nervous system encodes complex information. Two that are common within the sensory systems are line coding and population coding.

Labeled Line Coding

In the labeled line coding of information, one cell encodes for one type of sensory quality. Pain is a good example of this. If a pain receptor is activated, the resulting sensation will be pain, regardless of the manner in which the receptor is stimulated. In other words, the sensory neurons are specifically tuned to one sensory stimulus. If that receptor-cell type was dysfunctional, the sensation will not be perceived. For example, there is a mutation that prevents sodium channels in pain receptors (but not other cell types) from working. When this mutation occurs, the subject cannot feel pain.

Population Coding

In populating coding, one cell can encode more than one sensory modality, and it is the combination of many cells that make up the perception. An example of this is color vision. Each color photoreceptor is most sensitive to a specific color (blue, green, or red), but a range of wavelengths can elicit changes in firing rates in the neuron. Therefore, the responses from a population of color photoreceptors must be combined to perceive the full spectrum of color.

Higher level processing of taste and olfaction also uses population coding – sometimes the sense of smell is needed in addition to the sense of taste to fully perceive a flavor. Have you ever been congested from a cold and food just doesn't taste the same? That's due to this combining of the senses for a full perception.

Pathways

In general, the route sensory information takes from the periphery to the central nervous system is similar among most of the systems. Environmental stimuli become encoded by a specialized receptor in the periphery. Information then enters the central

nervous system via the spinal cord or brainstem and relays through the thalamus, a structure that sits deep in the forebrain. The only sensory system that does not relay through the thalamus is the olfactory system. The thalamus then sends projections out to the primary cortical regions for each sensory system.

Thalamic "relay" ++

It's common to hear that sensory information "relays" through the thalamus on the way to the cortex (for example, in the paragraph above). This language can give the impression that the thalamus is only responsible for making sure the sensory signal gets from periphery to the cortex. This greatly underestimates the thalamic role. The thalamus is known to contribute to the processing and modification of the sensory signal.

Attributions:

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7.3: Vision

Learning Objectives

- Identify the key structures of the eye and the role they play in vision.
- Compare and contrast the anatomy and functions of the rods and cones.
- Describe the function of the lens and the visual deficiencies that result from its dysfunction.

7.3.1 Overview

Humans rely largely on vision and seeing the world around them through sight. Most non human organisms rely more on the other senses to interpret the world around them. Research indicates that a large part of the cerebral cortex in humans is dedicated to vision. As the information reaches the visual cortex in the brain, multiple neurons identify shapes, colors, and motions. When light falls on the eyes, sensory receptors begin the process of transduction. As this process occurs, individuals begin to perceive the environment around them.

7.3.1.1 Anatomy of the Eye and it's Function

Think about entering a dark theater or room if you have been outside on a sunny day; often times it takes time to adjust to the change of light intensity in the environment. Specific parts of the non-neural, **accessory structure** for vision play an important role in this process of adjustment and just about all other aspects of processing the incoming visual stimuli.

The visual accessory structure is the eyeball. The muscles in the **iris** of the eye adjust to allow more light to enter the **pupil** (the round opening in the center of the iris). The iris of the eye is the colored part of the eye that constricts and dilates the pupil to adjust for different light intensities that we may encounter throughout the day. The light from objects then gets magnified by the lens and "projects" onto the back part of the eye known as the **retina**. **Photoreceptors** located in the retina are the specialized sensory neurons for vision that help distinguish the different characteristics of different objects.

The types of photoreceptors in the human eye include **rods and cones**; rods are typically more prevalent than cones. Rods give us sensitivity under dim lighting conditions and allow us to see the contrast of objects against a background, even at night. Cones allow us to see fine details in bright light and give us the ability to distinguish color. Cones are tightly packed around the **fovea** (the small central region of the retina) and more sparsely elsewhere. Rods populate the periphery (the region surrounding the fovea) and are almost absent from the fovea. As organisms move about their environment, the information from light reflected off objects both near and far is encoded by the brain in order to identify colors, shapes, and motion (see Figure 7.3.1). More detail on all of these elements and processes will be examined in subsequent sections.

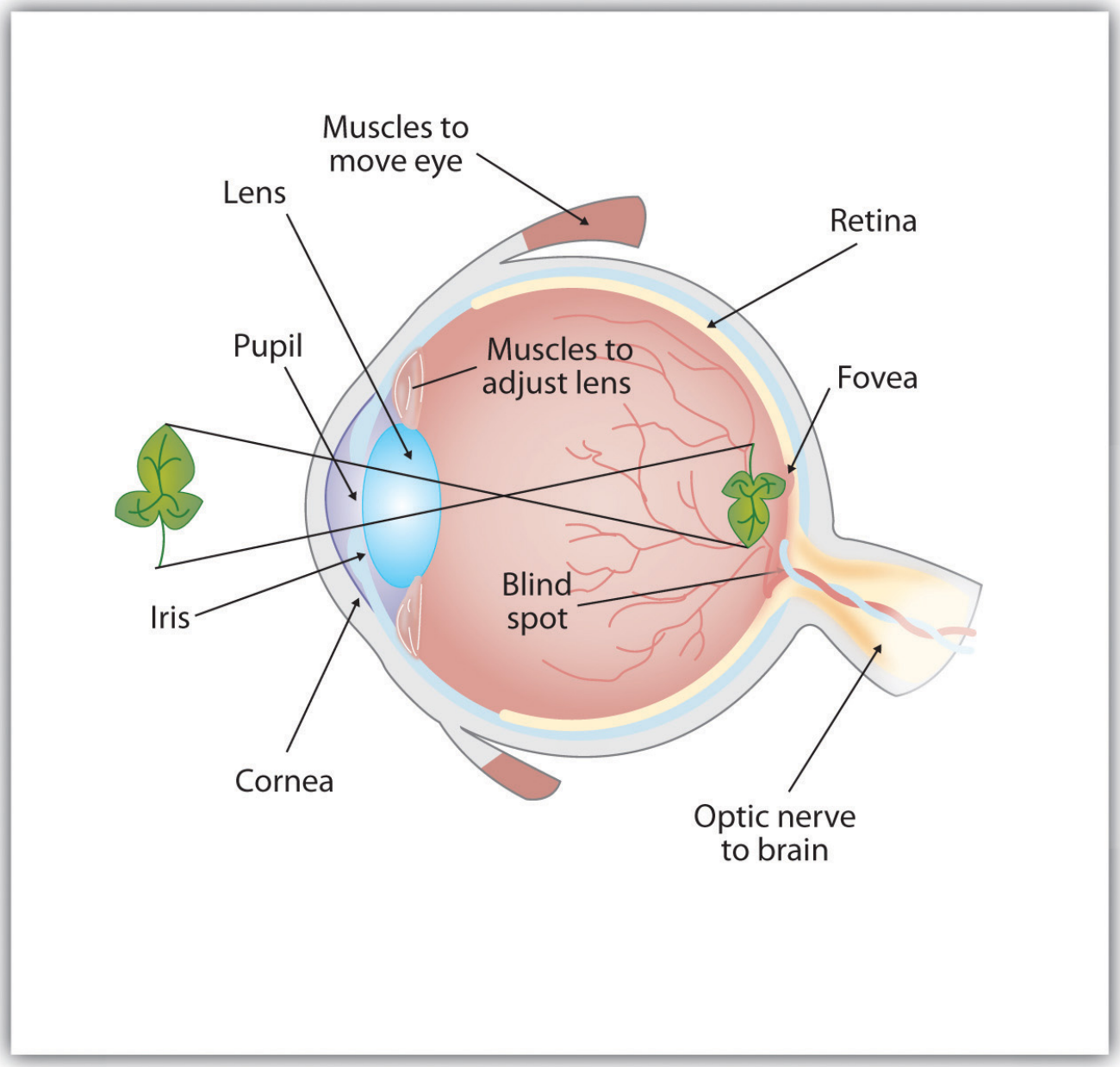


Figure 7.3.1: Light enters the eye through the transparent cornea, passing through the pupil at the center of the iris. The lens adjusts to focus the light on the retina, where it appears upside down and backward. Receptor cells on the retina send information via the optic nerve to the visual cortex. https://open.lib.umn.edu/intropsyc/c...04_s02_s01_f02

7.3.1.3 "Normal" Vision, Nearsightness, and Farsightness

Why do some many people need to correct their vision with glasses or contacts? Although much of the rest of the sections on vision in this chapter relate to neural processes, the reason for this common problem is due to issues occurring in the accessory structure for vision. Most of the time someone needs visual correction due to issues with how well certain muscles of the eye are able to adjust the structure and function of the lens . Because of this, the lens is one of the most critical features of the accessory structure in terms of producing a clear image from the very beginning of visual processing. Problems with the muscles around the lens or the lens itself can lead to what is commonly referred to as either nearsightedness or farsightedness. See Figure 7.3.2 below for more details.

7.3.1.4

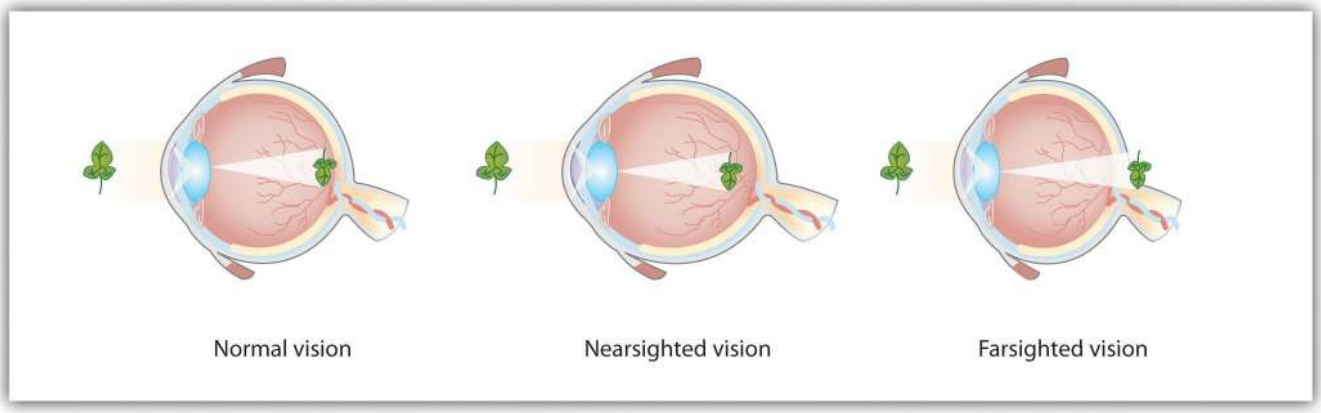


Figure 7.3.2 For people with normal vision (left), the lens properly focuses incoming light on the retina. For people who are nearsighted (center), images from far objects focus too far in front of the retina, whereas for people who are farsighted (right), images from near objects focus too far behind the retina. Eyeglasses solve the problem by adding a secondary, corrective, lens. https://open.lib.umn.edu/intropsyc/chapter/4-2-seeing/#stangor-ch04_s02_s01_f02

7.3.2 Attribution

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- Vision sections adapted by Isaias Hernandez from "Introduction to Psychology-University of Minnesota"; https://open.lib.umn.edu/intropsyc/c...04_s02_s01_f02
- All sections modified and adapted by Alan Keys, Ph. D., Dept. of Psychology, Sacramento City College, Sacramento, CA.

7.3.3 References

https://www.nei.nih.gov/learn-about-...olor-blindness

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7.3.1: Visual System Anatomy- The Retina

Learning Objectives

- Describe the key structural and functional components of the accessory structure for vision (i.e. eyeball)
- Identify the main cells of the retina, their configuration, and main functions
- Explain the sensation process of phototransduction
- Compare and contrast receptive fields and visual fields
- Describe the retinal and functional aspects of lateral inhibition

Anatomy of the Retina

Remember, most sensory systems have some form of **non-neural, accessory structures** which work to modify the incoming stimuli and direct it to the sensory neurons for a particular system. Proper functioning of the accessory structures are needed in order for the optimal stimulus to be processed by the sensory neurons.

As briefly described previously, the accessory structure for vision is basically the **eyeball** and and the substructures within it, with the exception of the retina. The front of the eye consists of the cornea, pupil, iris, and **lens**. The cornea is the transparent, external part of the eye. It covers the pupil and the iris and is the first location of light refraction. The pupil is the opening in the iris that allows light to enter the eye. The iris is the colored portion of the eye that surrounds the pupil and along with local muscles can control the size of the pupil to allow for an appropriate amount of light to enter the eye. The lens is located behind the pupil and iris. The **lens** refracts light to focus images on the retina. Proper focusing requires the lens to stretch or relax, a process called accommodation.

The **retina** is the light-sensitive region in the back of the eye where the photoreceptors, the specialized neural cells that respond to light, are located. The retina covers the entire back portion of the eye, so it's shaped like a bowl. In the middle of the bowl is the **fovea**, the region of highest visual acuity, meaning the area that can form the sharpest images. The **optic nerve** projects to the brain from the back of the eye, carrying information from the retinal cells. Where the optic nerve leaves, there are no photoreceptors since the axons from the neurons are coming together. This region is called the optic disc and is the location of the blind spot in our visual field.

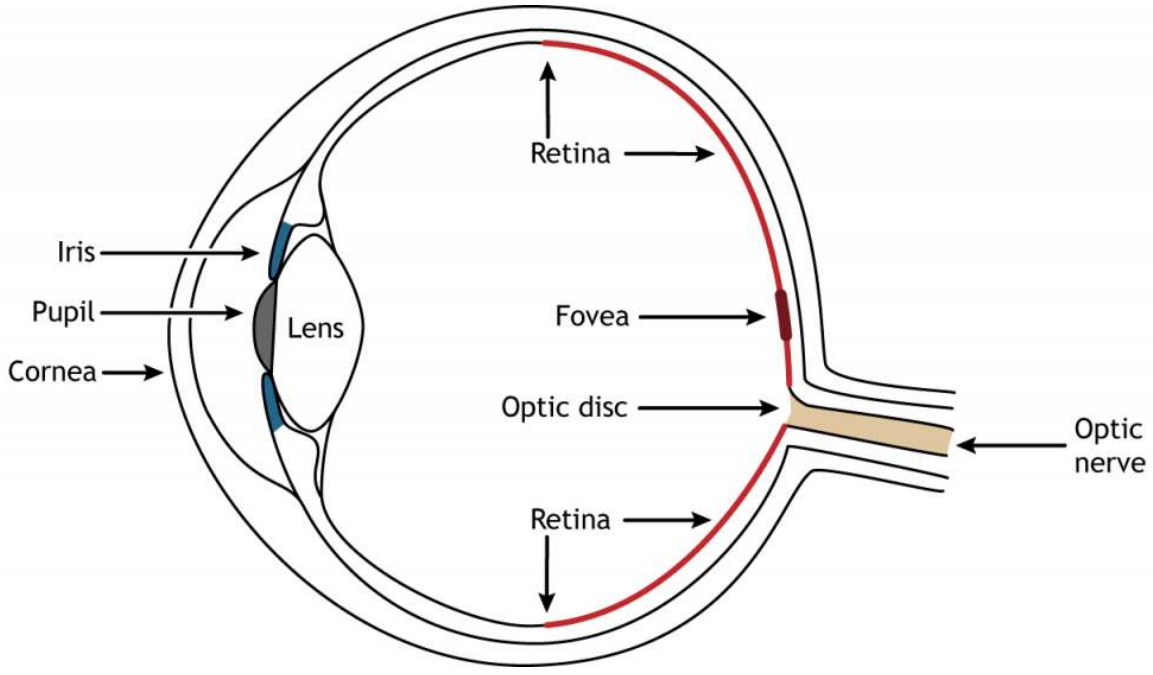


Figure 7.3.1.1: Cross section of the eye. The visible regions of the eye include the cornea, pupil (gray region), and iris (blue region). The lens sits behind the pupil and iris. The retina (red line) is located along the back of the eye. The fovea (dark red section) is a small portion of the retina where visual acuity is highest, and the optic disc is located where the optic nerve (tan region) leaves the eye. Details about the functions of each region are in the text. 'Eye Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Retinal Cells

There are 5 primary types of cells in the retina. In addition to the **photoreceptors**, there are four other cell types in the retina. The photoreceptors synapse on **bipolar** cells, and the bipolar cells synapse on the **ganglion** cells. **Horizontal and amacrine** cells allow for communication laterally between the neurons.

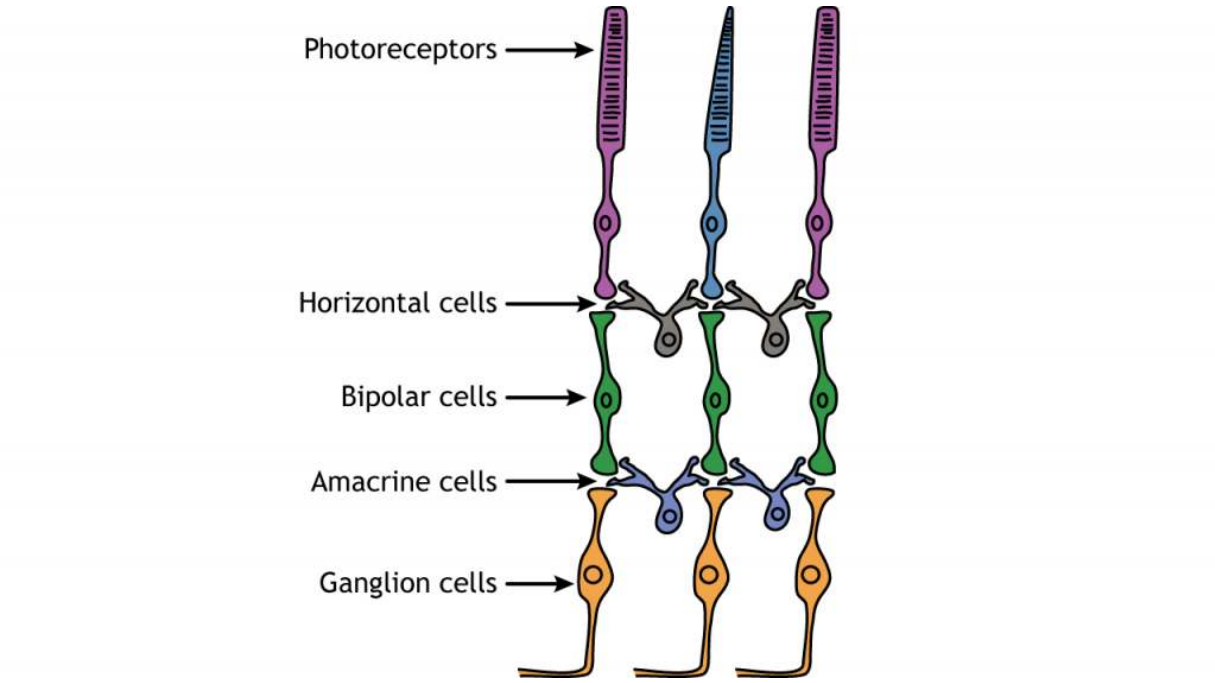


Figure 7.3.1.2: There are five cell types in the retina. The photoreceptors synapse on bipolar cells, and the bipolar cells synapse on ganglion cells. The horizonal cells allow for communication between photoreceptors by interacting with the photoreceptor-bipolar cell synapse, and the amacrine cells allow for communication between bipolar cells by interacting at the bipolar cell-ganglion cell synapse. 'Retinal Neurons' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Direction of Information

When light enters the eye and strikes the retina, it must pass through all the neuronal cell layers before reaching and activating the photoreceptors. The photoreceptors then initiate the synaptic communication back toward the ganglion cells.

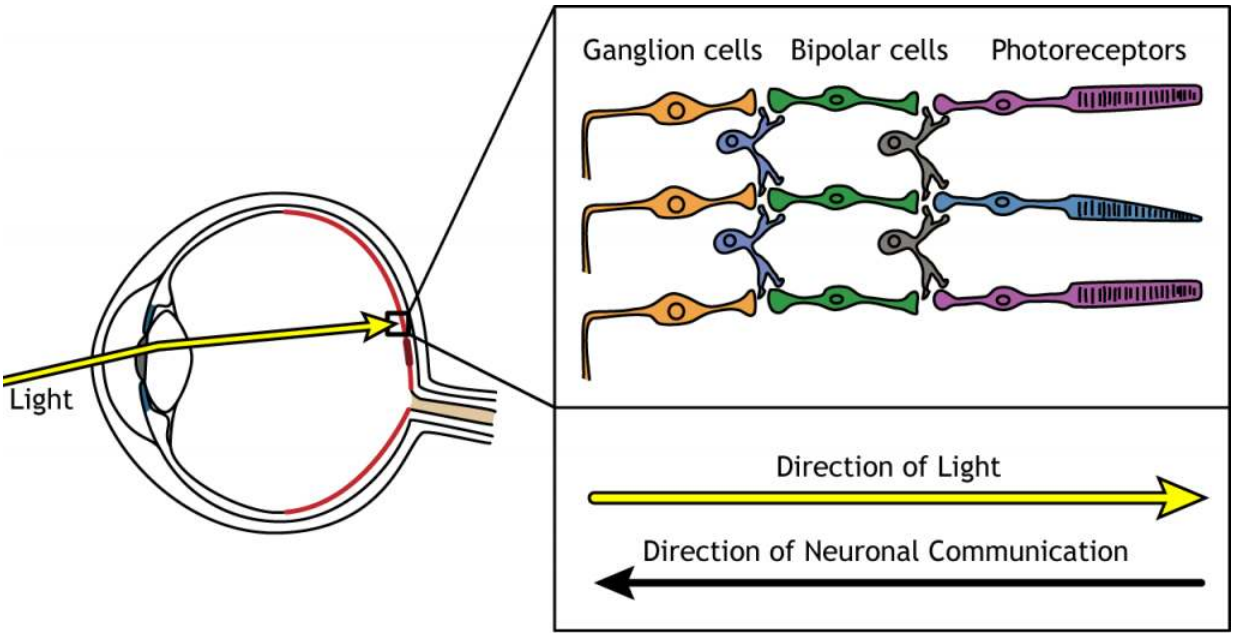


Figure 7.3.1.3: When light enters the eye, it must pass through the ganglion and bipolar cell layers before reaching the photoreceptors. The neuronal communication travels in the opposite direction from the photoreceptors toward the ganglion cells. 'Light in the Retina' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Photoreceptors

The photoreceptors are the specialized sensory neurons that respond to light. There are two types of photoreceptors: **rods and cones**. Rods are more sensitive to light, making them primarily responsible for vision in low-lighting conditions like at night. Cones are less sensitive to light and are most active in daylight conditions. The cones are also responsible for color vision.

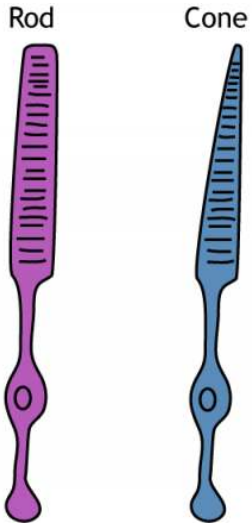


Figure 7.3.1.4: The rods and cones have different physical appearances and play separate roles in visual processing. 'Rod and Cone' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptor Density

In addition to having different visual functions, the rods and cones are also distributed across the retina in different densities. The cones are primarily found in the fovea, the region of the retina with the highest visual acuity. The remainder of the retina is predominantly rods. The region of the optic disc has no photoreceptors because the axons of the ganglion cells are leaving the retina and forming the optic nerve.

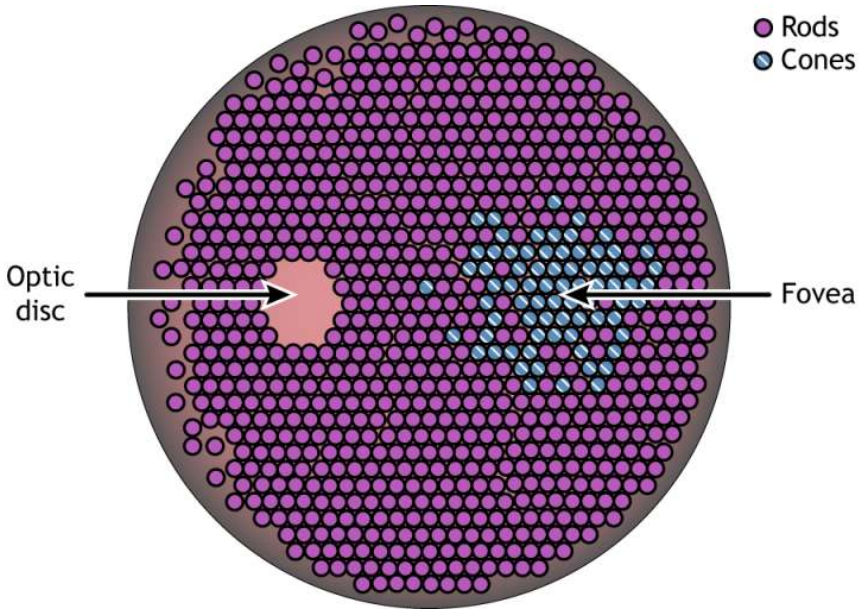


Figure 7.3.1.5: Rods and cones are distributed across the retina in different densities. Cones are located at the fovea. Rods are located everywhere else. The optic disc lacks all photoreceptors since the optic nerve fibers are exiting the eye at this location. 'Retinal Receptor Density' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Phototransduction in the Photoreceptors

The photoreceptors are responsible for "**sensation**" or sensory **transduction** in the visual system (i.e. sensation), converting light into electrical signals in the neurons. For our purposes, to examine the function of the photoreceptors, we will A) focus on black and white light (not color vision) and B) assume the cells are moving from either an area of dark to an area of light or vice versa.

Photoreceptors are unusual as far as neurons go in that they do not fire action potentials. Instead, they respond to light changes with graded receptor potentials (depolarization or hyperpolarization). Despite this, the photoreceptors still release the neurotransmitter, glutamate onto the bipolar cells. The amount of glutamate released changes along with the membrane potential, so a hyperpolarization will lead to less glutamate being released. Photoreceptors hyperpolarize in light and depolarize in dark. In the graphs shown below, the starting membrane potential will depend on the initial lighting condition.

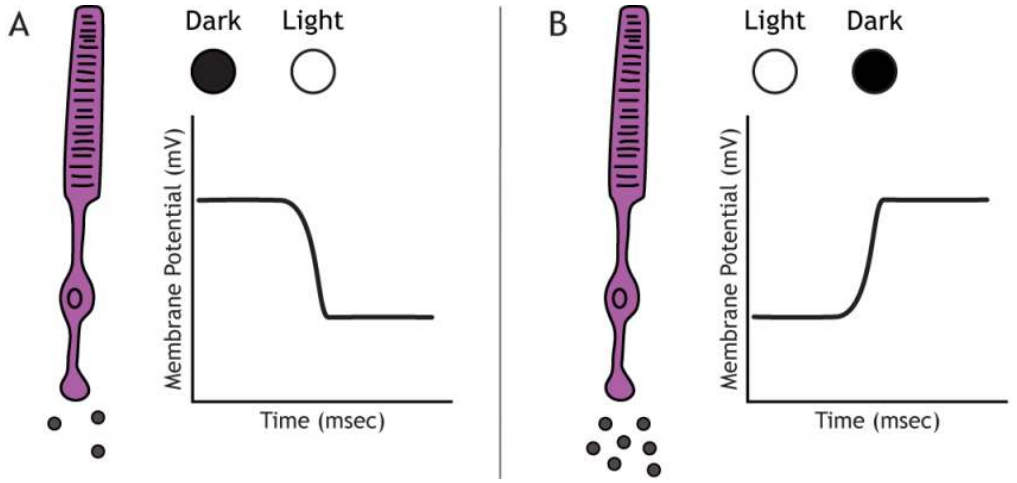


Figure 7.3.1.6: *Photoreceptors respond with graded potentials when moving from light to dark or vice versa. A) When moving from dark to light, the photoreceptor will hyperpolarize, and glutamate release will decrease. B) When moving from light to dark, the photoreceptor will depolarize, and glutamate release will increase. 'Photoreceptor Receptor Potentials' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

In the dark, the photoreceptor has a membrane potential that is more depolarized than the "typical" neuron we examined in previous chapters; the photoreceptor membrane potential is approximately -40 mV. Photoreceptors have open cation channels that allow the influx of sodium and calcium in the dark. These channels are gated by the presence of cyclic GMP (cGMP), a molecule important in second-messenger cascades that is present in the photoreceptor in the dark. When the photoreceptor moves into the light, the cell hyperpolarizes.

Transmission of Information within Retina

Photoreceptors synapse onto bipolar cells in the retina. There are two types of bipolar cells: OFF and ON. These cells respond in opposite ways to the glutamate released by the photoreceptors because they express different glutamate receptors. Like photoreceptors, the bipolar cells do not fire action potential and only respond with graded postsynaptic potentials. OFF bipolar cells depolarize (increase in voltage) in the dark; ON bipolar cells depolarize in the light

OFF Bipolar Cells

In OFF bipolar cells, the glutamate released by the photoreceptor is excitatory. OFF bipolar cells express ionotropic glutamate receptors. In the dark, glutamate released by the photoreceptor activates the ionotropic receptors, and sodium can flow into the cell, depolarizing the membrane potential. In the light, the absence of glutamate causes the ionotropic receptors to close, preventing sodium influx, hyperpolarizing the membrane potential.

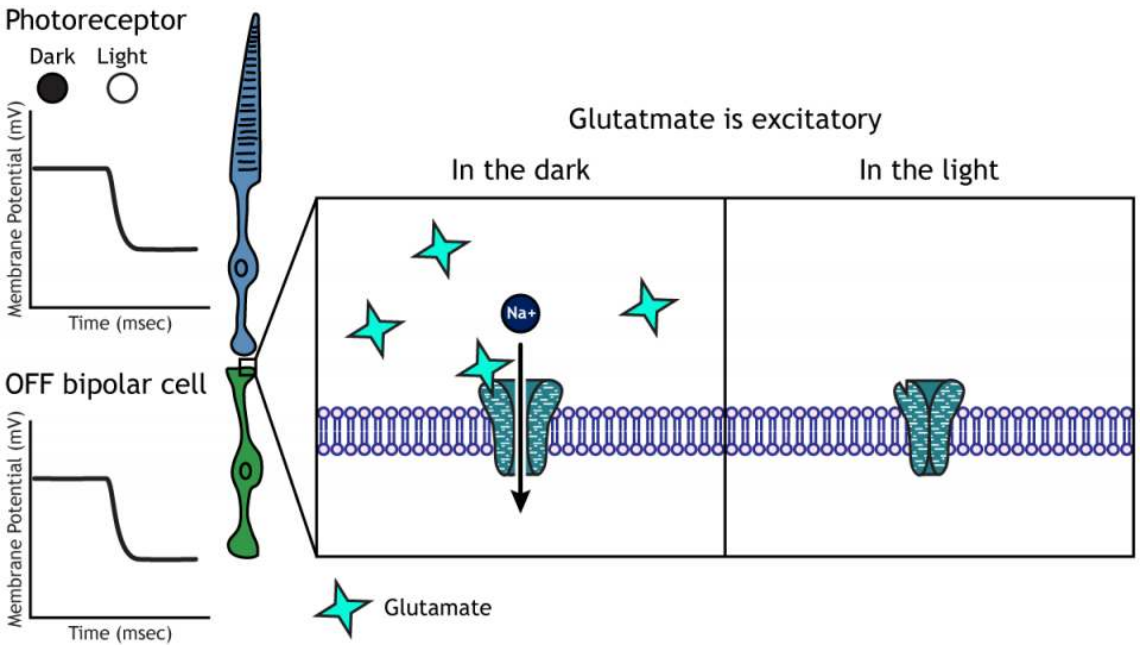


Figure 7.3.1.7: Photoreceptors hyperpolarize in light and decrease the amount of released glutamate. Glutamate is excitatory in OFF bipolar cells, opening ionotropic receptors and allowing sodium influx. In the dark, the OFF bipolar cells are depolarized, and in the light the OFF bipolar cells are hyperpolarized. 'Off Bipolar Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

ON Bipolar Cells

In ON bipolar cells, the glutamate released by the photoreceptor is inhibitory. ON bipolar cells express metabotropic glutamate receptors. In the dark, glutamate released by the photoreceptor activates the metabotropic receptors, and the G-proteins close cation channels in the membrane, stopping the influx of sodium and calcium, hyperpolarizing the membrane potential. In the light, the absence of glutamate results in the ion channels being open and allowing cation influx, depolarizing the membrane potential.

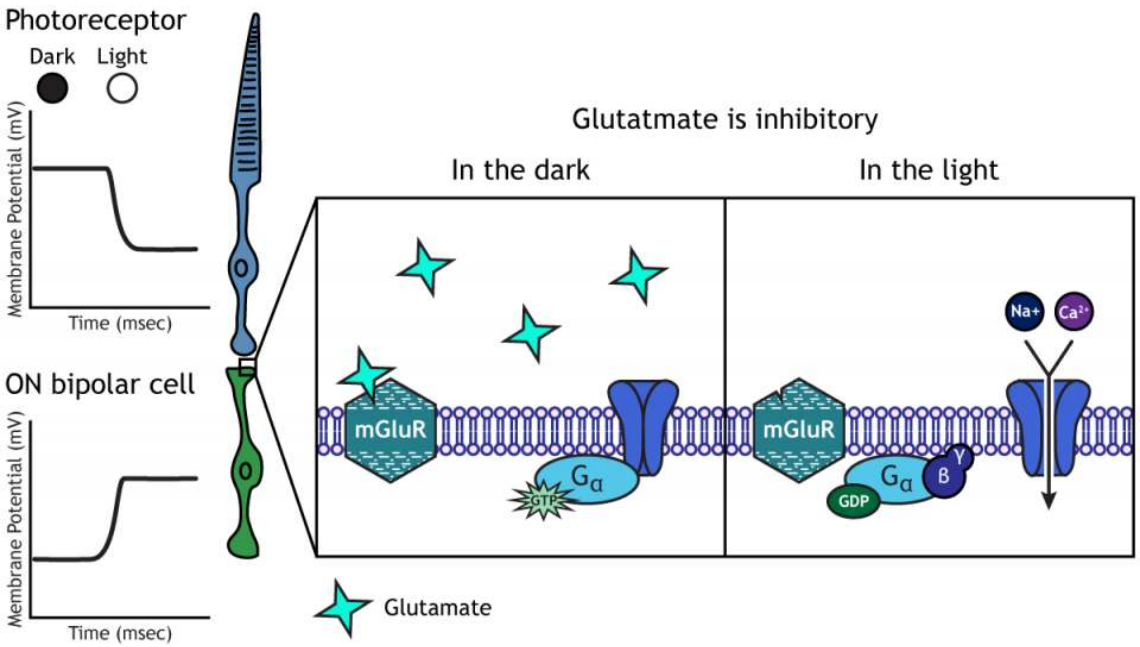


Figure 7.3.1.8: *Photoreceptors hyperpolarize in light and decrease the amount of released glutamate. Glutamate is inhibitory in ON bipolar cells, activating metabotropic receptors, which closes cation channels. In the dark, the ON bipolar cells are hyperpolarized, and in the light the ON bipolar cells are depolarized. 'ON Bipolar Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Ganglion Cells

OFF-center ganglion cells increase their firing rate in the dark; ON-center ganglion cells increase their firing rate in the light. OFF and ON bipolar cells synapse on OFF-center and ON-center ganglion cells, respectively. Ganglion cells are the only cell type to send information out of the retina, and they are also the only cell of the retina that fires action potentials. The ganglion cells fire in all lighting conditions, but it is the relative firing rate that encodes information about light. A move from dark to light will cause OFF-center ganglion cells to decrease their firing rate and ON-center ganglion cells to increase their firing rate.

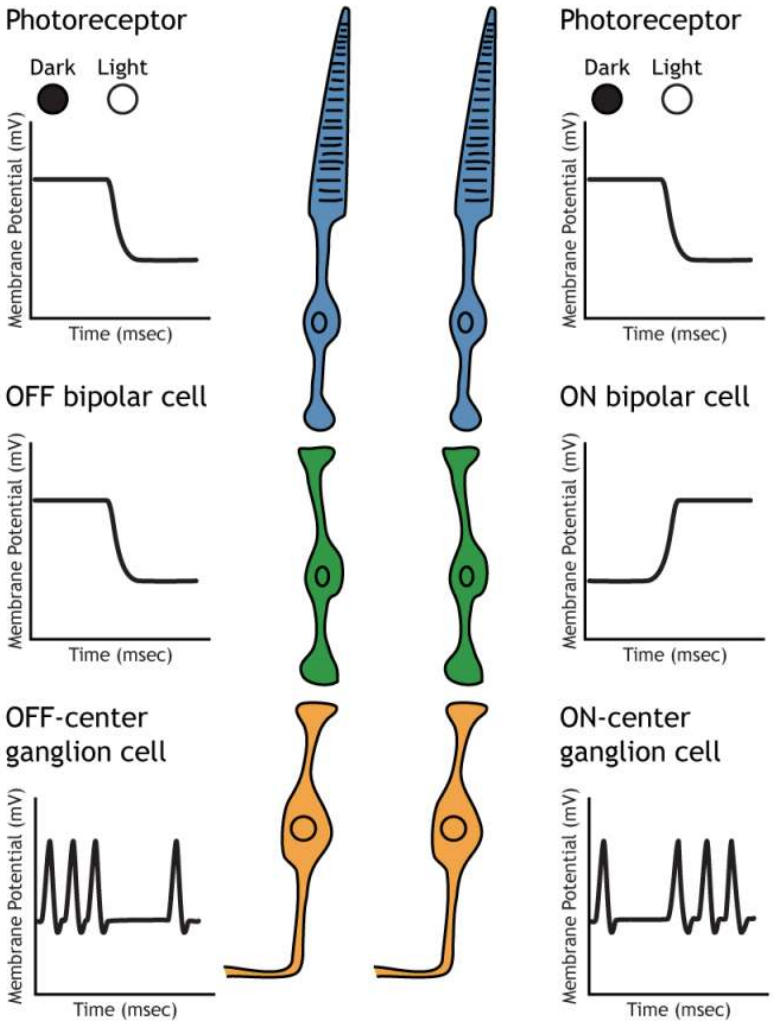


Figure 7.3.1.9: *A move from dark to light will hyperpolarize all photoreceptors. OFF bipolar cells will also hyperpolarize in light, which will lead to a decreased firing rate in OFF-center ganglion cells. ON bipolar cells will depolarize in light, which will lead to an increased firing rate in ON-center ganglion cells. 'Retinal Ganglion Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Receptive Fields

Each bipolar and ganglion cell responds to light stimulus in a specific area of the retina. This region of retina is the cell's **receptive field**. Receptive fields in the retina are circular. These retinal receptive fields correspond to the **visual fields** in the outside world that are projecting onto the retina. Visual fields and their relation to the visual pathways beyond the retina will be examined in the next section.

Size of the receptive field can vary. The fovea has smaller receptive fields than the peripheral retina. The size depends on the number of photoreceptors that synapse on a given bipolar cell and the number of bipolar cells that synapse on a given ganglion cell, also called the amount of convergence.

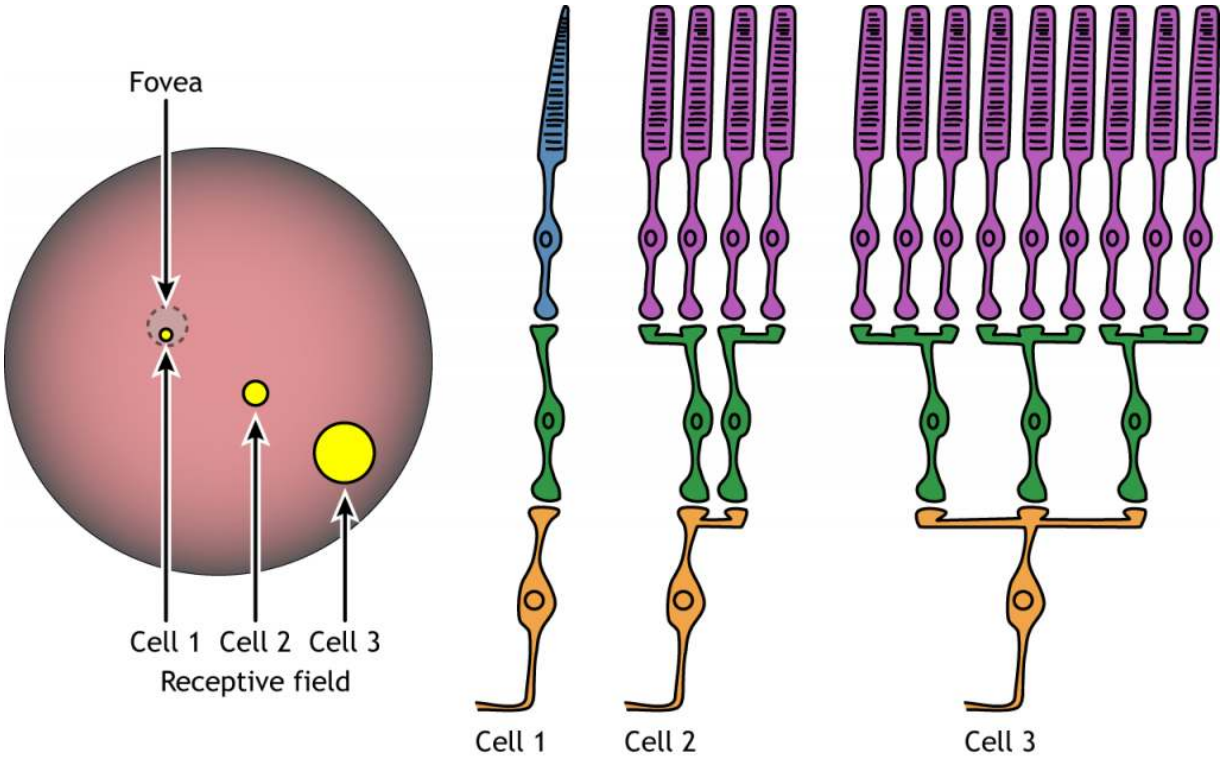


Figure 7.3.1.10: *Ganglion receptive field sizes can vary depending on location of the bipolar and ganglion cells and the amount of convergence onto those cells. When the photoreceptors are in or near the fovea (Cell 1), the receptive fields are small. In the fovea, each bipolar cell receives input from only one photoreceptor and then synapses on only one ganglion cell. Toward the periphery (Cells 2 and 3), more photoreceptors synapse on each bipolar cell, and more bipolar cells synapse on each ganglion cell, making the surface area of the receptive field larger. 'Retinal Receptive Field' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Receptive Field Example

Let's use an example of an ON bipolar cell to look at the structure of receptive fields in the retina. The bipolar and ganglion cell receptive fields are divided into two regions: the center and the surround. The center of the receptive field is a result of direct innervation between the photoreceptors, bipolar cells, and ganglion cells. If a light spot covers the center of the receptive field, the ON bipolar cell would depolarize, as discussed above; the light hits the photoreceptor, it hyperpolarizes, decreasing glutamate release. Less glutamate leads to less inhibition of the ON bipolar cell, and it depolarizes.

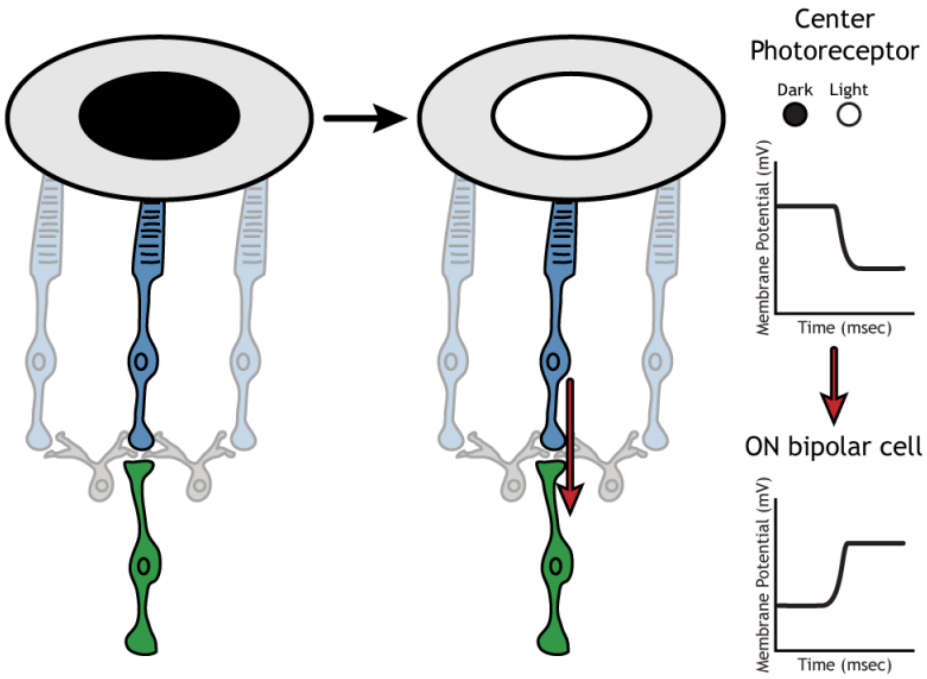


Figure 7.3.1.11: *A photoreceptor in the center of an ON bipolar cell's receptive field moves from dark to light. The photoreceptor will hyperpolarize, and the ON bipolar cell will depolarize. The red arrows show the direct synaptic communication from photoreceptor to ON bipolar cell. 'Light in Center' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

The surround portion of the receptive field is a result of indirect communication among the retinal neurons via horizontal and amacrine cells. The surround also has an opposing effect on the bipolar or ganglion cell compared to the effect of the center region. If a light spot covers the surround portion, the ON bipolar cell would respond by hyperpolarizing. The light would cause the photoreceptor in the surround to hyperpolarize. This would cause the horizontal cell to also hyperpolarize. Horizontal cells have inhibitory synaptic effects, so a hyperpolarization in the horizontal cell would lead to a depolarization in the center photoreceptor. The center photoreceptor would then cause a hyperpolarization in the ON bipolar cell. These effects mimic those seen when the center is in dark. So even though the center photoreceptor is not directly experiencing a change in lighting conditions, the neurons respond as if they were moving toward dark.

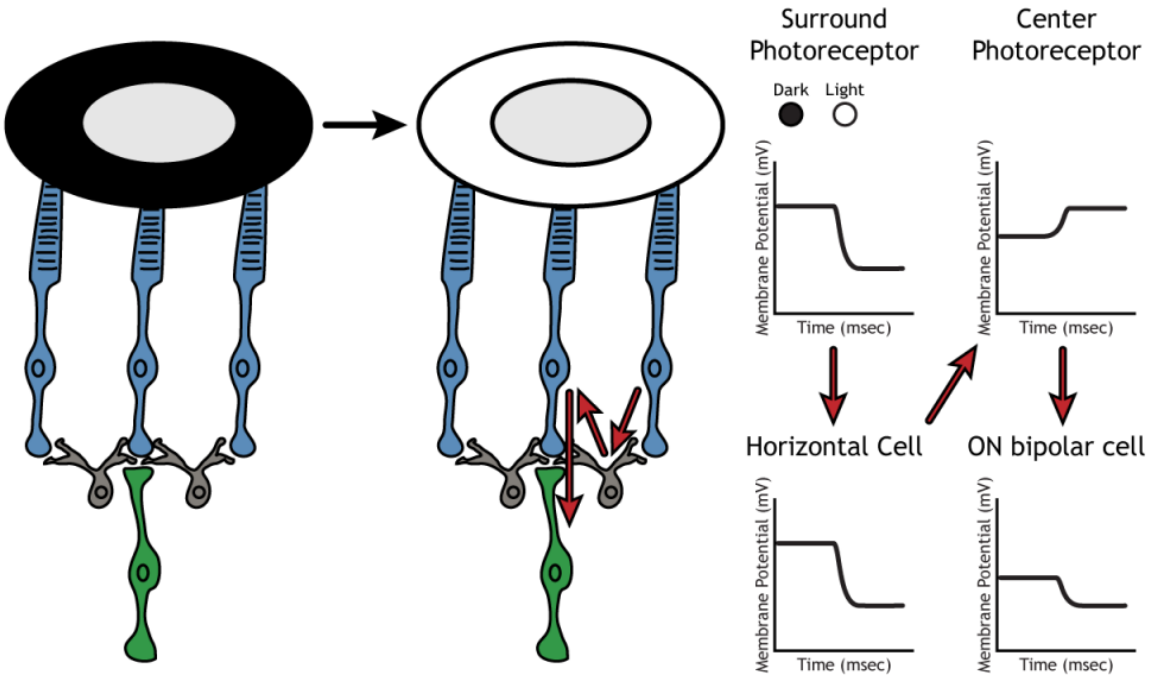


Figure 7.3.1.12: *A photoreceptor in the surround of an ON bipolar cell's receptive field moves from dark to light. The photoreceptor will hyperpolarize, and the postsynaptic horizontal cell will hyperpolarize. This will cause the center photoreceptor to depolarize, and the ON bipolar cell to hyperpolarize. The red arrows show the indirect synaptic communication between the surround photoreceptor and the ON bipolar cell. The surround photoreceptor synapses on the horizontal cell, which synapses on the center photoreceptor, which synapses on the bipolar cell. 'Light in Surround' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Lateral Inhibition

Lateral inhibition is critical for the enhanced perception of edges and borders.

The center-surround structure of the receptive field is critical for lateral inhibition to occur. Lateral inhibition is the ability of the sensory systems to enhance the perception of edges of stimuli. It is important to note that the photoreceptors that are in the surround of one bipolar cell would also be in the center of a different bipolar cell. This leads to a direct synaptic effect on one bipolar cell while also having an indirect effect on another bipolar cell.

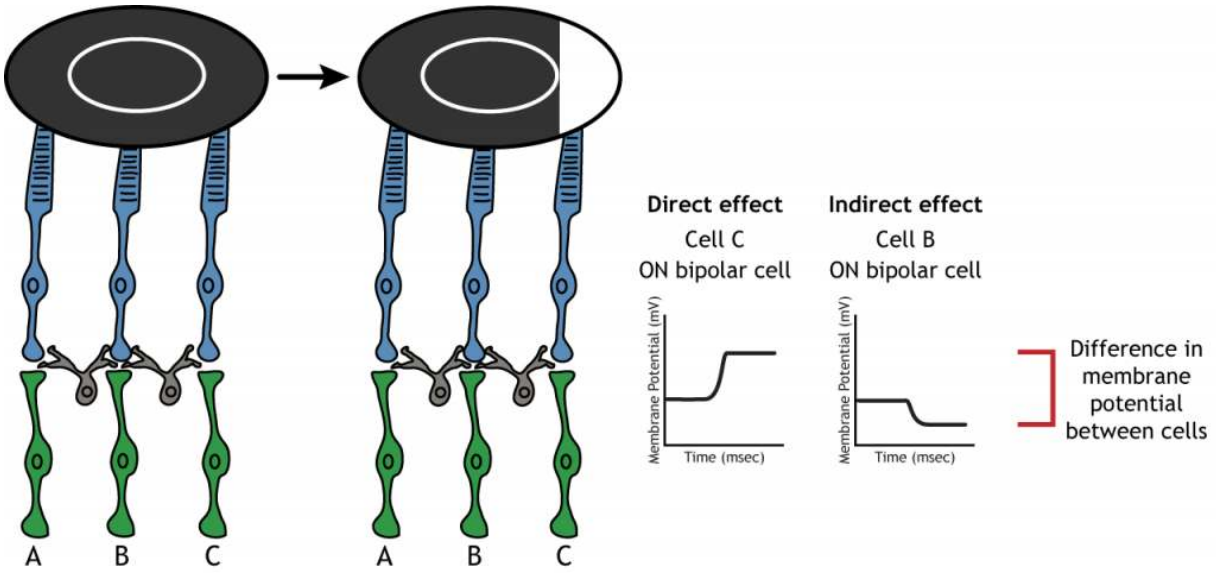


Figure 7.3.1.13: A*n edge of a light stimulus moves into the receptive field surround of ON bipolar cell B. This edge is also falling on the receptive field center of ON bipolar cell C. The light will cause bipolar cell C to depolarize because of the direct synapse with the photoreceptor. The light will also cause bipolar cell B to hyperpolarize because of the indirect synapses through the horizontal cell. This hyperpolarization causes a larger membrane potential difference between cells B and C that would occur if the horizontal cells were absent. The larger membrane potential difference between the cells will lead to an enhancement in the perception between the dark and light side of the edge. 'Lateral Inhibition' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Although some of the images used here will simplify the receptive field to one cell in the center and a couple in the surround, it is important to remember that photoreceptors cover the entire surface of the retina, and the receptive field is two-dimensional. Depending on the level of convergence on the bipolar and ganglion cells, receptive fields can contain many photoreceptors.

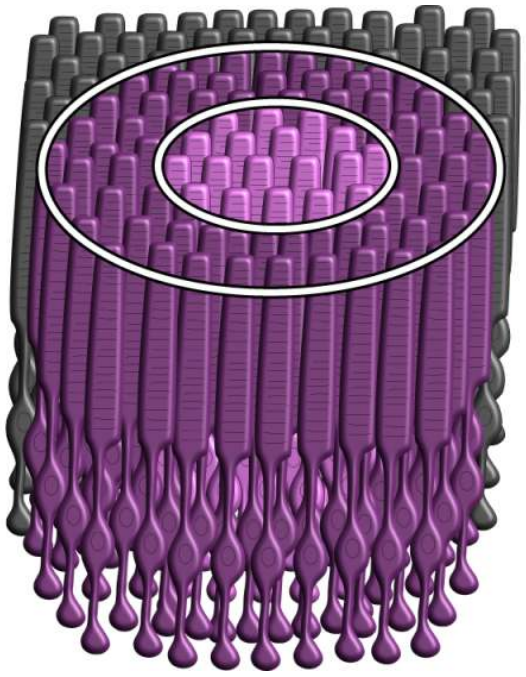


Figure 7.3.1.14: *The receptive fields exist in two-dimensions along the surface of the retina. Depending on the location of the receptive field, and the amount of convergence that occurs at the bipolar or ganglion cell, the receptive field may contain many photoreceptors. 'Retinal surface' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

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7.3.2: Visual System Anatomy- Visual fields and Brain Pathways

Learning Objectives

- Describe the key aspects of visual fields (i.e. binocular vs. monocular, hemifields)
- Explain the relationship between visual fields and the input pathways from the retina through the cortex
- Differentiate the ventral and dorsal streams in terms of their relationship to rod/cone function, cortical anatomy, and ultimate perception
- Identify non-thalamic pathways that play a role in visual processing

Visual Fields

Before learning the pathway that visual information takes from the retina to the cortex, it is necessary to understand how the retina views the world around us. The full visual field includes everything we can see without moving our head or eyes.

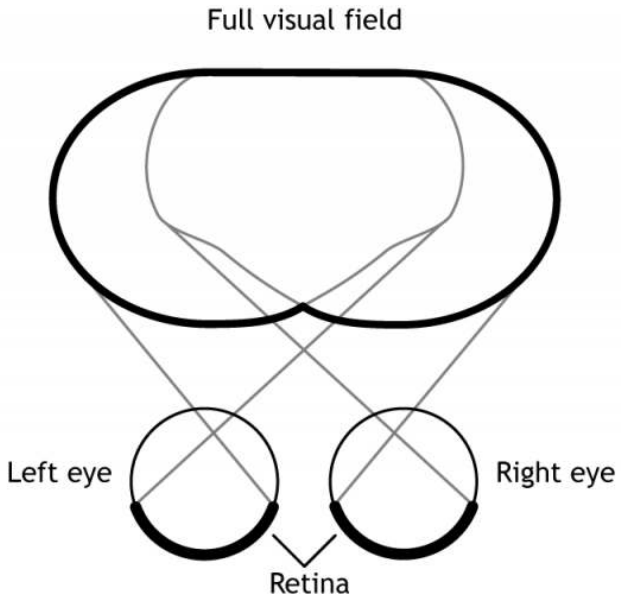


Figure 7.3.2.1: *The two eyes together can view the entire visual field, which is all the visual space we can see without moving our head or eyes. 'Full Visual Field' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

The full visual field can be divided in a few ways. Each individual eye is capable of seeing a portion of, but not the entire, visual field.

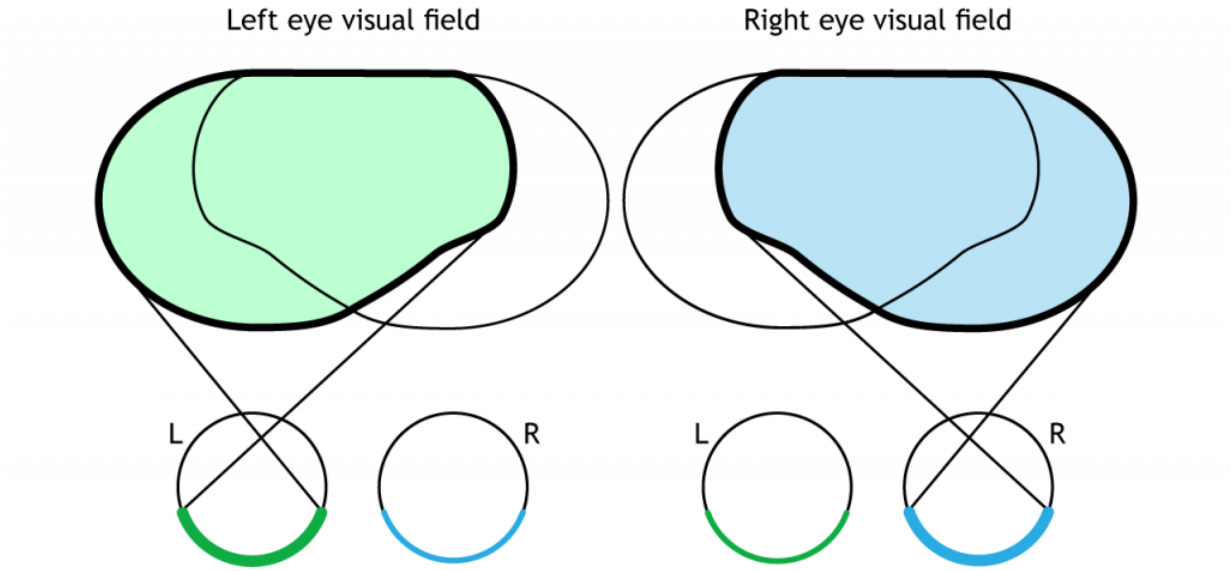


Figure 7.3.2.2: Each eye individually can view only a portion of the full visual field. 'Single Eye Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The full visual field can also be divided into the right and left hemifields. The hemifields range from the most peripheral point to the center point, splitting the full visual field into two equal regions. Both eyes are involved in viewing each hemifield. The fovea separates the retina into two sections: the nasal retina and the temporal retina. The nasal retina is the medial portion that is located toward the nose. The temporal retina is the lateral portion that is located toward the temples and temporal lobe. The nasal retina from one eye along with the temporal retina from the other eye are able to view an entire hemifield.

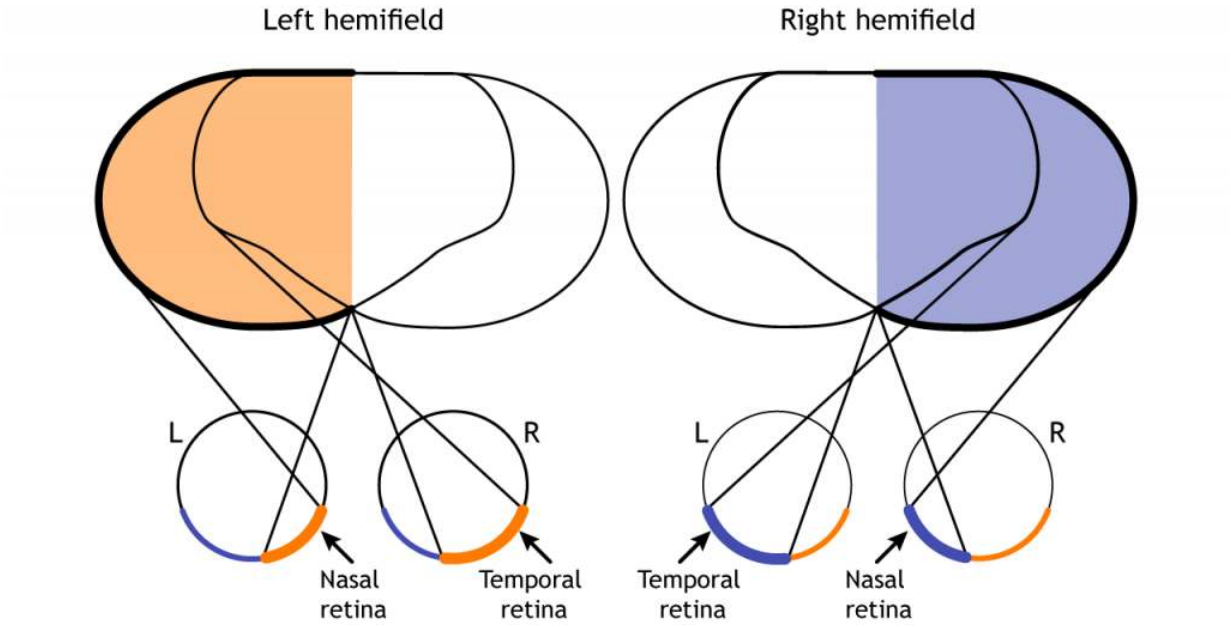


Figure 7.3.2.3:*The full visual field can be divided into left and right hemifields. Both eyes contribute to viewing these regions. The nasal retina of the left eye and the temporal retina of the right eye view the left hemifield. The nasal retina of the right eye and the temporal retina of the left eye view the right hemifield. 'Visual Hemifields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Finally, the full visual field can be separated into monocular and binocular regions. Each monocular field is visual space that can only be viewed by one eye. The binocular region is visual space that can be viewed by both eyes.

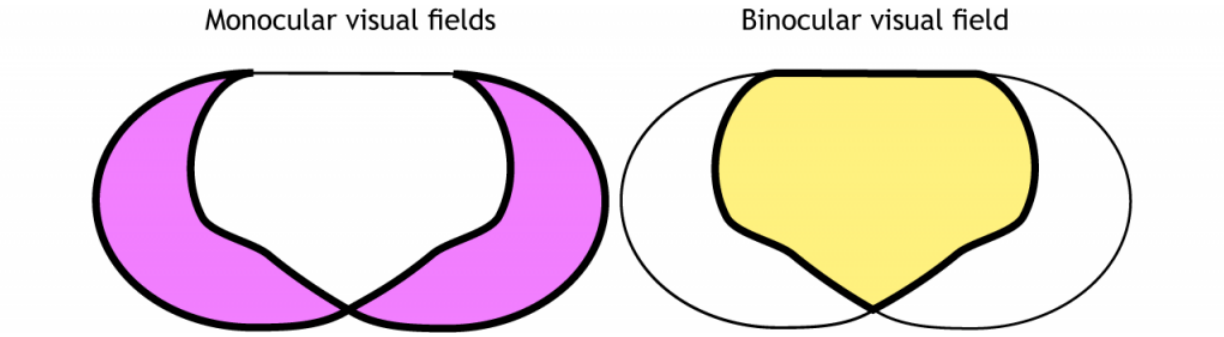


Figure 7.3.2.4: *Monocular visual fields are viewed by only one eye and are located toward the periphery of the full visual field. The binocular visual field is viewed by both eyes and is located in the center of the full visual field. 'Monocular and Binocular Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Pathway to Brain

The right visual field is processed by the left side of the brain; the left visual field is processed by the right side of the brain. Visual information from each eye leaves the retina via the ganglion cell axons at the optic disc, creating the optic nerve. Prior to entering the brain, axons from the nasal portion of each retina cross the midline at the optic chiasm. Since the axons from the nasal retina cross to the opposite side of the nervous system but the temporal retina axons do not, this leads to the brain processing input from the contralateral (opposite side) visual hemifield. Therefore, the right side of the brain receives visual information from the left hemifield and vice versa.

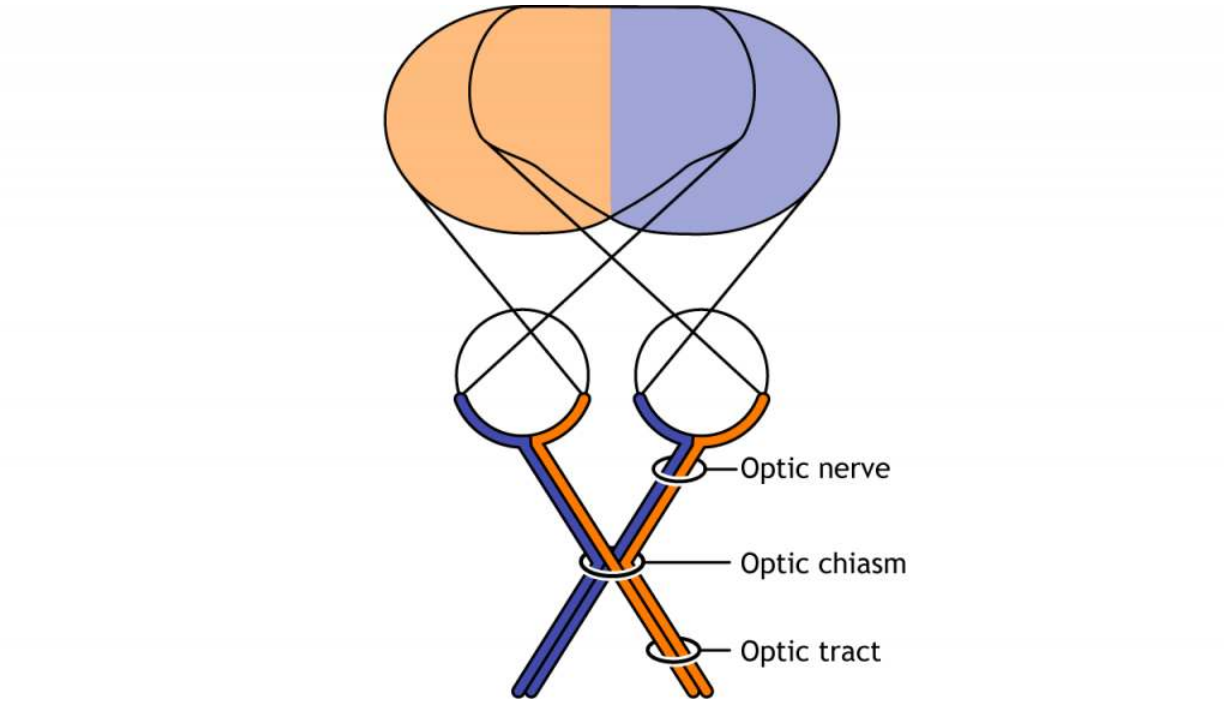


Figure 7.3.2.5:*Information from each eye is carried away from the retina by the optic nerve. Information perceived by neurons in the nasal retina of each eye crosses the midline at the optic chiasm. Information from the contralateral visual hemifield then travels to the brain. 'Pathway from Retina' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

View the optic nerve (cranial nerve II) using the BrainFacts.org 3D Brain

The optic tract enters the brain and ascends to synapse in the lateral geniculate nucleus of the thalamus. From there, axons project to the primary visual cortex, also called the striate cortex or V1, located in the occipital lobe.

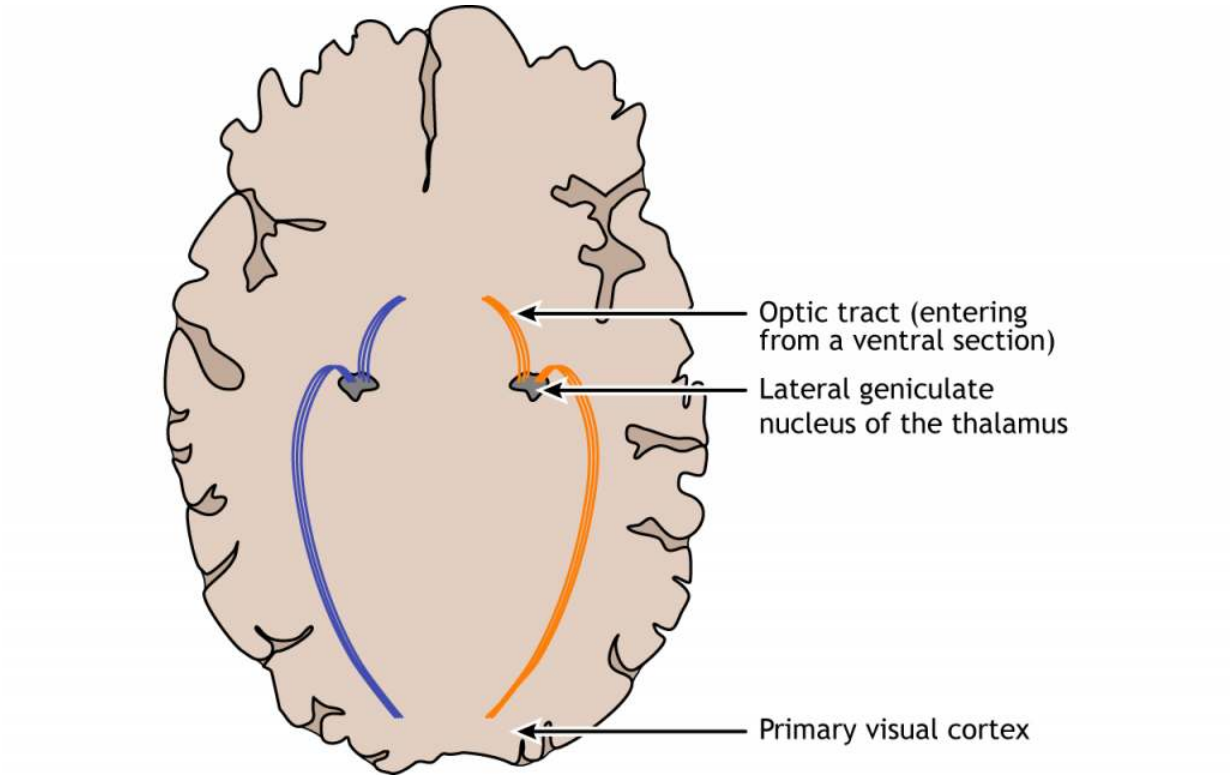


Figure 7.3.2.6:*A horizontal section of the brain. The optic tract enters the brain and projects dorsally to the thalamus. Information is then sent to the primary visual cortex in the occipital lobe. 'CNS Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

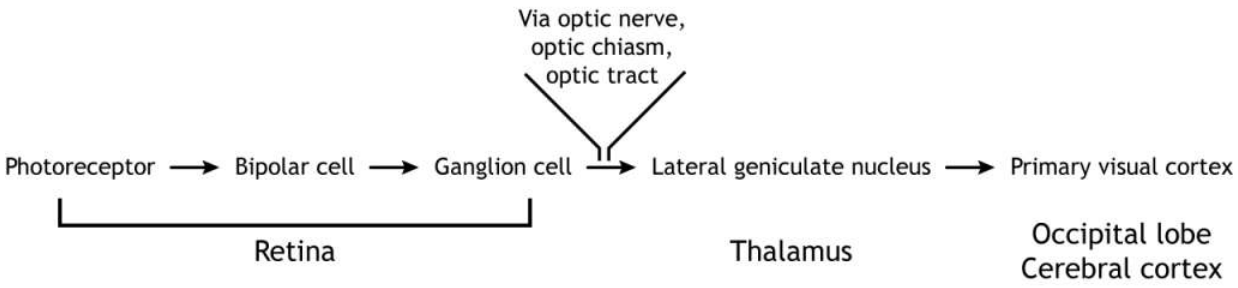


Figure 7.3.2.7:*Visual information that is sent through the full visual pathway, therefore, moves from photoreceptor to bipolar cell to ganglion cell in the retina. It leaves the retina via the optic nerve, optic chiasm, and optic tract to the lateral geniculate nucleus of the thalamus and then travels to the primary visual cortex. 'Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

View the thalamus using the BrainFacts.org 3D Brain

View the primary visual cortex using the BrainFacts.org 3D Brain

Receptive Fields

As information moves from the retina to the cortex, receptive fields become larger and more complex. Receptive fields in the thalamus continue to be circular in shape like the receptive fields of the retinal neurons. However, once information reaches the primary visual cortex, these circular receptive fields combine to create receptive fields that are activated by lines. Hence, our *initial perception* or awareness of visual input is that of lines of contrast.

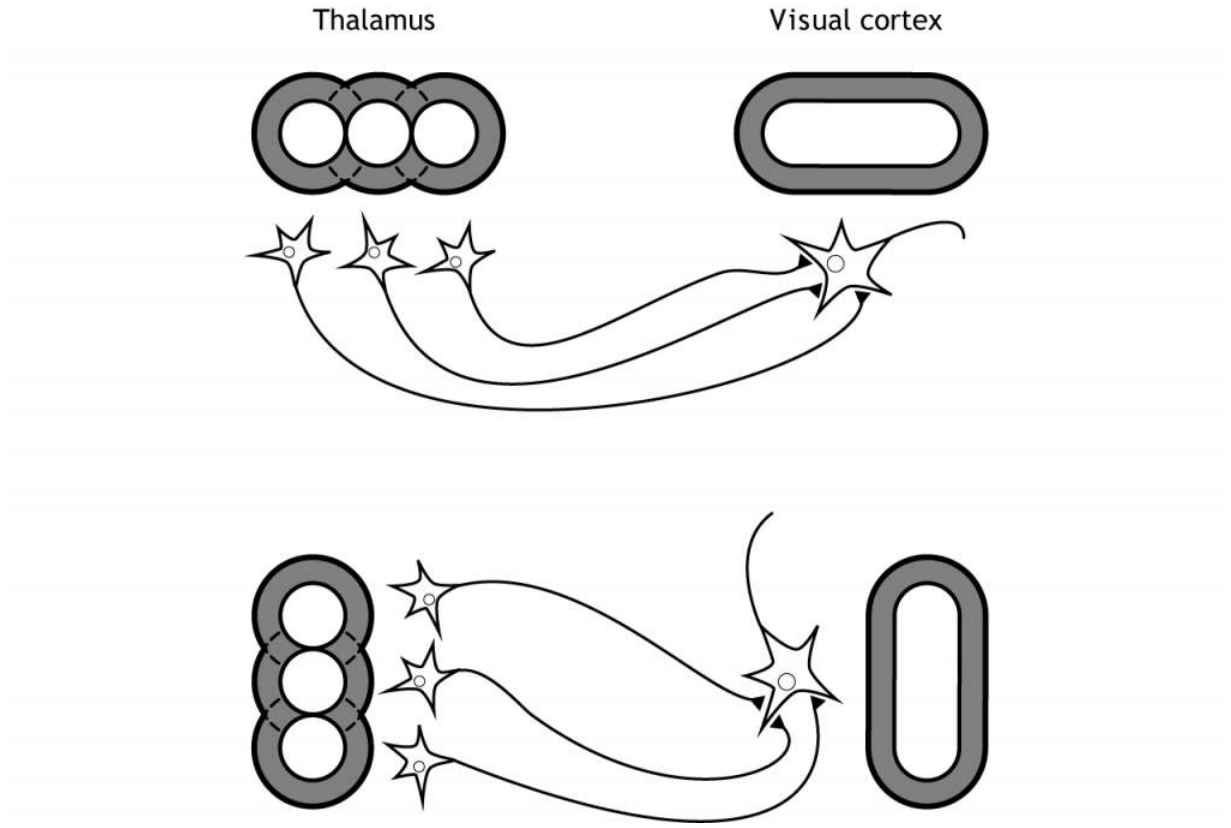


Figure 7.3.2.8:*Circular receptive fields located in the thalamus combine to form straight receptive fields in the visual cortex. The orientation of the line direction in the visual cortex depends on the location of the thalamic retinal fields. 'CNS Receptive Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

These receptive fields cause neurons in the primary visual cortex to respond best to a line in a specific orientation. The firing rate of the neuron will increase as the line rotates toward the "preferred" orientation. The firing rate will be highest when the line is in the exact preferred orientation. Different orientations are preferred by different neurons.

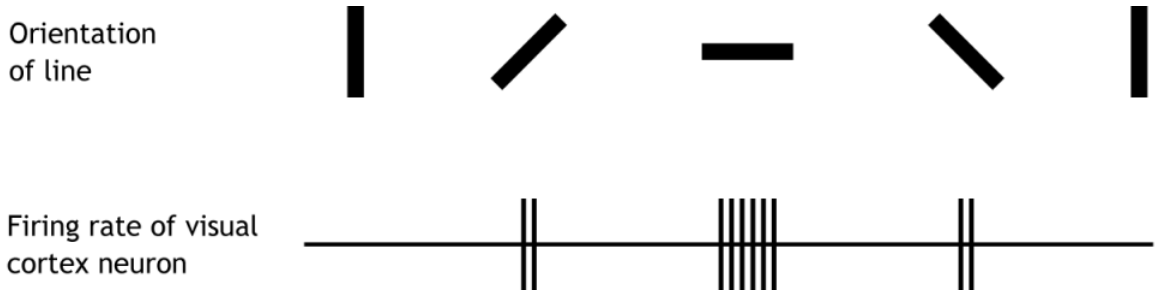


Figure 7.3.2.9: *Neurons in the primary visual cortex show increased firing rates in response to a preferred line orientation. Lines rotated away from the preferred orientation will not cause activity. 'CNS Receptive Field Responses' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Higher-Level Processing of Sensory Information

Sensory system processing of input does not end upon reaching the primary sensory cortex in any sensory system. Information typically gets sent from the primary sensory cortex to other sensory association regions throughout the brain. The characteristics of sensory information becomes more complex as this higher-level processing occurs.

Streams of Processing Beyond Primary Visual Cortex

In the visual system, there are two broad streams of information that leave the primary visual cortex. Information that travels from the primary visual cortex down through the inferior temporal lobe is responsible for determining object recognition, or what an object is. This is referred to as the **Ventral Stream** of visual processing. Differentiating between an apple and a person occurs in

this stream. Information that travels from the primary visual cortex up through the parietal lobe is responsible for motion or spatial components of vision. This is referred to as the **Dorsal Stream** of visual processing. Dorsal and Ventral are directionality terms, which basically mean toward the top and toward the bottom.

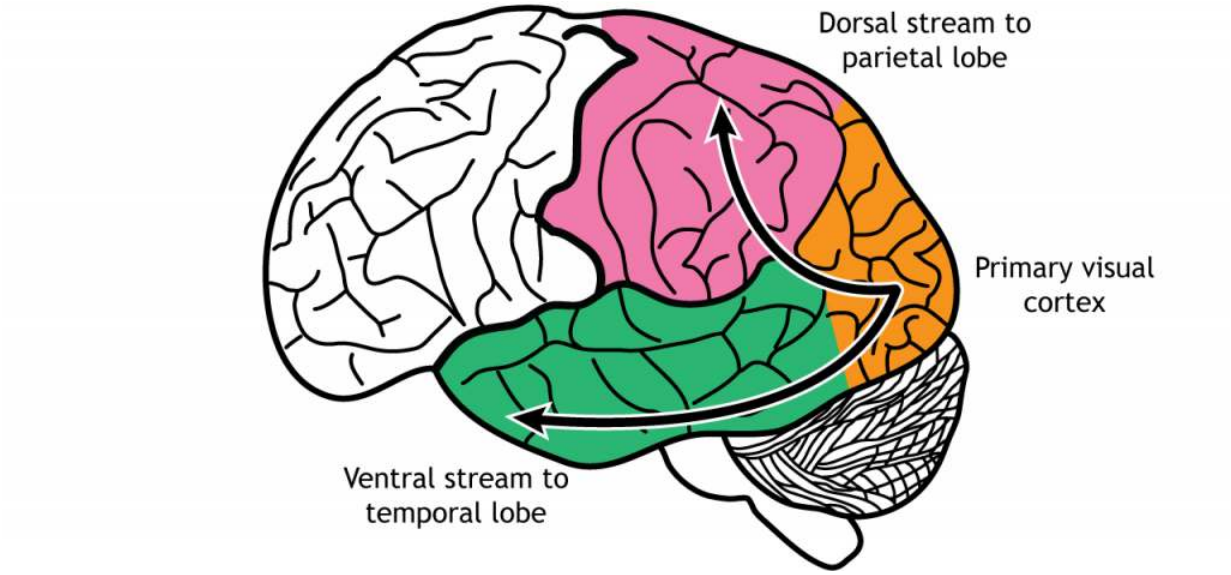


Figure 7.3.2.10:*Information continues to be processed after reaching the primary visual cortex. The dorsal stream travels to the parietal cortex and is important for spatial components of vision. The ventral stream travels to the temporal lobe and is important for object recognition. 'Visual Streams' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Dorsal Stream

One of the most important regions in the dorsal pathway is region MT, also called V5. In this region, neurons are preferentially activated by a specific direction of movement by an object – for example, left to right or up to down. As an example, remember the receptive fields in the primary visual cortex were activated by lines at a specific orientation. Like that, in V5, the neurons would be activated by lines moving in a specific direction.

As information continues to be processed through the dorsal stream, the neurons become selective for more complex motions. The dorsal stream is also important for processing our actions in response to visual stimulation, for example, reaching for an object in the visual field or navigating around objects while walking.

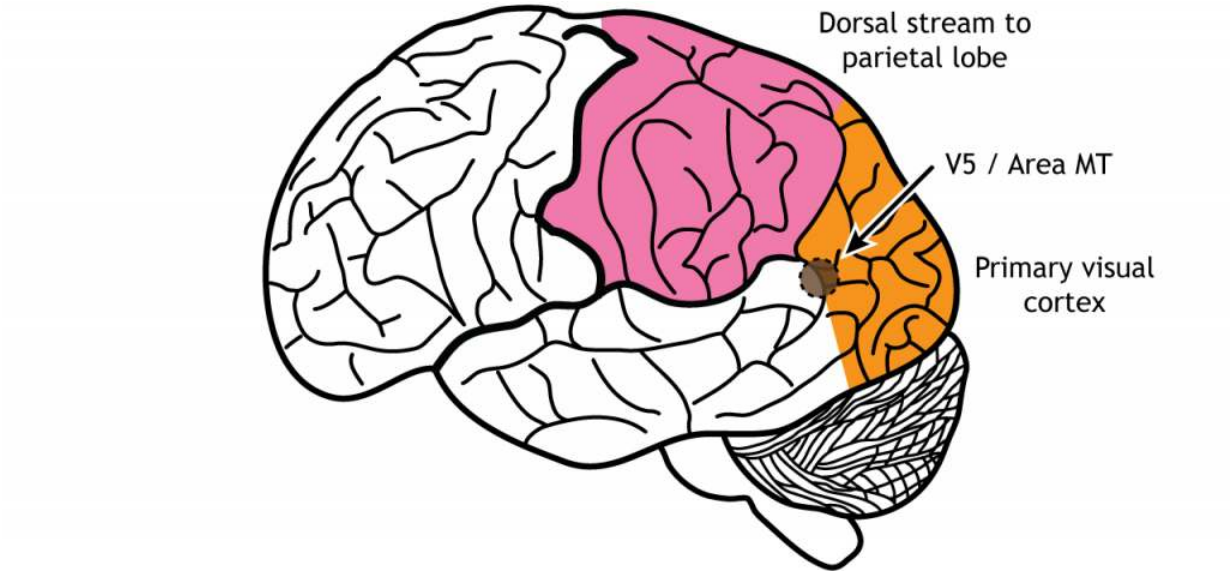


Figure 7.3.2.11: *Area MT, also called V5, is an early processing region of the dorsal stream through the parietal lobe. Neurons in the region are activated by direction of an object in a specific direction. 'Area MT' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Ventral Stream

Object identification is a key function of our visual system. The ventral visual stream is responsible for this process. Like the more complex activation characteristics of region MT in the dorsal stream, neurons in Area V4 in the ventral stream show more complex receptive fields and show sensitivity to shape and color identification. As visual information continues to be processed through the inferior temporal lobe, differentiation of objects occurs. For example, in a region called the fusiform face area, located in the fusiform gyrus, which lies on the ventral aspect of the temporal lobe, neurons are activated by faces and can be specialized to one specific face.

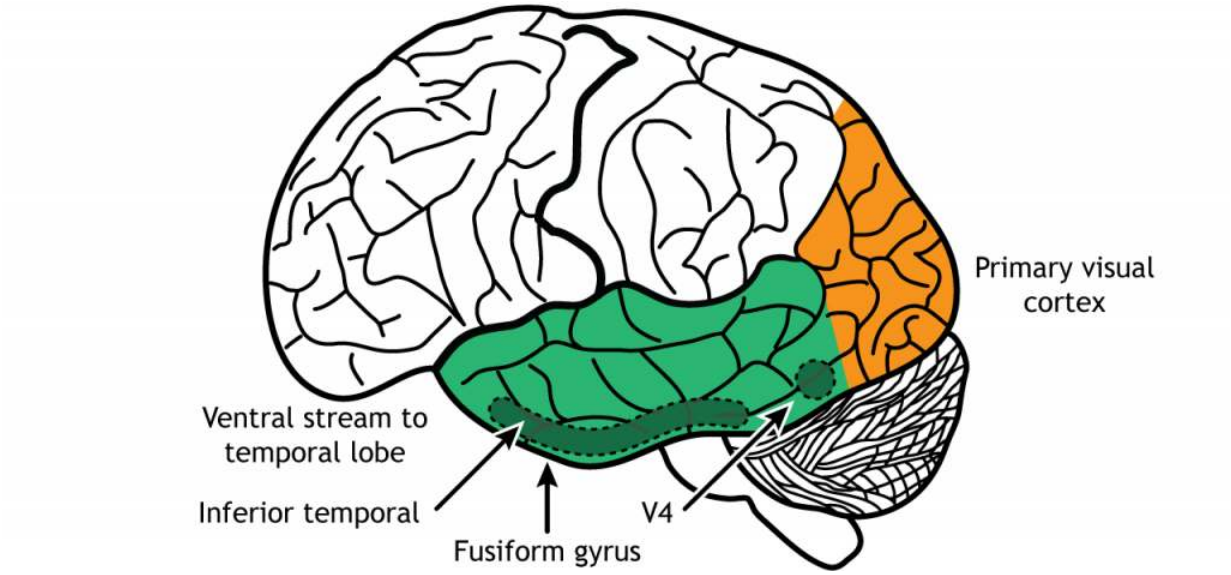


Figure 7.3.2.12:*The ventral stream is first processed by area V4, which recognizes shapes and color. Information the continues through the inferior temporal lobe and sends information to regions like the fusiform gyrus, which is an area responsible for the recognition of faces. 'Ventral Stream' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

The inferior temporal lobe also makes reciprocal connections with the structures in the limbic system. The limbic system plays an important role in processing emotions and memory, both of which are significant components to visual perception. The amygdala ties visual stimuli with emotions and provides value to objects. A family member will have emotional ties that a stranger will not. The hippocampus is responsible for learning and memory and helps establish memories of visual stimuli.

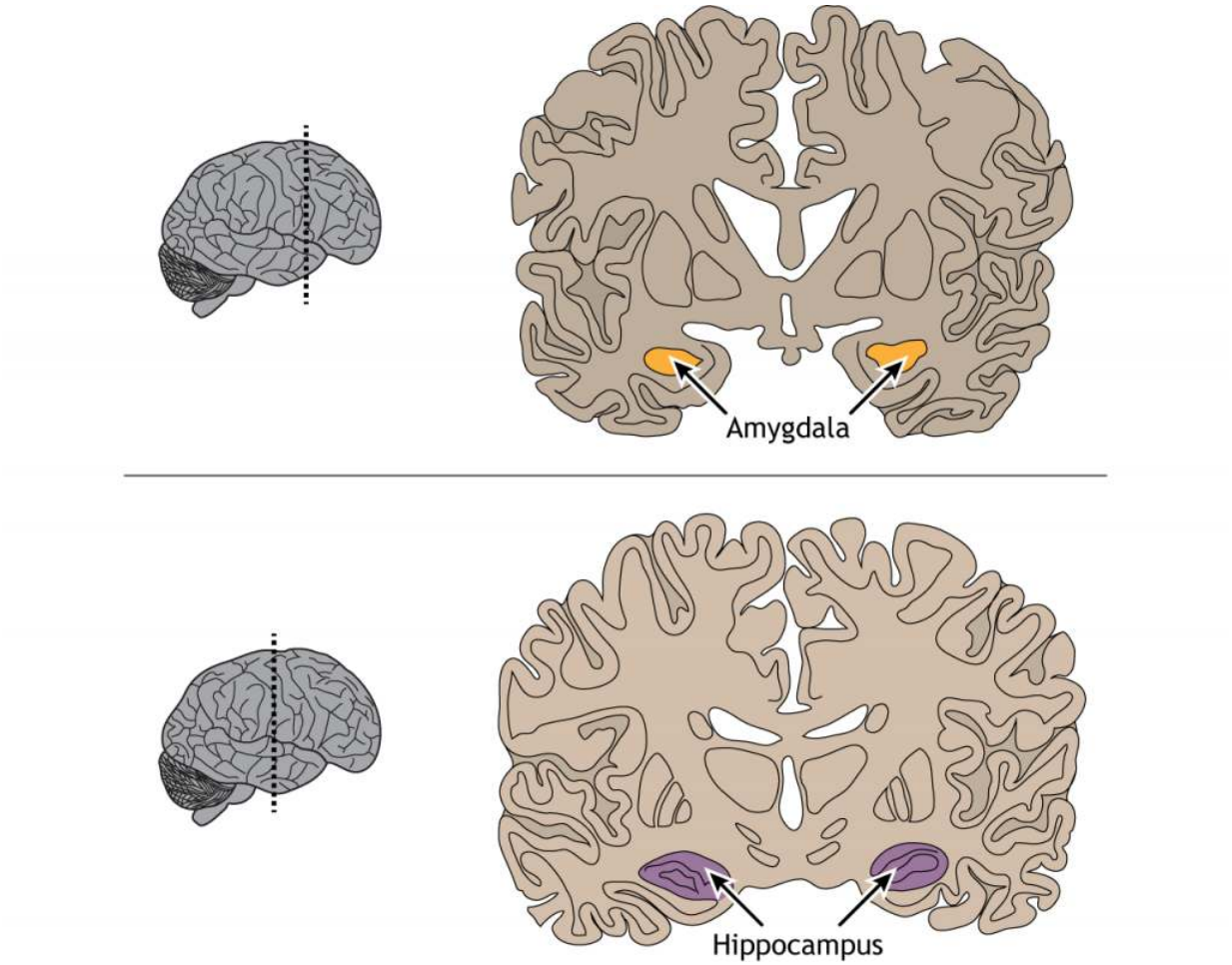


Figure 7.3.2.13:*The limbic system structures, the amygdala and the hippocampus, also play important roles in visual processing. Both regions are located deep in the temporal lobe and have reciprocal connections with the ventral stream as is it moves through the temporal lobe. 'Deep Temporal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

View the amygdala using the BrainFacts.org 3D Brain

View the hippocampus using the BrainFacts.org 3D Brain

Pathways through the Amygdala

The amygdala receives visual information through multiple pathways. In addition to the projections to the amygdala via the ventral stream, the amygdala also appears to rely on input from the thalamus that is independent of the ventral stream pathway. A shorter pathway travels from the retina to the amygdala via the thalamus. It is believed that this pathway allows for a rapid responses to the threats and allows visual stimuli to activate the amygdala quicker than processing through the visual cortex. In fact, studies have shown that pictures of angry or fearful faces can cause amygdala activation without conscious awareness of seeing the image, a result of images being shown for only milliseconds to the subject. The amygdala also receives special input in other sensory systems that further contribute to its ability to respond to potential dangerous stimuli.

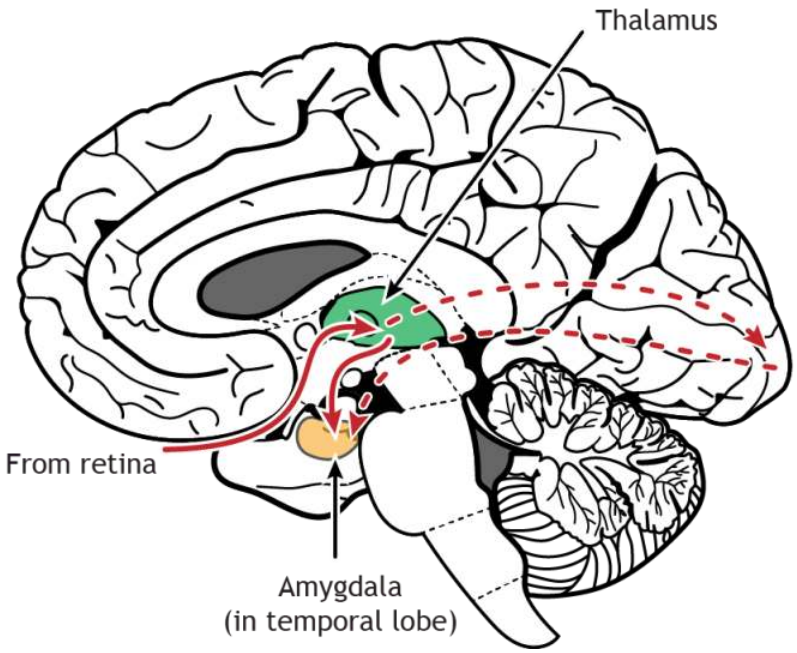


Figure 7.3.2.14: *Information from the retina travels to the thalamus. From the thalamus, there is a direct pathway to the amygdala (solid red arrows) in addition to the pathway to the occipital lobe and ventral stream (dashed red arrows). 'Amygdala Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Non-Thalamic Pathways

The retina sends projections to more regions than just the thalamus. Although most retinal output projects to the lateral geniculate nucleus of the thalamus and then to the primary visual cortex, there are some axons that project to other areas of the brain. A subset of specialized retinal ganglion cells project to the suprachiasmatic nucleus in the hypothalamus. This region is critical for circadian rhythms and the sleep/wake cycle. Other retinal neurons send axons to the pretectum, a midbrain region that communicates with motor nuclei and is responsible for pupillary control. Finally, other ganglion cells project to the superior colliculus, another midbrain region. This pathway is responsible for movements that will orient the head and eyes toward an object to focus the object in the center of the visual field, the region of highest visual acuity.

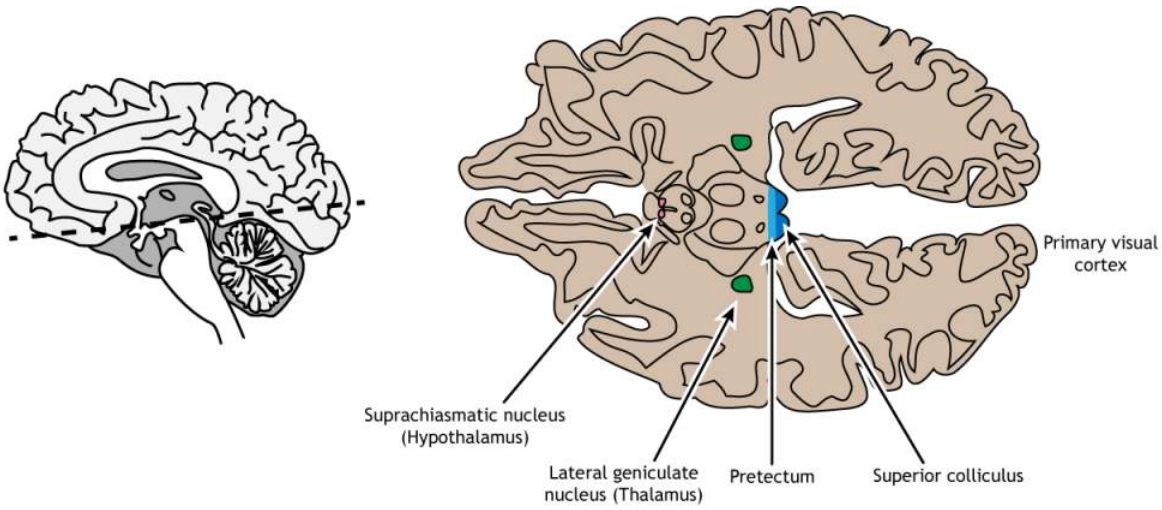


Figure 7.3.2.15:*In addition to the thalamus, the retinal neurons send projections to other regions of the brain. The suprachiasmatic nucleus (pink) is located in the hypothalamus and is important for biological rhythms. The pretectum (light blue) is a midbrain structure that plays a role in muscle control of the pupil. Finally, the retina projects to the superior colliculus (blue), another midbrain region important in eye and head movements. The lateral geniculate nucleus of the thalamus (green) is also shown. 'Non-Thalamic Retinal Pathways' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

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7.3.3: Visual System- Theories of Color Vision, Depth, and Motion

Learning Objectives

- Compare and contrast the trichomatic and opponent process theories of color perception, including their underlying neural mechanisms
- Describe the key aspects of both monocular and binocular depth perception
- Explain the basic phenomena related to motion perception

Color Perception

Research indicates that humans can distinguish between millions of different color variations (Gerald , 1972). Although humans can distinguish between a wide variety of variations there are three primary colors that form the base of these variations; red, green, and blue. The ability for these colors to form these variations is based on the hue or shade of the colors. The electromagnetic spectrum illustrated below shows that visible light for humans is just a small slice of the entire spectrum, which includes radiation that we cannot see as light because it is below the frequency of visible red light and above the frequency of visible violet light.

The Electromagnetic Spectrum Figure 7.3.3.1

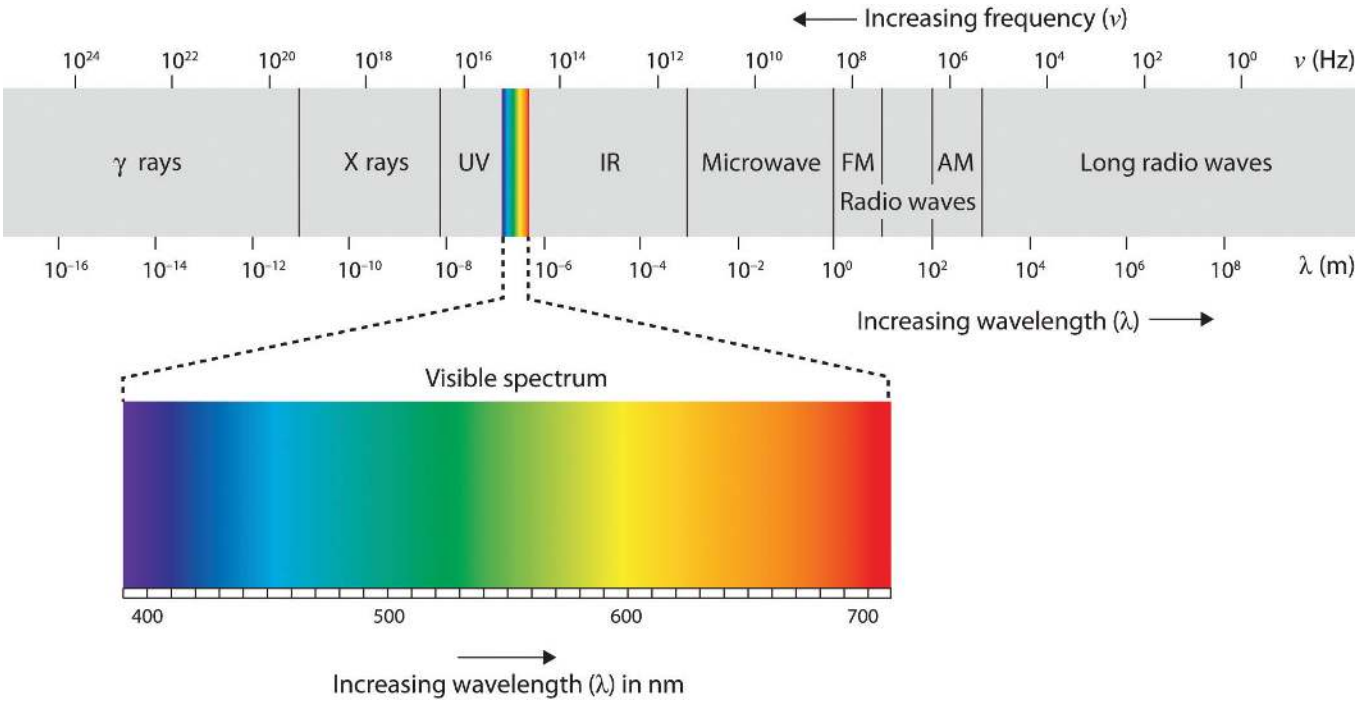


Figure 7.3.3.1: Only a small fraction of the electromagnetic energy that surrounds us (the visible spectrum) is detectable by the human eye.

Trichomatic Theory (Young-Helmholtz) Theory of Color Vision

In his important research on color vision, Hermann von Helmholtz theorized that color is perceived because the cones in the retina come in three types. One type of cone reacts primarily to blue light (short wavelengths), another reacts primarily to green light (medium wavelengths), and a third reacts primarily to red light (long wavelengths). The visual cortex then detects and compares the strength of the signals from each of the three types of cones, creating the experience of color. According to this Young-Helmholtz **trichromatic color theory**, *what color we see depends on the mix of the signals from the three types of cones*. If the brain is receiving primarily red and blue signals, for instance, it will perceive purple; if it is receiving primarily red and green signals it will perceive yellow; and if it is receiving messages from all three types of cones it will perceive white.

The different functions of the three types of cones are apparent in people who experience color blindness. Color blindness can be defined as having decreased capacity to see color or distinguish differences between colors. Red–green color blindness is the most

common form, followed by blue–yellow color blindness and total color blindness. Red–green color blindness affects up to 8% of males and 0.5% of females of Northern European descent. Red-green color blindness is a result of an absence of long or medium wavelength cones or to the production of abnormal opsin pigments in these cones that affect red-green color vision (see Figure 7.3.3.2).

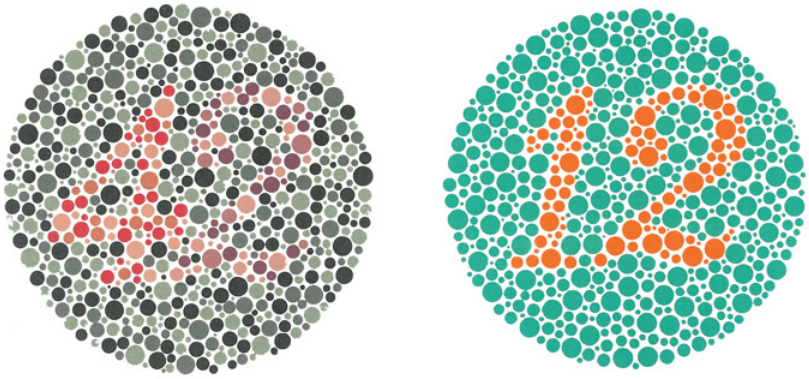


Figure 7.3.3.2: People with normal color vision can see the number 42 in the first image and the number 12 in the second (they are vague but apparent). However, people who are color blind cannot see the numbers at all. Wikimedia Commons.

Opponent Process Theory

An alternative approach to the Young-Helmholtz theory, known as the **opponent-process color theory**, *proposes that we analyze sensory information not in terms of three colors but rather in three sets of "opponent colors": red-green, yellow-blue, and white-black.* Evidence for the opponent-process theory comes from the fact that some neurons in the retina and in the visual cortex are excited by one color (e.g., red) but inhibited by another color (e.g., green).

One example of opponent processing occurs in the experience of an afterimage. If you stare at the flag on the left for about 30 seconds (the longer you look, the better the effect), and then move your eyes to the blank area to the right of it, you will see the afterimage. When we stare at the green stripes, our green receptors habituate and begin to process less strongly, whereas the red receptors remain at full strength. When we switch our gaze, we see primarily the red part of the opponent process. Similar processes create blue after yellow and white after black (see Figure 7.3.3.3).



Figure 7.3.3.3: U.S. Flag. The presence of an afterimage is best explained by the opponent-process theory of color perception. Stare at the flag for a few seconds, and then move your gaze to the blank space next to it. Do you see the afterimage? Mike Swanson – U.S. Flag (inverted) – public domain.

Depth Perception

Depth perception is *the ability to perceive three-dimensional space and to accurately judge distance*. Without depth perception, we would be unable to drive a car, thread a needle, or simply navigate our way around the supermarket (Howard & Rogers, 2001).

Research has found that depth perception is in part based on innate capacities and in part learned through experience (Witherington, 2005).

Psychologists Eleanor Gibson and Richard Walk (1960) tested the ability to perceive depth in 6- to 14-month-old infants by placing them on a **visual cliff**, *a mechanism that gives the perception of a dangerous drop-off, in which infants can be safely tested for their perception of depth* (see Figure 7.3.3.4). The infants were placed on one side of the "cliff," while their mothers called to them from the other side. Gibson and Walk found that most infants either crawled away from the cliff or remained on the board and cried because they wanted to go to their mothers, but the infants perceived a chasm that they instinctively could not cross. Further research has found that even very young children who cannot yet crawl are fearful of heights (Campos, Langer, & Krowitz, 1970). On the other hand, studies have also found that infants improve their hand-eye coordination as they learn to better grasp objects and as they gain more experience in crawling, indicating that depth perception is also learned (Adolph, 2000).



Figure 7.3.3.4: Visual Cliff- A mother urging her child from across the deep side of the visual cliff. Despite a transparent surface covering the cliff, the child hesitates to move forward. (From Gibson and Walk (1960). Copyright 1960 Nature Publishing Group., CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons)

Depth perception is the result of our use of **depth cues**, *messages from our bodies and the external environment that supply us with information about space and distance*. **Binocular depth cues** are *depth cues that are created by retinal image disparity—that is, the space between our eyes, and thus which require the coordination of both eyes.* One outcome of retinal disparity is that the images projected on each eye are slightly different from each other. The visual cortex automatically merges the two images into one, enabling us to perceive depth. Three-dimensional movies make use of retinal disparity by using 3-D glasses that the viewer wears to create a different image on each eye. The perceptual system quickly, easily, and unconsciously turns the disparity into 3-D.

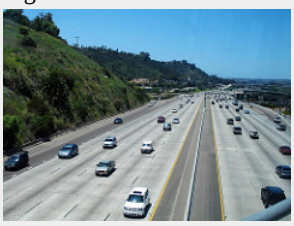
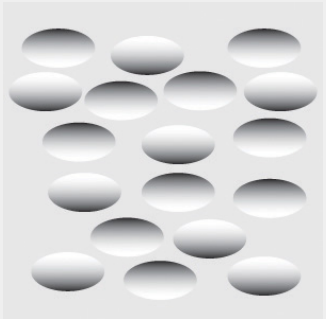
An important binocular depth cue is **convergence**, *the inward turning of our eyes that is required to focus on objects that are less than about 50 feet away from us*. The visual cortex uses the size of the convergence angle between the eyes to judge the object's distance. You will be able to feel your eyes converging if you slowly bring a finger closer to your nose while continuing to focus on it. When you close one eye, you no longer feel the tension—convergence is a binocular depth cue that requires both eyes to work.

The visual system also uses *accommodation* to help determine depth. As the lens changes its curvature to focus on distant or close objects, information relayed from the muscles attached to the lens helps us determine an object's distance. Accommodation is only effective at short viewing distances, however, so while it comes in handy when threading a needle or tying shoelaces, it is far less effective when driving or playing sports.

Although the best cues to depth occur when both eyes work together, we are able to see depth even with one eye closed. **Monocular depth cues** are *depth cues that help us perceive depth using only one eye* (Sekuler & Blake, 2006). Some of the most important are summarized in Table 7.3.3.1 "Monocular Depth Cues That Help Us Judge Depth at a Distance".

Table 7.3.3.5 Monocular Depth Cues That Help Us Judge Depth at a Distance

Name	Description	Example	Image

Name	Description	Example	Image
Position	We tend to see objects higher up in our field of vision as farther away.	The fence posts at right appear farther away not only because they become smaller but also because they appear higher up in the picture.	Figure  Andrew Huff – Rotted Fence – CC BY 2.0.
Relative size	Assuming that the objects in a scene are the same size, smaller objects are perceived as farther away.	At right, the cars in the distance appear smaller than those nearer to us.	Figure  Allan Ferguson – Trolley Crosses Freeway – CC BY 2.0.
Linear perspective	Parallel lines appear to converge at a distance.	We know that the tracks at right are parallel. When they appear closer together, we determine they are farther away.	Figure  Bo Insogna, TheLightningMan.com – Lightning Striking By The Train Tracks – CC BY-NC-ND 2.0.
Light and shadow	The eye receives more reflected light from objects that are closer to us. Normally, light comes from above, so darker images are in shadow.	We see the images at right as extending and indented according to their shadowing. If we invert the picture, the images will reverse.	Figure 

Name	Description	Example	Image
Interposition	When one object overlaps another object, we view it as closer.	At right, because the blue star covers the pink bar, it is seen as closer than the yellow moon.	Figure 
Aerial perspective	Objects that appear hazy, or that are covered with smog or dust, appear farther away.	The artist who painted the picture on the right used aerial perspective to make the distant hills more hazy and thus appear farther away.	Figure  Frans Koppelaar – Landscape near Bologna – CC BY-SA 2.5.

Motion Detection

Many animals, including human beings, have very sophisticated perceptual skills that allow them to coordinate their own motion with the motion of moving objects in order to create a collision with that object. Bats and birds use this mechanism to catch up with prey, dogs use it to catch a Frisbee, and humans use it to catch a moving football. The brain detects motion partly from the changing size of an image on the retina (objects that look bigger are usually closer to us) and in part from the relative brightness of objects.

We also experience motion when objects near each other change their appearance. The **beta effect** refers to *the perception of motion that occurs when different images are presented next to each other in succession* (see Note “Beta Effect and Phi Phenomenon”). The visual cortex fills in the missing part of the motion and we see the object moving. The beta effect is used in movies to create the experience of motion. A related effect is the **phi phenomenon**, in which *we perceive a sensation of motion caused by the appearance and disappearance of objects that are near each other*. The phi phenomenon looks like a moving zone or cloud of background color surrounding the flashing objects. The beta effect and the phi phenomenon are other examples of the importance of the gestalt—our tendency to “see more than the sum of the parts.”

Beta Effect and Phi Phenomenon

In the beta effect, our eyes detect motion from a series of still images, each with the object in a different place. This is the fundamental mechanism of motion pictures (movies). In the phi phenomenon, the perception of motion is based on the momentary hiding of an image.

Phi phenomenon: http://upload.wikimedia.org/Wikipedia/commons/6/6e/Lilac-Chaser.gif

Beta effect: http://upload.wikimedia.org/Wikipedia/commons/0/09/Phi_phenomenom_no_watermark.gif

Attribution

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- Vision sections adapted by Isaias Hernandez from "Introduction to Psychology-University of Minnesota"; https://open.lib.umn.edu/intropsyc/c...04_s02_s01_f02

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https://www.nei.nih.gov/learn-about-...olor-blindness

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7.4: Hearing

7.4.1 Hearing

Learning Objectives

- Label key structures of the ear, identify their functions, and describe the role they play in hearing.
- Explain how we encode and perceive pitch.
- Explain how we localize sound.
- Describe how hearing and the vestibular system are associated.

7.4.2 Overview

The perception of sound is critical for the survival of many species. Although it is clearly possible for humans with hearing limitations to function and thrive, it is definitely one of the most important senses in terms of navigating our world and communicating with others. This text uses vision as a model system to illustrate the wonder and complexities of sensation and perception. Hence, a more detailed treatment of all aspects of visual processing was presented. The remaining senses will be presented with a more general exploration of their sensation and perception processes. This section will provide an overview of the basic anatomy and function of the auditory system, how we perceive pitch, and how we know where sound is coming from.

7.4.3 Auditory Processing and the Ear

It has been argued that humans can hear a variety of sounds and distinguish between a large variation of them. This ability begins with the unique architecture of the accessory structure for hearing, the ear. The complex anatomy of the ear in humans can be divided into three sections. As detailed in Figure 7.4.1 (Left), these sections include the **external, middle, and inner ear**. With the exception of the final component of the inner ear, these three sections are all part of the **non-neural accessory structure** for hearing. Just like with other senses, these accessory structures act to convert and transfer the incoming environmental stimuli into something that the specialized receptor cells can respond to. Some parts of this accessory apparatus, such as the small bones of the middle ear are particularly delicate and prone to deficits that can lead to hearing loss.

The environmental **stimuli** for hearing are basically **air vibrations**. Unlike light waves which travel in a vacuum, these air disturbances or "**sound waves**" are transferred when molecules bump into each other in the air and, if the waves are of high enough amplitude result in our ultimate perception of them. However, before we get close to perception, these waves must first make their way through the outer and middle ear before reaching the "sensation" step which occurs in the cochlea of the inner ear.

The **specialized, sensory receptor cells** for audition are located along the **basilar membrane** in the middle of three, fluid-filled canals of the cochlea. These cells are called **auditory hair cells** due to the cilia or hair-like structure of their dendrites. See Figure 7.4.1 (Right). When the dendrites or cilia of these cells move they produce electrical changes or impulses which then travel along the **auditory nerve** into the brain. Ultimately, this activity reaches the **primary auditory cortex** and beyond to produce perception.

The illustration below summarizes the complex system of the ear and how the anatomical structures and connections between them lead to the ability to perceive the sounds of nature, appreciate beauty of music and utilize language to communicate with others who speak the same language (see Figure 7.4.1).

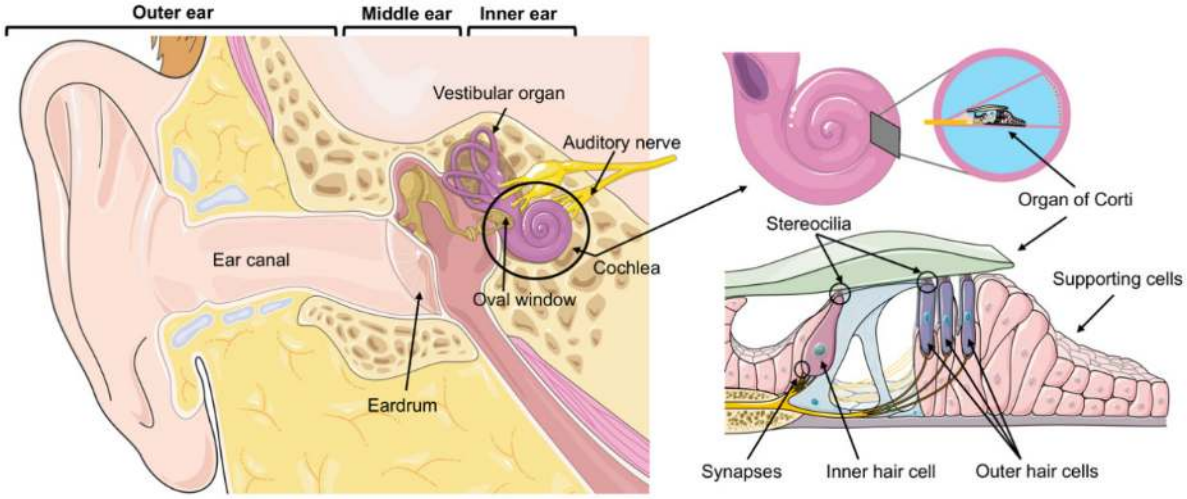


Figure 7.4.1 – ***Accessory Structures of the Ear (Left):*** The Outer ear contains the external pinna (not labelled), ear canal, and tympanic membrane ("eardrum"). The Middle ear contains three small bones called ossicles . The Inner ear contains the cochlea. ***Neural Component - Organ of Corti (Right):*** The spiral-shaped cochlea is the auditory sensory organ where mechanical sound waves are transmitted into electrical signals by the hair cells of the organ of Corti. See the text for further details. The figure was created with Servier Medical Art templates by Servier, which are licensed under a CC BY 3.0; **https://smart.servier.com** (accessed on 16 January 2021). See Cortada, et al. (2021)

7.4.4 Theories of Auditory Perception

The incoming sound waves come in different **frequencies**, with low frequency sounds ultimately being perceived as lower pitched and higher frequency sounds being perceived as higher pitched. In particular, the human ear is most responsive to sounds that are in the same frequency as the human voice. This is why parents and mothers in particular are able to pick out the sound of their children's voice amongst other children's voices and we are often able to identify another person from the sound of their voice without having to see them physically. The complex system of the ear allows us to process sounds almost instantly.

There are a few theories that have been proposed to help account as to why individuals can distinguish between pitch perception and frequencies. Two commonly accepted ones are detailed here.

The **temporal theory** of pitch perception asserts that frequency is coded by the differential **activity level of individual sensory neurons**. This would mean that a given hair cell would fire action potentials related to the frequency of the sound wave. While this is a very intuitive explanation, we detect such a broad range of frequencies (20–20,000 Hz) that the frequency of action potentials fired by hair cells cannot account for the entire range. Because of properties related to sodium channels on the neuronal membrane that are involved in action potentials, there is a point at which a cell cannot fire any faster (Shamma, 2001).

The **place theory** of pitch perception suggests that different portions of the **basilar membrane moves** up and down in response to incoming sound waves. More specifically, the base of the basilar membrane responds best to high frequencies and the tip of the basilar membrane responds best to low frequencies. Therefore, hair cells that are in the base portion would be labeled as high-pitch

receptors, while those in the tip of basilar membrane would be labeled as low-pitch receptors (Shamma, 2001). In reality, both theories explain different aspects of pitch perception. At frequencies up to about 4000 Hz, it is clear that both the rate of action potentials and place contribute to our perception of pitch. However, much higher frequency sounds can only be encoded using place cues (Shamma, 2001).

7.4.5 Sound Localization

Similar to the need for recognizing different pitches and frequencies, knowing where particular sounds are coming from (**sound localization**) is an important part of navigating the environment around us. The auditory system has the ability to use monaural (one ear) and binaural (two ears) cues to locate where a particular sound might be coming from. Each pinna interacts with incoming sound waves differently, depending on the sound's source relative to our bodies. This interaction provides a monaural cue that is helpful in locating sounds that occur above or below and in front or behind us. The sound waves received by your two ears from sounds that come from directly above, below, in front, or behind you would be identical; therefore, monaural cues are essential (Grothe, Pecka, & McAlpine, 2010).

Binaural cues, on the other hand, provide information on the location of a sound along a horizontal axis by relying on differences in patterns of vibration of the eardrum between our two ears. If a sound comes from an off-center location, it creates two types of binaural cues: interaural level differences and interaural timing differences. **Interaural level difference** refers to the fact that a sound coming from the right side of your body is more intense at your right ear than at your left ear because of the attenuation of the sound wave as it passes through your head. **Interaural timing difference** refers to the small difference in the time at which a given sound wave arrives at each ear, illustrated in Figure 7.4.2. Certain brain areas monitor these differences to construct where along a horizontal axis a sound originates (Grothe et al., 2010).

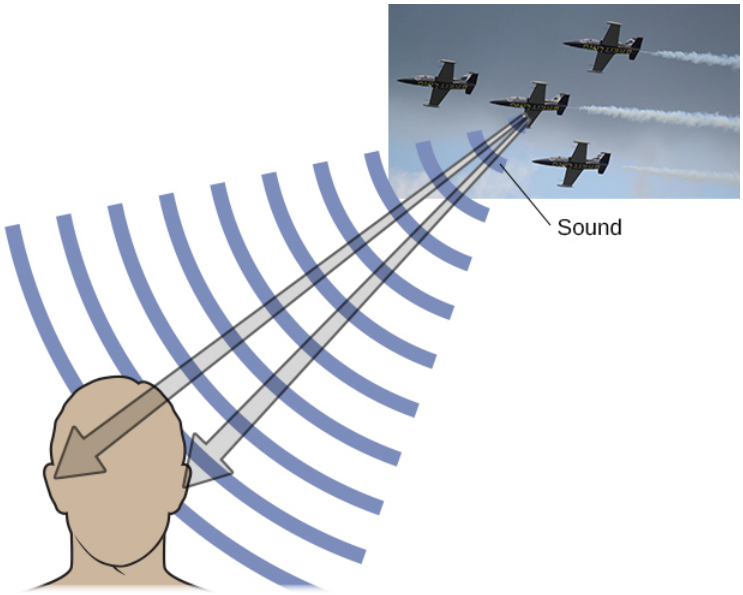


Figure 7.4.2: Localizing sound involves the use of both monaural and binaural cues. (From Psychology - Openstax: modification of work by Max Pfandl, CC BY 3.0)

7.4.5.1 Hearing Loss

- About 2 to 3 out of every 1,000 children in the United States are born with a detectable level of hearing loss in one or both ears (https://www.nidcd.nih.gov/health/sta...istics-hearing).
- More than 90 percent of deaf children are born to hearing parents (https://www.nidcd.nih.gov/health/sta...istics-hearing).
- Approximately 15% of American adults (37.5 million) aged 18 and over report some trouble hearing (https://www.nidcd.nih.gov/health/sta...istics-hearing)

Conductive hearing loss can be caused by physical damage to the ear (such as to the eardrums); this condition reduces the ability of the ear to transfer vibrations from the outer ear to the inner ear. Conductive hearing loss can also be a result of fusion of the ossicles (three bones in the middle ear). Sensorineural hearing loss, which is caused by damage to the cilia (of the hair cells) or to the auditory nerve, is not as common as conductive hearing loss but the likelihood of this condition increases with age (Tennesen,

2007). As we continue to get older damage to the cilia increases; by the age of 65 years old 40% of individuals will have had damage to the cilia (Chisolm, Willott, & Lister, 2003).

Individuals who have experienced sensorineural hearing loss may benefit from a cochlear implant. Data From the National Institutes of Health shows that as of December 2019, approximately 736,900 cochlear implants have been implanted worldwide. In the United States, roughly 118,100 devices have been implanted in adults and 65,000 in children The following video explains the process of a cochlear implant.

7.4.5.2 Deafness and Deaf Culture

In most modern nations people who are born or become deaf at an early age have developed their own system of communication and culture amongst themselves and people close to them. It has been argued that encouraging deaf people to sign is a more appropriate adjustment as opposed to encouraging them to speak, read lips or have cochlear implant surgeries. However, more recent studies suggest that due to advancements in technology, cochlear implants increase the likelihood of a person being able to have and engage in some auditory and speaking activities if implanted early enough (Dettman, Pinder, Briggs, Dowell, & Leigh, 2007; Dorman & Wilson, 2004). As a result parents often face the difficult decision of whether to take advantage of new technologies and approaches of providing support to deaf students in mainstream classroom settings or utilizing American Sign Language (ASL) schools and encouraging more immersion in those settings.

7.4.5.3 Hearing and the Vestibular System

The vestibular system has some similarities with the auditory system. It utilizes hair cells just like the auditory system, but it excites them in different ways. There are five vestibular receptor organs in the inner ear: the utricle, the saccule, and three semicircular canals. Together, they make up what's known as the vestibular labyrinth that is shown in Figure 7.4.3. The utricle and saccule respond to acceleration in a straight line, such as gravity. The roughly 30,000 hair cells in the utricle and 16,000 hair cells in the saccule lie below a gelatinous layer, with their stereocilia projecting into the gelatin. Embedded in this gelatin are calcium carbonate crystals—like tiny rocks. When the head is tilted, the crystals continue to be pulled straight down by gravity, but the new angle of the head causes the gelatin to shift, thereby bending the stereocilia. The bending of the stereocilia stimulates the neurons, and they signal to the brain that the head is tilted, allowing the maintenance of balance. It is the vestibular branch of the vestibulocochlear cranial nerve that deals with balance.



Figure 7.4.3 The structure of the vestibular canals shown atop the snail-like structure of the cochlea. From smart.servier.com. CC BY 3.0.

7.4.6 Attributions

- Hearing sections adapted by Isaias Hernandez from "Anatomy and Physiology from Oregon State University"; https://open.oregonstate.education/a.../15-3-hearing/
- Hearing sections adapted by Isaias Hernandez from "Psychology 2e from OpenStax"; https://openstax.org/books/psycholog...es/5-4-hearing

7.4.7 References

Cortada, M., Levano, S., & Bodmer, D. (2021). mTOR Signaling in the Inner Ear as Potential Target to Treat Hearing Loss. *International Journal of Molecular Sciences*, *22*(12), 6368. MDPI AG. Retrieved from http://dx.doi.org/10.3390/ijms22126368

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7.5: Touch

Learning Objectives

1. Describe the role of social and affective touch in development and bonding.
2. Describe how the somatosensory system allows for the sensing of touch, temperature, and position in space.
3. Describe the process of transduction in the senses of touch and proprioception.
4. Explain how expectations and context affect pain and touch experiences.

7.5.1 Overview

The somatosensory system is one of the most **varied sensory systems** on just about every level from initial types of stimuli to the wide range of ultimate perceptions.This system is regulated by specialized receptors that are spread throughout the body and measure a number of different sensory modalities in the body. These sensations can be divided into three main divisions: external stimuli, internal stimuli, and the sense of where the body is in space.

Perception of **external stimuli** can include the sense of **touch** (via mechanoreceptors), **pain** (via nociceptors), and **temperature** (via thermal receptors). Perception of **internal stimuli** can include organ (visceral) sensation and pain (via multiple receptor types) and blood chemical composition (via chemoreceptors). Finally, **proprioception** (via proprioceptors) is the **sense of where the body is in space**. The ability of an individual to touch their nose easily while their eyes are closed is an example of the proprioception system.

This section will provide an overview of most of these types of somatosensory inputs and the neural mechanisms that govern them.

7.5.2 Somatosensory Cell Bodies

All **somatosensory receptor** neurons have their cell bodies located in the dorsal root ganglion, a structure found just outside the dorsal aspect of the spinal cord (See Figure 7.5.1). The receptor neurons, also called primary afferent fibers, of the somatosensory system are bipolar neurons, meaning they have one process from the cell body that splits into two branches. One travels to the location of the receptor (e.g. the skin for touch) via the spinal nerves, and one travels into the spinal cord at the dorsal horn via the dorsal root. The axon can either synapse in the spinal cord or ascend to the brain in the dorsal column.

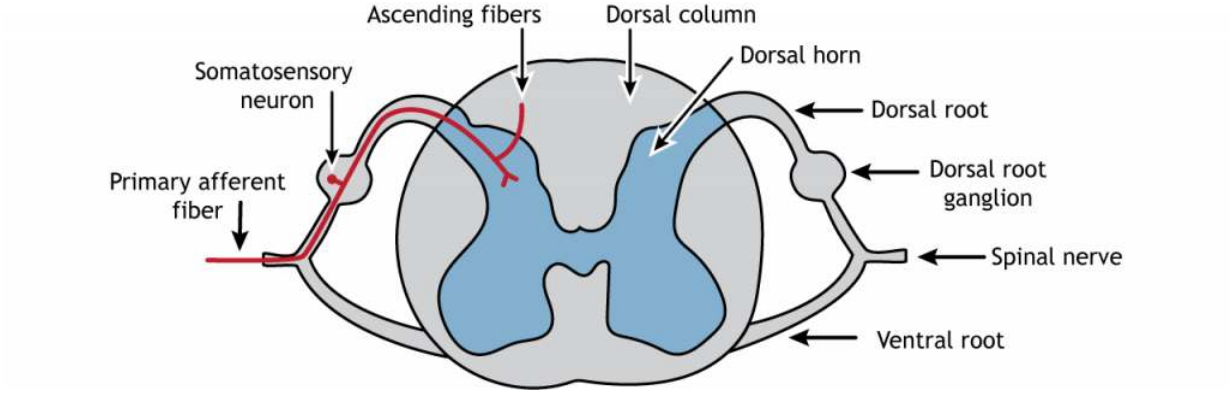


Figure 7.5.1: *Primary afferent fibers travel from the periphery or target organs through the spinal nerve to the dorsal root ganglion where the cell body of the neuron is located. The axons then continue through the dorsal root into the dorsal horn of the spinal cord. Axons can branch and synapse in the spinal cord, or they can ascend to the brain via the dorsal column. 'Somatosensory Spinal Cord' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

7.5.3 Touch

The sense of touch is one of the most important senses in human development, particularly with regard to attachment to others. It has long been viewed as an essential part of childhood development (Baysinger, Plubell, & Harlow, 1973; Feldman, 2007; Haradon, Bascom, Dragomir, & Scripcaru, 1994) and also helps us feel socially attached to others (Field et al., 1997; Kelter, 2009). Touch is an essential part of everyday activities ranging from touching our food to eat to sharing human affection with another individual. Recent studies indicate that slow affectionate touch, rather than faster neutral touch, can serve as a buffer against physical pain. In addition, the same slow affectionate touch can reduce feelings of social exclusion and increase social bonding.

Skin is the largest organ in our body and has a variety of nerve endings that allow us to feel sensations such as pressure, pain, cold, and heat. The skin on our bodies also serves as a protector to important vital organs.

Touch and pain are aspects of the somatosensory system, which provides our brain with information about our own body (**interoception**) and properties of the immediate external world (**exteroception**) (Craig, 2002). We have somatosensory receptors located all over the body, from the surface of our skin to the depth of our joints. As indicated previously, the information they send to the central nervous system is generally divided into four modalities: **cutaneous senses** (senses of the skin), **proprioception** (body position), **kinesthesis** (body movement), and **nociception** (pain, discomfort).

7.5.3.1 Cutaneous Senses (senses of the skin)

Cutaneous senses respond to **tactile, thermal, and pruritic** (itchy) stimuli, and events that cause tissue damage (**pain**). Cutaneous mechanoreceptors are located in the skin. They provide the senses of touch, pressure, vibration, proprioception, and others. They all utilize nerves known as Aβ fibers from the skin that are mostly dedicated to touch, except for the mechano-receiving free nerve endings, which use Aδ fibers to process information primarily relating to acute pain; sharp, immediate, and relatively short-lasting.

The can be categorized by morphology, by the type of sensation they perceive, and by the rate of adaptation. Furthermore, each has a different receptive field:

- Ruffini's end organs detect tension deep in the skin.
- Meissner's corpuscles detect changes in texture (vibrations around 50 Hz) and adapt rapidly.
- Pacinian corpuscles detect rapid vibrations (about 200–300 Hz).
- Merkel's discs detect sustained touch and pressure.
- Mechanoreceiving free nerve endings detect touch, pressure, and stretching.
- Hair follicle receptors are located in hair follicles and sense the position changes of hair strands.

7.5.3.1.1 Ruffini Ending

The Ruffini ending (Ruffini corpuscle or bulbous corpuscle) is a class of slowly adapting mechanoreceptors thought to exist only in the glabrous dermis and subcutaneous tissue of humans. It is named after Angelo Ruffini (an Italian histologist and embryologist).

This spindle-shaped receptor is sensitive to skin stretch, and contributes to the kinesthetic sense of and control of finger position and movement. It is believed to be useful for monitoring the slippage of objects along the surface of the skin, allowing the modulation of grip on an object.

Ruffini endings are located in the deep layers of the skin. They register mechanical information within joints, more specifically angle change, with a specificity of up to two degrees, as well as continuous pressure states. They also act as thermoreceptors that respond for a long time, such as holding hands with someone during a walk. In a case of a deep burn to the body, there will be no pain as these receptors will be burned off.

7.5.3.1.2 Meissner's Corpuscles

Meissner's corpuscles (or tactile corpuscles) are responsible for sensitivity to light touch. In particular, they have the highest sensitivity (lowest threshold) when sensing vibrations lower than 50 hertz. They are rapidly adaptive receptors.

7.5.3.1.3 Pacinian Corpuscles

Pacinian corpuscles (or lamellar corpuscles) are responsible for sensitivity to vibration and pressure. The vibrational role may be used to detect surface texture, e.g., rough versus smooth.

7.5.3.1.4 Merkel Nerve

Merkel nerve endings are mechanoreceptors found in the skin and mucosa of vertebrates that provide touch information to the brain. The information they provide are those regarding pressure and texture. Each ending consists of a Merkel cell in close apposition with an enlarged nerve terminal.

This is sometimes referred to as a Merkel cell–neurite complex, or a Merkel disk receptor. A single afferent nerve fiber branches to innervate up to 90 such endings. They are classified as slowly adapting type I mechanoreceptors.

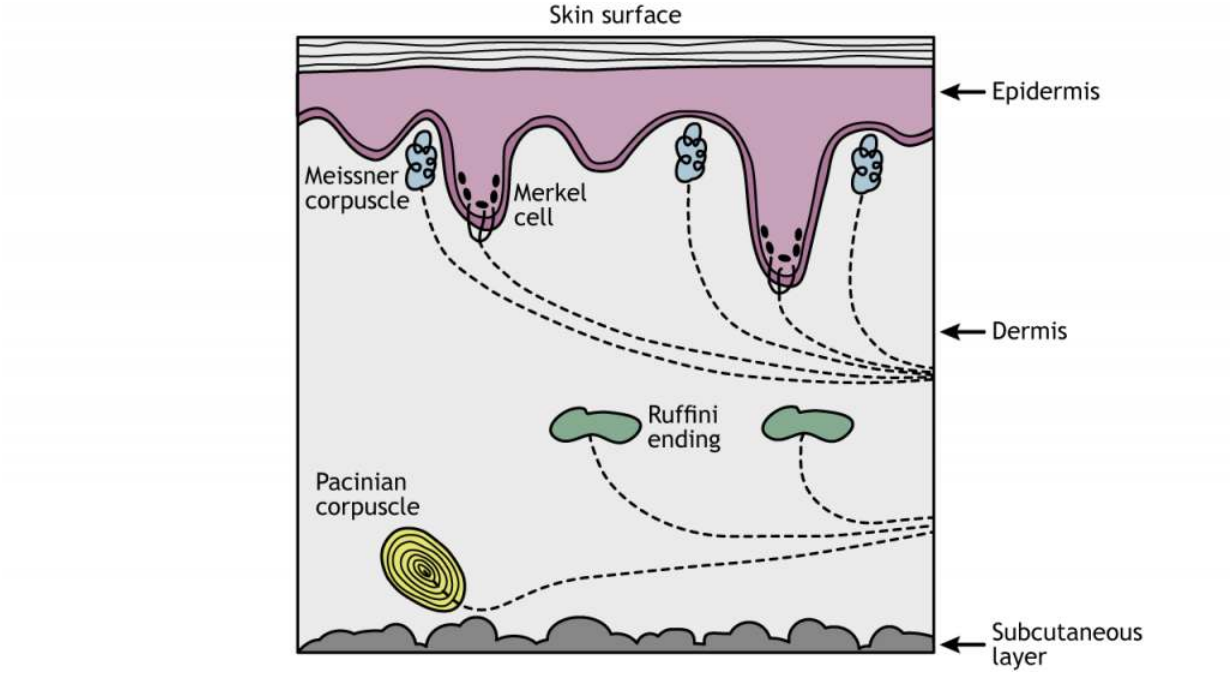


Figure 7.5.2: The different mechanoreceptor types are located in different regions of the skin and are responsible for perception of different characteristics of a touch stimulus. Pacinian corpuscles and Ruffini endings are located deep in the dermis. Meissner corpuscles are located in the dermis near the epidermis, and Merkel cells are located in the epidermis, near the surface of the skin. 'Mechanoreceptors' by Casey Henley (CC BY-NC-SA) 4.0 International License.

7.5.3.2 Proprioception (body position)

Proprioception refers to the sense of knowing how one's body is positioned in three-dimensional space. Proprioception is the sense of the relative position of neighboring parts of the body and the strength of effort being employed in movement. It is distinguished from exteroception (perception of the outside world) and interoception (perception of pain, hunger, and the movement of internal organs). The initiation of proprioception is the activation of a proprioreceptor in the periphery. The proprioceptive sense is believed to be composed of information from sensory neurons located in the inner ear (motion and orientation) and in the stretch receptors located in the muscles and the joint-supporting ligaments (stance). Conscious proprioception is communicated by the posterior (dorsal) column–medial lemniscus pathway to the cerebrum. Unconscious proprioception is communicated primarily via the dorsal and ventral spinocerebellar tracts to the cerebellum.

An unconscious reaction is seen in the human proprioceptive reflex, or Law of Righting, a reflex that corrects the orientation of the body when it is taken out of its normal upright position. In the event that the body tilts in any direction, the person will tilt their head back to level the eyes against the horizon. Infants are often seen doing this as soon as they gain control of their neck muscles. This control comes from the cerebellum, the part of the brain that affects balance.

Muscle spindles are sensory receptors within the belly of a muscle that primarily detect changes in the length of a muscle. They convey length information to the central nervous system via sensory neurons. This information can be processed by the brain to determine the position of body parts. The responses of muscle spindles to changes in length also play an important role in regulating the contraction of muscles.

The Golgi organ (also called Golgi tendon organ, tendon organ, neurotendinous organ or neurotendinous spindle) is a proprioceptive sensory receptor that provides the sensory component of the Golgi tendon reflex. The Golgi organ should not be confused with the Golgi apparatus—an organelle in the eukaryotic cell —or the Golgi stain, which is a histologic stain for neuron

cell bodies. The Golgi tendon reflex is a normal component of the reflex arc of the peripheral nervous system. In a Golgi tendon reflex, skeletal muscle contraction causes the agonist muscle to simultaneously lengthen and relax. This reflex is also called the inverse myotatic reflex, because it is the inverse of the stretch reflex. Although muscle tension is increasing during the contraction, alpha motor neurons in the spinal cord that supply the muscle are inhibited and antagonistic muscles are activated.

7.5.3.3 Kinesthesis (body movement)

Kinesthesis or Kinesthesia is a term that is often used interchangeably with proprioception. Some users differentiate the kinesthetic sense from proprioception by excluding the sense of equilibrium or balance from kinesthesia. An inner ear infection, for example, might degrade the sense of balance. This would degrade the proprioceptive sense, but not the kinesthetic sense. The infected person would be able to walk, but only by using their sense of sight to maintain balance; the person may have difficulty walking when their eyes are closed.

Proprioception and kinesthesia are seen as interrelated and there is considerable disagreement regarding the definition of these terms. Some of this difficulty stems from Sherrington's original description of joint position sense (or the ability to determine where a particular body part exactly is in space) and kinesthesia (or the sensation that the body part has moved) under a more general heading of proprioception. Clinical aspects of proprioception are measured in tests that measure a subject's ability to detect an externally imposed passive movement, or the ability to reposition a joint to a predetermined position. Often it is assumed that the ability of one of these aspects will be related to another, unfortunately experimental evidence suggests there is no strong relation between these two aspects. This suggests that while these components may well be related in a cognitive manner, they seem to be separate physiologically.

Much of the forgoing work is dependent on the notion that proprioception is essentially a feedback mechanism: that is the body moves (or is moved) and then the information about this is returned to the brain whereby subsequent adjustments could be made. More recent work into the mechanism of ankle sprains suggest that the role of reflexes may be more limited due to their long latencies (even at the spinal cord level) as ankle sprain events occur in perhaps 100 milliseconds or less. As a result, a model has been proposed to include a 'feedforward' component of proprioception where the subject will also have central information about the body's position prior to attaining it.

Kinesthesia is a key component in **muscle memory** and **hand-eye coordination** and training can improve this sense. The ability to swing a golf club, or to catch a ball, requires a finely-tuned sense of the position of the joints. This sense needs to become automatic through training to enable a person to concentrate on other aspects of performance, such as maintaining motivation or seeing where other people are.

7.5.3.4 Nociception (pain, discomfort)

Nociception deals with a series of events and processes required for an organism to receive a **painful** stimulus, convert it to a molecular signal, and recognize and characterize the signal in order to trigger an appropriate defense response. This serves as an important function because our brains can often turn off or reduce the feelings of pain depending on the situation we may be experiencing or involved in. An example involves athletes who often do not feel pain until after they have completed the game or event they are participating in (Bantick, Wise, Ploghaus, Clare, Smith, & Tracey, 2002). In essence their brain is involved in a complicated process that requires them to utilize multiple systems to stay focused on the activity. The endorphins that are released when we are engaged or excited by a situation or event around us act as natural pain killers (Sternberg, Bailin, Grant, & Gracely, 1998).

7.5.4 Spinal Pathways: From the Body to the Brain

All of the various types of somatosensory input described above must make its way up to cortical areas of the brain to ultimately be perceived and acted upon. As mention in the cutaneous section, there is may be multiple pathways that an input can take depending on the nature of the stimuli being processes. These incoming pathways are often referred to as afferent axons to denote that the information will ultimately travel via axons making their way into the central nervous system.

Primary afferent axons are divided into four groups based on size and conduction speed. The groups, unfortunately, have different names depending on if the axons come from the skin (Aα, Aβ, Aδ, and C fibers; examples are touch or pain) or the muscles (Group I, II, III and IV fibers; example is proprioception). The fastest axons are the Aα or Group I type; they have the largest diameter and are heavily myelinated. The C fibers have the smallest diameter, are unmyelinated, and are the slowest at conducting action potentials. See Figure 7.5.3 for an illustration of how these fibers enter the nervous and make their way up to the brain. Note that

the axons cross to the opposite side at some point, so the cortex ultimately processes information from the contralateral (opposite) side of the body.

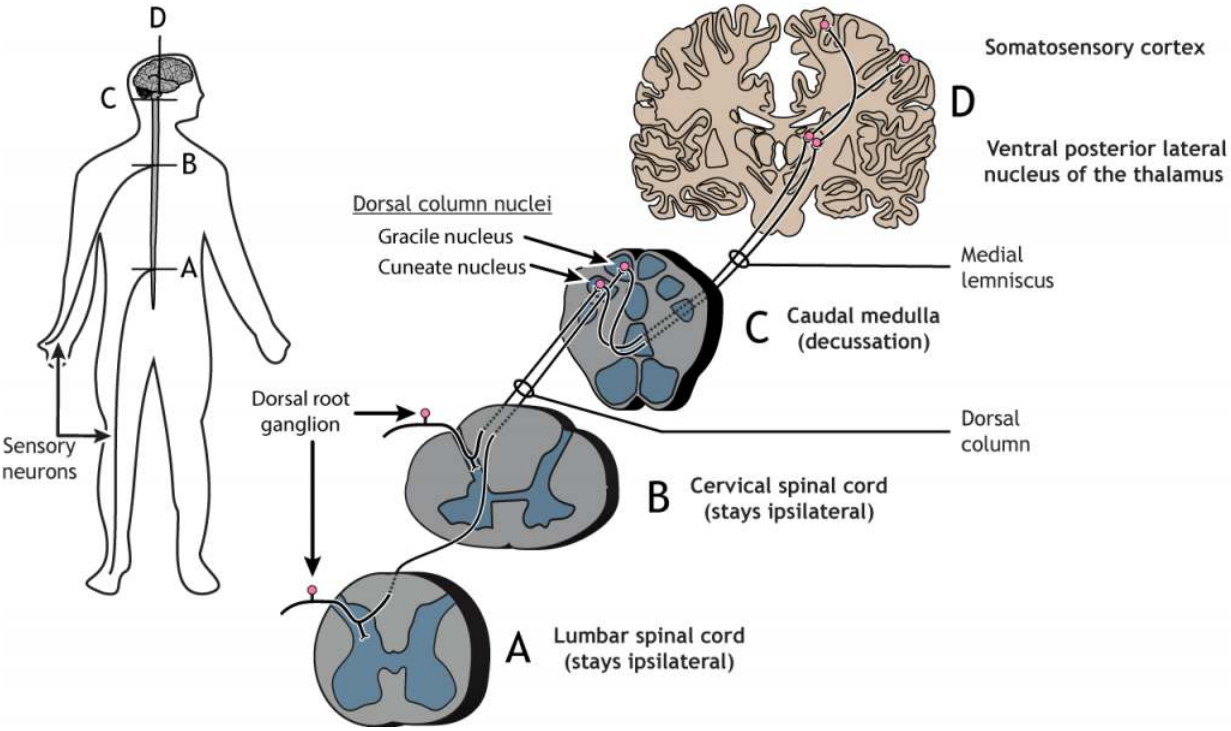


Figure 7.5.3: Somatosensory information from the neck and body travels through the dorsal column – medial lemniscus pathway, named for structures within the pathway. Axons enter the spinal cord and ascend through the dorsal column to the medulla where decussation, or crossing the midline, occurs. Information continues to the thalamus via the medial lemniscus, and then reaches the somatosensory cortex. Details of the pathway are found in the text. 'Touch Pathway from Body' by Casey Henley (CC BY-NC-SA 4.0 International License).

7.5.5 The Primary Somatosensory Cortex

The **primary somatosensory cortex** is divided into four regions, each with its own input and function: areas 1, 2, 3a, and 3b. Most touch information from mechanoreceptors inputs to region 3b, whereas most proprioceptive information from the muscles inputs to region 3a. These regions then send and receive information from areas 1 and 2. As processing of somatosensory information continues, the stimuli required to activate neurons becomes more complex. For example, area 1 is involved in sensing texture, and area 2 is involved in sensing size and shape of an object. (see Figure 7.5.4).

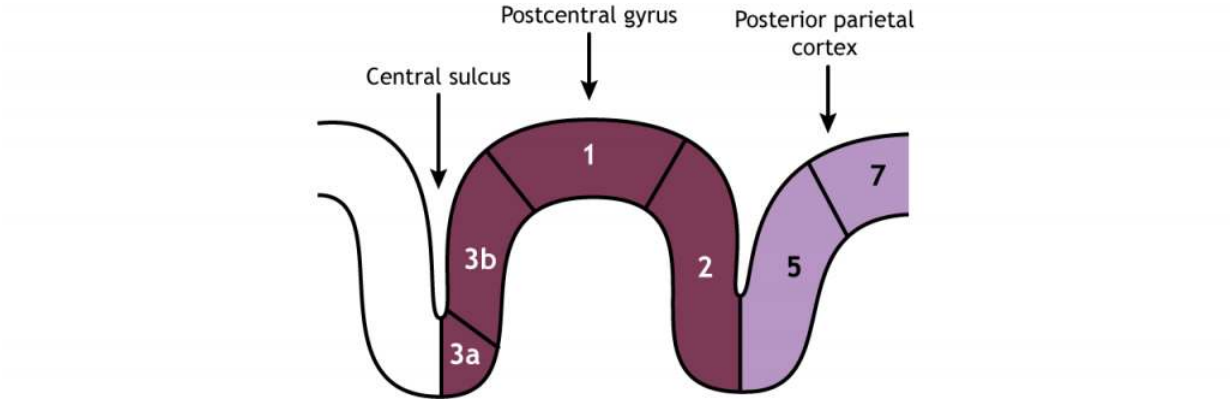


Figure 7.5.4: *The somatosensory cortex, located in the postcentral gyrus, just posterior to the central sulcus, is divided into 4 areas: 3a, 3b, 1, and 2. The posterior parietal cortex, an output region of the somatosensory cortex, lies just posterior to the postcentral gyrus and is divided into areas 5 and 7. 'Postcentral Gyrus' by Casey Henley (CC BY-NC-SA) 4.0 International License.*

Testing of the senses begins with examining the regions known as **dermatomes** that connect to the cortical region where somatosensation is perceived in the postcentral gyrus. To test the sensory fields, a simple stimulus of the light touch of the soft end

of a cotton-tipped applicator is applied at various locations on the skin. The spinal nerves, which contain sensory fibers with dendritic endings in the skin, connect with the skin in a topographically organized manner, illustrated as dermatomes (Figure 7.5.5 - it is not necessary to memorize the terms in this figure). For example, the fibers of the eighth cervical nerve innervate the medial surface of the forearm and extend out to the fingers. In addition to testing perception at different positions on the skin, it is necessary to test sensory perception within the dermatome from distal to proximal locations in the appendages, or lateral to medial locations in the trunk. In testing the eighth cervical nerve, the patient would be asked if the touch of the cotton to the fingers or the medial forearm was perceptible, and whether there were any differences in the sensations.

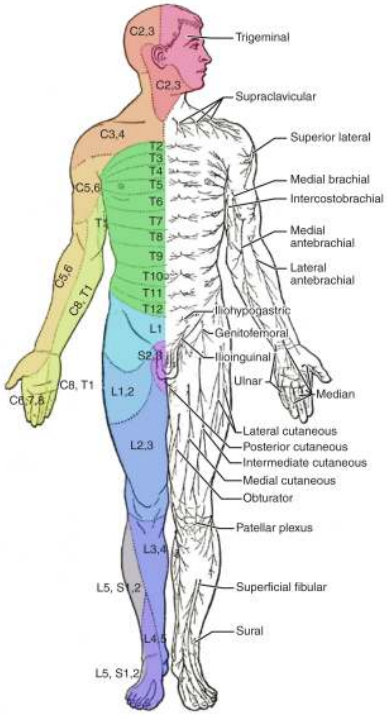


Figure 7.5.5 – ***Dermatomes:*** *The surface of the skin can be divided into topographic regions that relate to the location of sensory endings in the skin based on the spinal nerve that contains those fibers. (credit: modification of work by Mikael Häggström)* *https://open.oregonstate.education/a...otor-pathways/*

7.5.6 Attributions

- Touch sections adapted by Isaias Hernandez from "NOBA-Biological Psychology, Touch and Pain"; https://nobaproject.com/modules/touch-and-pain#:~:text=Touch%20and%20pain%20are%20aspects,)%20(Craig%2C%202002).
- Touch sections adapted by Isaias Hernandez from "Introduction to Psychology, University of Minnesota'"; https://open.lib.umn.edu/intropsyc/chapter/4-4-tasting-smelling-and-touching/
- Touch sections adapted by Isaias Hernandez from "Boundless Anatomy and Physiology from Lumen"; https://courses.lumenlearning.com/boundless-ap/chapter/pain/
- Touch sections adapted by Isaias Hernandez from "Kinesthia, Psychology Wiki"; https://en.Wikipedia.org/wiki/Kinaesthetics
- Touch sections adapted by Isaias Hernandez from "Nociception, Wikipedia"; https://en.Wikipedia.org/wiki/Nociception
- Touch sections adapted by Isaias Hernandez from "Foundations of Neuroscience, Michigan State University"; https://openbooks.lib.msu.edu/neuroscience/chapter/touch-the-skin/
- Touch sections adapted by Isaias Hernandez from "Anatomy and Physiology, Oregon State University"; https://open.oregonstate.education/aandp/chapter/14-5-sensory-and-motor-pathways/
- Further revision of most sections by Alan Keys, Ph.D., Sacramento City College, Sacramento, CA.

7.5.7 References

- von Mohr, M., Kirsch, L.P. & Fotopoulou, A. The soothing function of touch: affective touch reduces feelings of social exclusion. *Sci Rep* **7,** 13516 (2017). https://doi.org/10.1038/s41598-017-13355-7

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7.6: Taste and Smell

7.6.1 Taste and Smell

Learning Objectives

1. Explain why taste and smell are the most interconnected senses
2. Identify the five primary tastes in humans: sweet, sour, bitter, salty, and umami
3. Identify how the five primary tastes allow individuals to adapt to changes in the environment and increase chances of survival
4. Explain how olfactory receptors are responsive to different odorants
5. Describe the general structure of the olfactory and gustatory pathways from the periphery to the cortex

7.6.2 Overview

Being able to sense chemicals in the environment through taste (gustation) and smell (olfaction) can help an organism find food, avoid poisons, and attract mates. Taste and smell, are the most interconnected senses in that both involve molecules of the stimulus entering the body and bonding to receptors. Smell lets an animal sense the presence of food and other chemicals in the environment that can impact their survival. Similarly, the sense of taste allows animals to discriminate between types of foods. Different tasting foods have different attributes, both helpful and harmful. For example, sweet-tasting substances tend to be highly caloric, which could be necessary for survival in lean times. Bitterness is often associated with toxicity, and sourness is often associated with spoiled food. Salty foods are valuable in maintaining homeostasis by helping the body retain water and by providing ions necessary for proper cell function. Similar types of discriminations are made with a much broader range of odorants in the olfactory system. This section will review the peripheral and central anatomy of these interacting, chemical sensory systems.

7.6.3 Smell

Odorants (odor molecules) enter the nose and dissolve in the olfactory epithelium, the mucosa at the back of the nasal cavity (See Figure 7.6.1). The **olfactory epithelium** is a collection of specialized olfactory receptors in the back of the nasal cavity that spans an area about 5 cm^2 in humans. Recall that sensory cells are neurons. An **olfactory receptor**, which is a dendrite of a specialized neuron, responds when it binds certain molecules inhaled from the environment by sending impulses directly to the olfactory bulb of the brain. Humans have about 12 million olfactory receptors, distributed among hundreds of different receptor types that respond to different odors. Twelve million seems like a large number of receptors, but compare that to other animals: rabbits have about 100 million, most dogs have about 1 billion, and bloodhounds—dogs selectively bred for their sense of smell—have about 4 billion. The overall size of the olfactory epithelium also differs between species, with that of bloodhounds, for example, being many times larger than that of humans.

Olfactory neurons are **bipolar neurons** (neurons with two processes from the cell body). Each neuron has a single dendrite buried in the olfactory epithelium, and extending from this dendrite are 5 to 20 receptor-laden, hair-like cilia that trap odorant molecules. The sensory receptors on the cilia are proteins, and it is the variations in their amino acid chains that make the receptors sensitive to different odorants. Each olfactory sensory neuron has only one type of receptor on its cilia, and the receptors are specialized to detect specific odorants, so the bipolar neurons themselves are specialized. When an odorant binds with a receptor that recognizes it, the sensory neuron associated with the receptor is stimulated.

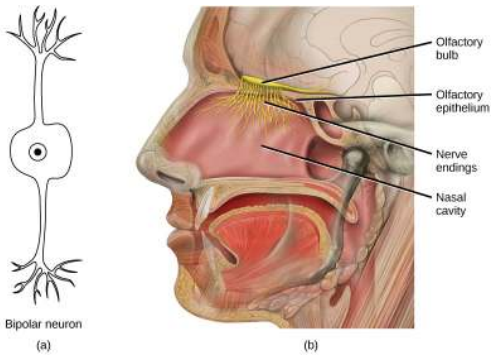


Figure 7.6.1: In the human olfactory system, (a) bipolar olfactory neurons extend from (b) the olfactory epithelium, where olfactory receptors are located, to the olfactory bulb. (credit: modification of work by Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist from "Human Biology, OpenStax"; https://openstax.org/books/biology-2e/pages/36-3-taste-and-smell, CC BY 4.0)

7.6.3.1 Smell Perception and Pathways to Cortex

Olfactory stimulation is the only sensory information that directly reaches the cerebral cortex first, whereas other sensations are relayed through the thalamus. Figure 7.6.2 illustrates the seemingly complex array of cortical and subcortical projections of the olfactory pathways coming from the olfactory cells of the nose. The main factors to note here are that smell is linked to areas involved with emotion, motivation, and memory in addition to perception. This makes sense when you stop to think of how powerful a particular smell can be in triggering a significant emotional response or vivid memory.

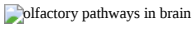


Figure 7.6.2: Simplified diagram of brain regions involved in the processing of olfactory information. Odor information from cells in the nose project into the primary olfactory cortex, which include the anterior olfactory nucleus (not shown), piriform cortex, olfactory tubercle, amygdaloid complex, and entorhinal cortex. From these primary olfactory cortical regions, odor information is projected to the thalamus, **orbitofrontal cortex**, insula cortex and hippocampus. From Olfactory Pathways 10.4172/2471-2701.1000169. CC BY-NC-ND 4.0

7.6.3.2 Taste

Detecting a taste (gustation) is fairly similar to detecting an odor (olfaction), given that both taste and smell rely on chemical receptors being stimulated by certain molecules. Humans can perceive five basic tastes: salty, sour, bitter, sweet, and umami (savory). Bitter taste often indicates a dangerous substance like a poison, sweet taste signifies a high energy food, salty taste indicates a substance with high salt content, sour taste indicates an acidic food, and umami taste indicates a high protein food.

The primary organ of taste is the taste bud. A **taste bud** is a cluster of gustatory receptors (taste cells) that are located within the bumps on the tongue called **papillae** (singular: papilla) (See Figures 7.6.3 and 7.6.4). There are several structurally distinct papillae. Filiform papillae, which are located across the tongue, are tactile, providing friction that helps the tongue move substances, and contain no taste cells. In contrast, fungiform papillae, which are located mainly on the anterior two-thirds of the tongue, each contain one to eight taste buds and also have receptors for pressure and temperature. The large circumvallate papillae contain up to 100 taste buds and form a V near the posterior margin of the tongue.

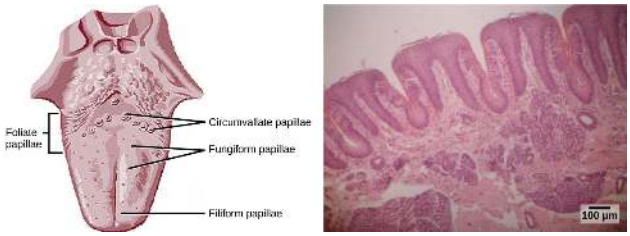


Figure 7.6.3: The human tongue. (a) Foliate, circumvallate, and fungiform papillae are located on different regions of the tongue. (b) Foliate papillae are prominent protrusions on this light micrograph. (credit a: modification of work by NCI; scale-bar data from Matt Russell from "Human Biology, OpenStax"; https://openstax.org/books/biology-2e/pages/36-3-taste-and-smell, CC BY 4.0)

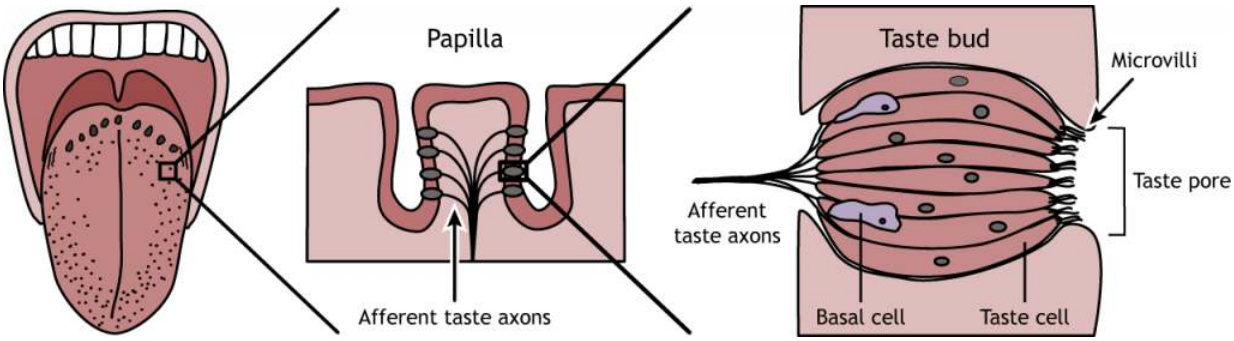


Figure 7.6.4: *The visible bumps on the surface of the tongue are papillae that house taste buds. Taste buds are made up of taste cells and basal cells. The taste cells synapse on afferent axons that send information to the central nervous system. Tastants in food access the taste cells via the taste pore, where the food particles interact with the microvilli of the taste cells. 'Tongue Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.*

Each taste bud's taste cells are replaced every 10 to 14 days. These are elongated cells with hair-like processes called microvilli at the tips that extend into the taste bud pore. Food molecules (**tastants**) are dissolved in saliva, and they bind with and stimulate the receptors on the microvilli. The receptors for tastants are located across the outer portion and front of the tongue, outside of the middle area where the filiform papillae are most prominent.

In humans, there are five primary tastes, each receptor is specific to its stimulus (tastant). Transduction of the five tastes happens through different mechanisms that reflect the molecular composition of the tastant. These tastants bind to their respective receptors, thereby exciting the specialized neurons associated with them. Tasting abilities and sense of smell change with age. In humans, the senses decline dramatically by age 50 and continue to decline. A child may find a food to be too spicy, whereas an elderly person may find the same food to be bland and unappetizing.

7.6.3.3 Taste Perception: Pathways to Cortex

The neural pathways from the taste buds into the brain and ultimately to the primary gustatory cortex included multiple connections and relay points along the way. Certain reflexive actions in response to tastes are controlled by the lower parts of the circuitry in the brainstem, while the higher, holistic perception of tastes and flavor require cortical activity. See Figure 7.6.5 for a streamlined representation of this pathway.

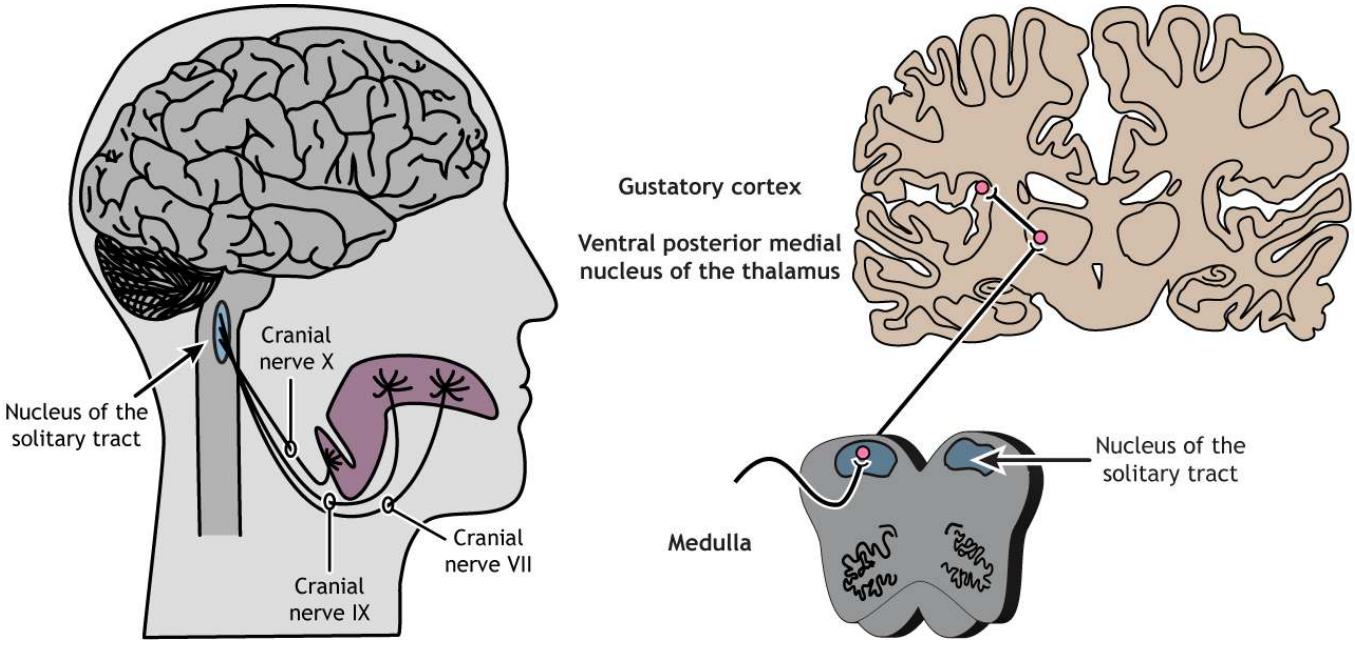


Figure 7.6.5: Taste information from the tongue travels through cranial nerves VII, IX, and X to the nucleus of the solitary tract in the medulla. Neurons in the brainstem project to the ventral posterior medial nucleus of the thalamus and then on to the gustatory cortex. 'Taste Pathway' by Casey Henley *is licensed under a (CC BY-NC-SA) 4.0 International License.*

Flavor

How do 5 basic tastes turn into the myriad complex taste sensations we experience when eating food? Olfaction plays an important role in the perception of flavor, as do vision and touch. Taste information combines with information from these other sensory systems in the **orbitofrontal cortex** located in the frontal lobe. This region is believed to be important for the pleasant and rewarding aspects of food. Additionally, as taste is processed in higher-order regions of the CNS, information is combined using more complex coding mechanisms.

View the orbitofrontal cortex using the BrainFacts.org 3D Brain

7.6.4 Attributions

- Taste and Smell sections adapted by Isaias Hernandez from "Human Biology, OpenStax"; https://openstax.org/books/biology-2e/pages/36-3-taste-and-smell
- Taste and Smell sections adapted by Isaias Hernandez from "Foundations of Neuroscience, Michigan State University"; https://openbooks.lib.msu.edu/neuroscience/chapter/taste/
- Further revisions and modifications by Alan Keys, Ph.D., Sacramento City College, Sacramento, CA.
- Olfactory Pathways from Misiak, Magdalena & Hipolito, MariaMananita & Ressom, Habtom & Obisesan, Thomas & Manaye, Kebreten & Nwulia, Evaristus. (2017). Apo E4 Alleles and Impaired Olfaction as Predictors of Alzheimer's Disease. *Clinical and Experimental Psychology. 03*. 10.4172/2471-2701.1000169. CC BY-NC-ND 4.0

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7.7: Psychophysical Methods

Learning Objectives

Differentiate between experiments measuring absolute thresholds, difference thresholds, and magnitude estimations

Describe at least two different methods of estimating a threshold

Understand what a subliminal message is

Explain Weber's law (also called Weber-Fechner law)

7.7.1 Overview

Psychophysics quantitatively investigates the relationship between physical stimuli and the sensations and perceptions they produce. Psychophysics has been described as the scientific study of the relation between stimulus and sensation or, more completely, as the analysis of perceptual processes by studying the effect on a subject's experience or behaviour of systematically varying the properties of a stimulus along one or more physical dimensions.

The sensitivity of a given sensory system to the relevant stimuli can be expressed as an **absolute threshold**. **Absolute threshold** refers to the minimum amount of stimulus energy that must be present for the stimulus to be detected 50% of the time. Another way to think about this is by considering how dim a light can be or how soft a sound can be and still be detected half of the time. The sensitivity of our sensory receptors can be quite amazing. It has been estimated that on a clear night, the rods (sensitive sensory cells in the back of the eye) can detect a candle flame 30 miles away (Okawa & Sampath, 2007). Under quiet conditions, the hair cells (receptor cells of the inner ear) can detect the tick of a clock 20 feet away (Galanter, 1962).

It is also possible for us to get messages that are presented below the threshold for conscious awareness—these are called **subliminal messages**. A message below the absolute threshold is not strong enough to excite sensory receptors that send nerve impulses to the brain; when this occurs that threshold is said to be subliminal: We receive it, but we are not consciously aware of it. Over the years there has been a great deal of speculation about the use of **subliminal messages** in advertising, rock music, and self-help audio programs. Research evidence shows that in laboratory settings, people can process and respond to information outside of awareness. But this does not mean that we obey these messages or are heavily influenced by these messages; in fact, hidden messages have little effect on behavior outside the laboratory (Kunst-Wilson & Zajonc, 1980; Rensink, 2004; Nelson, 2008; Radel, Sarrazin, Legrain, & Gobancé, 2009; Loersch, Durso, & Petty, 2013).

7.7.2 Methods for Estimating Thresholds

When we design experiments, we have to decide how we're going to approach a **threshold estimation**. Here are three common techniques:

- **Method of Limits**. The experimenter can increase the stimulus intensity (or intensity difference) until the observer detects the stimulus (or the change). For example, turn up the volume until the observer first detects the sound. This is intuitive, but it is also subject to bias — the estimated threshold is likely to be different, for example, if we start high and work down versus starting low and working up.
- **Method of Adjustment.** This is very much like the Method of Limits, except that the experimenter gives the observer control of the stimulus adjustment with the instructions to: "adjust the stimulus until it's clearly visible" or "adjust the color of the patch until it matches the test patch."
- **Method of Constant Stimuli**. This is the most reliable, but also the most time-consuming. You decide ahead of time what levels you are going to measure, do each one a fixed number of times, and record percent correct (or the number of detections) for each level. If you randomize the order, you can get rid of bias.

Absolute thresholds are generally measured under rigidly controlled conditions in situations that are optimal for sensitivity. Sometimes we are more interested in how much difference in stimuli is required to detect a difference between them. This is known as the **just noticeable difference** (jnd) or **difference threshold**. Unlike the **absolute threshold**, the **difference threshold** changes depending on the stimulus intensity. As an example, imagine yourself in a very dark movie theater. If an audience member were to receive a text message on their cell phone which caused their screen to light up, chances are that many people would notice the change in illumination in the theater. However, if the same thing happened in a brightly lit arena during a basketball game, very few people would notice. The cell phone brightness does not change, but its ability to be detected as a change in illumination varies

dramatically between the two contexts. **Ernst Weber** proposed this theory of change in **difference threshold** in the 1830s, and it has become known as **Weber's law**.

Weber's law is approximately true for many aspects of our senses — for brightness perception, visual contrast perception, loudness perception, and visual distance estimation, our sensitivity to change decreases as the stimulus gets bigger or stronger. However, there are many senses for which the opposite is true: our sensitivity increases as the stimulus increases. With electric shock, for example, a small increase in the size of the shock is much more noticeable when the shock is large than when it is small. A psychophysical researcher named **Stanley Smith Stevens** asked people to estimate the magnitude of their sensations for many different kinds of stimuli at different intensities, and then tried to fit lines through the data to predict people's sensory experiences (Stevens, 1967). What he discovered was that most senses could be described by a power law of the form $\mathbf{P \propto S^n}$ (where P is the perceived magnitude, $\propto$ means "is proportional to", S is the physical stimulus magnitude, and n is a positive number). If n is greater than 1, then the slope (rate of change of perception) is getting larger as the stimulus gets larger, and sensitivity increases as stimulus intensity increases. A function like this is described as being expansive or supra-linear. If n is less than 1, then the slope decreases as the stimulus gets larger (the function "rolls over"). These sensations are described as being compressive. **Weber's Law** is only (approximately) true for compressive (sublinear) functions; **Stevens' Power Law** is useful for describing a wider range of senses see Figure 7.7.1 below.

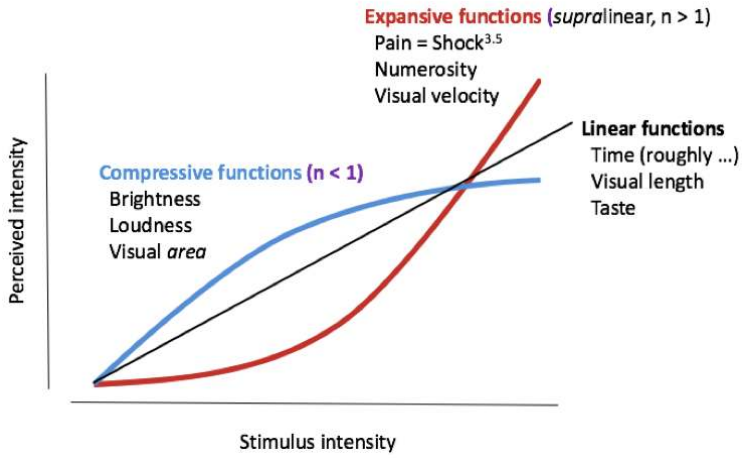


Figure 7.7.1: *Different sensory systems exhibit different relationships between perceived magnitude and stimulus intensity. Sometimes, it makes the most sense to discount or ignore increases in stimulus intensity above a certain point; compressive sensory modalities with a power-law exponent less than 1 accomplish this. Other times, we need heightened sensitivity to stimuli with increased intensity; expansive sensory modalities, described by a power law with exponent greater than 1, accomplish this. Not all perception is non-linear, however; some senses are best described by a linear relationship between stimulus and perception. From "Introduction to Sensation and Perception. Chapter - Psychophysical-Methods" (CC BY 4.0)*

Both **Stevens' Power Law** and **Weber's Law** are only approximately true. They are useful for describing, in broad strokes, how our perception of a stimulus depends on its intensity or size. They are rarely accurate for describing perception of stimuli that are near the absolute detection threshold. Still, they are useful for describing how people will expectably react to normal everyday stimuli.

7.7.3 Sensation and Perception Summary

The world as we experience it is most often multimodal, involving combinations of our senses into one perceptual experience. The combination of senses that allow us to enjoy aspects of our everyday life requires our senses to be integrated. Interestingly, we actually respond more strongly to multimodal stimuli compared to the sum of each single modality together, an effect called the **superadditive effect of multisensory integration**. This can explain how you're still able to understand what friends are saying to you at a loud concert, as long as you are able to get visual cues from watching them speak. If you were having a quiet conversation

at a café, you likely wouldn't need these additional cues. Because we are able to process multimodal sensory stimuli, and the results of those processes are qualitatively different from those of unimodal stimuli, it's a fair assumption that the brain is doing something qualitatively different when they're being processed. There has been a growing body of evidence since the mid-1990's on the neural correlates of **multisensory integration**.

7.7.4 Attribution

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7.8: Gestalt Principles of Perception

7.8.1 Gestalt Principles

Learning Objectives

- Explain the figure-ground relationship
- Define Gestalt principles of grouping
- Describe how perceptual set is influenced by an individual's characteristics and mental state
- Understand the influence stereotypes or prejudice can have on perceptual bias

7.8.2 **Overview**

Gestalt theorists have been incredibly influential in the areas of sensation and perception. Gestalt principles such as figure-ground relationship, grouping by proximity or similarity, the law of good continuation, and closure are all used to help explain how we organize sensory information. Our perceptions are not infallible, and they can be influenced by bias, prejudice, and other factors.

7.8.3 Gestalt Psychology

In the early part of the 20th century, Max Wertheimer published a paper demonstrating that individuals perceived motion in rapidly flickering static images. Research conducted by Wertheimer and his colleagues proposed that perception involved more than simply combining sensory stimuli and led to a new field of psychology known as **Gestalt psychology**. The word **gestalt** literally means form or pattern, but its use reflects the idea that the **whole is different from the sum of its parts**. In other words, the brain creates a perception that is more than simply the sum of available sensory inputs, and it does so in predictable ways. Gestalt psychologists translated these predictable ways into principles by which we organize sensory information. As a result, Gestalt psychology has been extremely influential in the area of sensation and perception (Rock & Palmer, 1990).

7.8.3.1 Figure-ground relationship

One Gestalt principle is the **figure-ground relationship**. According to this principle, we tend to segment our visual world into figure and ground. Figure is the object or person that is the focus of the visual field, while the ground is the background. As the figure below shows, our perception can vary tremendously, depending on what is perceived as figure and what is perceived as ground. Presumably, our ability to interpret sensory information depends on what we label as figure and what we label as ground in any particular case, although this assumption has been called into question (Peterson & Gibson, 1994; Vecera & O'Reilly, 1998). See Figure 7.8.1 below.

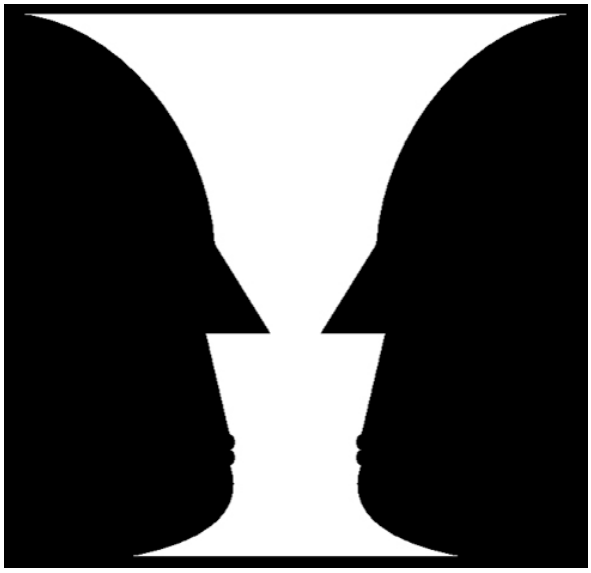


Figure 7.8.1: The concept of figure-ground relationship explains why this image can be perceived either as a vase or as a pair of faces.

7.8.3.2 Principle of proximity

Another Gestalt principle for organizing sensory stimuli into meaningful perception is **proximity**. This principle asserts that things that are close to one another tend to be grouped together, as Figure 7.8.2 below demonstrates.

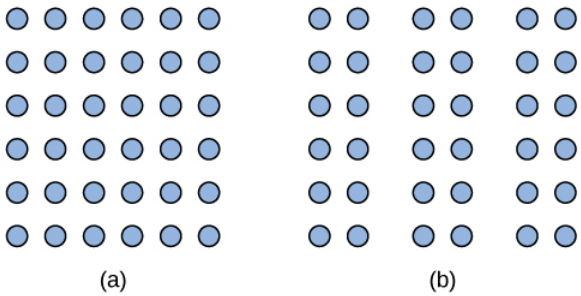


Figure 7.8.2: The Gestalt principle of proximity suggests that you see (a) one block of dots on the left side and (b) three columns on the right side.

How we read something provides another illustration of the **proximity concept**. For example, we read this sentence like this, notl iket hiso rt hat. We group the letters of a given word together because there are no spaces between the letters, and we perceive words because there are spaces between each word. Here are some more examples: Cany oum akes enseo ft hiss entence? What doth es e wor dsmea n?

7.8.3.3 Principle of similarity

We also often use the **principle of similarity** to group things in our visual fields. According to this principle, things that are alike tend to be grouped together as Figure 7.8.3 below illustrates.

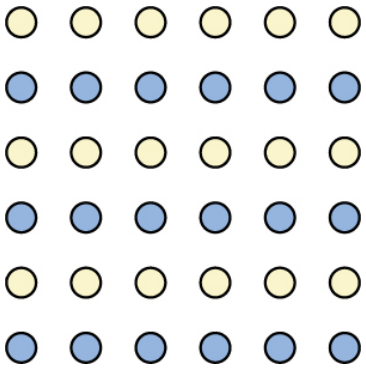


Figure 7.8.3 When looking at this array of dots, we likely perceive alternating rows of colors. We are grouping these dots according to the principle of similarity.

Another example is when watching an American football game, we tend to group individuals based on the colors of their uniforms. While watching an offensive drive (a series of plays which help the offense score), we can get a sense of the two teams simply by grouping along this dimension. Two additional Gestalt principles are the **law of continuity** (or good continuation) and the **principle of closure**.

7.8.3.4 Law of continuity

The **law of continuity** suggests that we are more likely to perceive continuous, smooth flowing lines rather than jagged, broken lines as illustrated in the figure below.

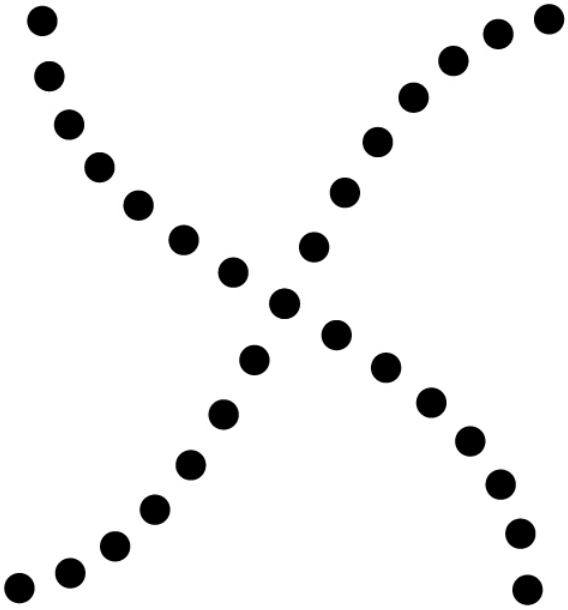


Figure 7.8.4 Good continuation would suggest that we are more likely to perceive this as two overlapping lines, rather than four lines meeting in the center.

7.8.3.5 Principle of closure

The **principle of closure** states that we organize our perceptions into complete objects rather than as a series of parts as illustrated in Figure 7.8.5



Figure 7.8.5Closure suggests that we will perceive a complete circle and rectangle rather than a series of segments.

7.8.3.6 Pattern perception

According to Gestalt theorists, **pattern perception**, or our ability to discriminate among different figures and shapes, occurs by following the principles described above. You probably feel fairly certain that your perception accurately matches the real world, but this is not always the case. Our perceptions are based on **perceptual hypotheses**: educated guesses that we make while interpreting sensory information. These hypotheses are informed by a number of factors, including our personalities, experiences, and expectations. We use these hypotheses to generate our perceptual set. For instance, research has demonstrated that those who are given verbal priming produce a biased interpretation of complex ambiguous figures (Goolkasian & Woodbury, 2010).

7.8.4 Aspects of Bias, Prejudice, and Cultural Factors

In this chapter, you have learned that perception is a complex process. Built from sensations, but influenced by our own experiences, biases, prejudices, and cultures, perceptions can be very different from person to person. Research suggests that implicit racial prejudice and stereotypes affect perception. For instance, several studies have demonstrated that non-Black participants identify weapons faster and are more likely to identify non-weapons as weapons when the image of the weapon is paired with the image of a Black person (Payne, 2001; Payne, Shimizu, & Jacoby, 2005). Furthermore, White individuals' decisions to shoot an armed target in a video game is made more quickly when the target is Black (Correll, Park, Judd, & Wittenbrink, 2002; Correll, Urland, & Ito, 2006). This research is important, considering the number of very high-profile cases in the last few decades in which young Blacks were killed by people who claimed to believe that the unarmed individuals were armed and/or represented some threat to their personal safety. In the article *Stereotypes and Prejudice in the Perception of the "Other"* (Fedor, 2014), it is argued that **otherness** (that which is other than the concept being considered; often it means a person other than oneself) can lead to problematic interpersonal communication that often becomes permanent and may result in the prevention of

community collaboration and development. The full article can be found here, https://www.sciencedirect.com/science/article/pii/S1877042814049702.

7.8.5 Attribution

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CHAPTER OVERVIEW

8: Movement

8.1 Overview

This chapter will explore some of the basic elements of the neural control of movement. A brief discussion of the various muscle systems of the body will be provided along with the role that each plays in our ability to navigate through our environment and keep our vital organs, such as the heart and lungs, operating. The amazing influence of microscopic, synaptic communication from neurons to muscle fibers will be illustrated with a look at the neuromuscular junction and the motor units that control muscle contraction. We will then zoom out a bit and review the multiple central and peripheral nervous system circuits involved with the control of both voluntary and involuntary motor functions. Lastly, the impact of specific disease states and neural damage to motor function will be examined.

8.1: Classification of Muscle Types and Functions

8.2: Synaptic Control of Movement- Neuromuscular Junction and Motor Units

8.3: Spinal Reflexes

8.4: Motor Circuitry- Neural Structures and Pathways

8.5: Impact of Disease States and Neural Damage on Motor Control

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8.1: Classification of Muscle Types and Functions

Learning Objectives

- Identify the three types of muscle tissue
- Compare and contrast the functions of each muscle tissue type
- Explain how muscle tissue can enable motion

8.1.1 Muscle Tissue: Key Properties and Classifications

Muscle tissue is generally characterized by properties that allow movement. A critical property is that muscles are ***excitable*** and are able to respond to a variety of stimuli. They are ***contractile***, meaning they can shorten and generate a pulling force. When attached between two movable objects, in other words, bones, contractions of the muscles cause the bones to move.

Some muscle movement is ***voluntary***, which means it is under conscious control. For example, a person decides to open a book and read a chapter on Psychology. Other movements are ***involuntary***, meaning they are *not* typically under conscious control, such as the contraction of your pupil in bright light or the rhythmic contraction of your heart muscles.

Muscle tissue used for voluntary and involuntary movement can be classified into three main types according to structure and function: **Skeletal, Cardiac, and Smooth**. Table 1 below illustrates the distinctions between these three muscle types.

8.1.1.1 Comparison of Structural and Functional Properties of Muscle Types

Table 1: Muscle Types - Structure, Function, and Location

Tissue	Histology	Function	Location
Skeletal	Long cylindrical fiber, striated, many peripherally located nuclei	Voluntary movement, produces heat, protects organs	Attached to bones and around entrance points to body (e.g., mouth, anus)
Cardiac	Short, branched, striated, single central nucleus	Contracts to pump blood	Heart
Smooth	Short, spindle-shaped, no evident striation, single nucleus in each fiber	Involuntary movement, moves food, involuntary control of respiration, moves secretions, regulates flow of blood in arteries by contraction	Walls of major organs and passageways

Skeletal muscle is attached to bones and its contraction makes possible locomotion (i.e. walking), facial expressions, maintaining posture, and other voluntary movements of the body. Skeletal muscles also generate heat as a byproduct of their contraction and thus participate in thermal regulation. Shivering is an involuntary contraction of skeletal muscles in response to perceived lower than normal body temperature.

Skeletal muscles act not only to produce movement but also to stop movement, such as resisting gravity to maintain posture. Small, constant adjustments of the skeletal muscles are needed to hold a body upright or balanced in any position. Muscles also prevent excess movement of the bones and joints, maintaining skeletal stability and preventing skeletal structure damage or deformation. Joints can become misaligned or dislocated entirely by pulling on the associated bones; muscles work to keep joints stable.

Skeletal muscles are also located throughout the body at the openings of internal tracts to control the movement of various substances. These muscles allow functions, such as swallowing, urination, and defecation, to be under voluntary control. Skeletal muscles also protect internal organs (particularly abdominal and pelvic organs) by acting as an external barrier or shield to external trauma and by supporting the weight of the organs.

Skeletal muscle tissue is arranged in bundles surrounded by connective tissue. Under the light microscope, muscle cells appear striated (striped) with many nuclei squeezed along the membranes. The **striation** is due to the regular alternation of the contractile proteins actin and myosin, along with the structural proteins that couple the contractile proteins to connective tissues. The cells are multinucleated as a result of the fusion of many precursor cells to form each long muscle fiber.

Cardiac muscle forms the contractile walls of the heart. The cells of cardiac muscle, known as cardiomyocytes, also appear striated under the microscope. Unlike skeletal muscle fibers, cardiomyocytes are single cells typically with a single centrally located nucleus. A principal characteristic of cardiomyocytes is that they contract on their own intrinsic rhythms without any external stimulation. Cardiomyocytes attach to one another with specialized cell junctions called intercalated discs. Intercalated discs have both anchoring junctions and gap junctions. Attached cells form long, branching cardiac muscle fibers that are, essentially, a mechanical and electrochemical syncytium allowing the cells to synchronize their actions. The cardiac muscle pumps blood through the body and is under involuntary control. The attachment junctions hold adjacent cells together across the dynamic pressure changes of the cardiac cycle.

Smooth muscle tissue contraction is responsible for involuntary movements in the internal organs. It forms the contractile component of the digestive, urinary, and reproductive systems as well as the airways and arteries. Each cell is spindle shaped with a single nucleus and no visible striations (Figure 4.18).

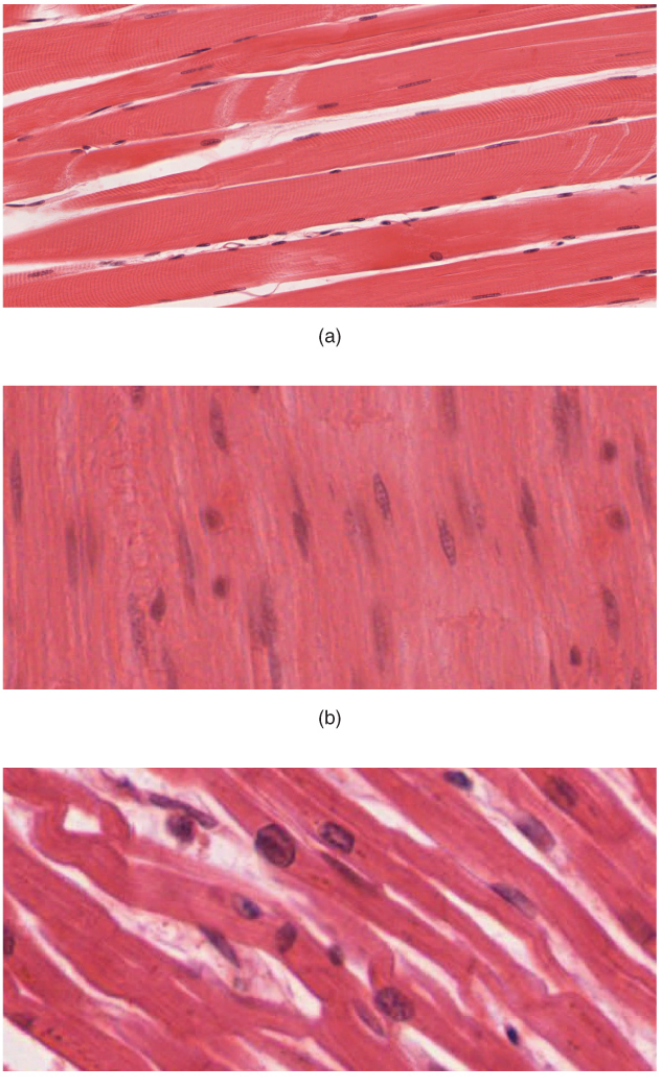


Figure 8.1.1: **Muscle Tissue** (a) Skeletal muscle cells have prominent striation and nuclei on their periphery. (b) Smooth muscle cells have a single nucleus and no visible striations. (c) Cardiac muscle cells appear striated and have a single nucleus. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

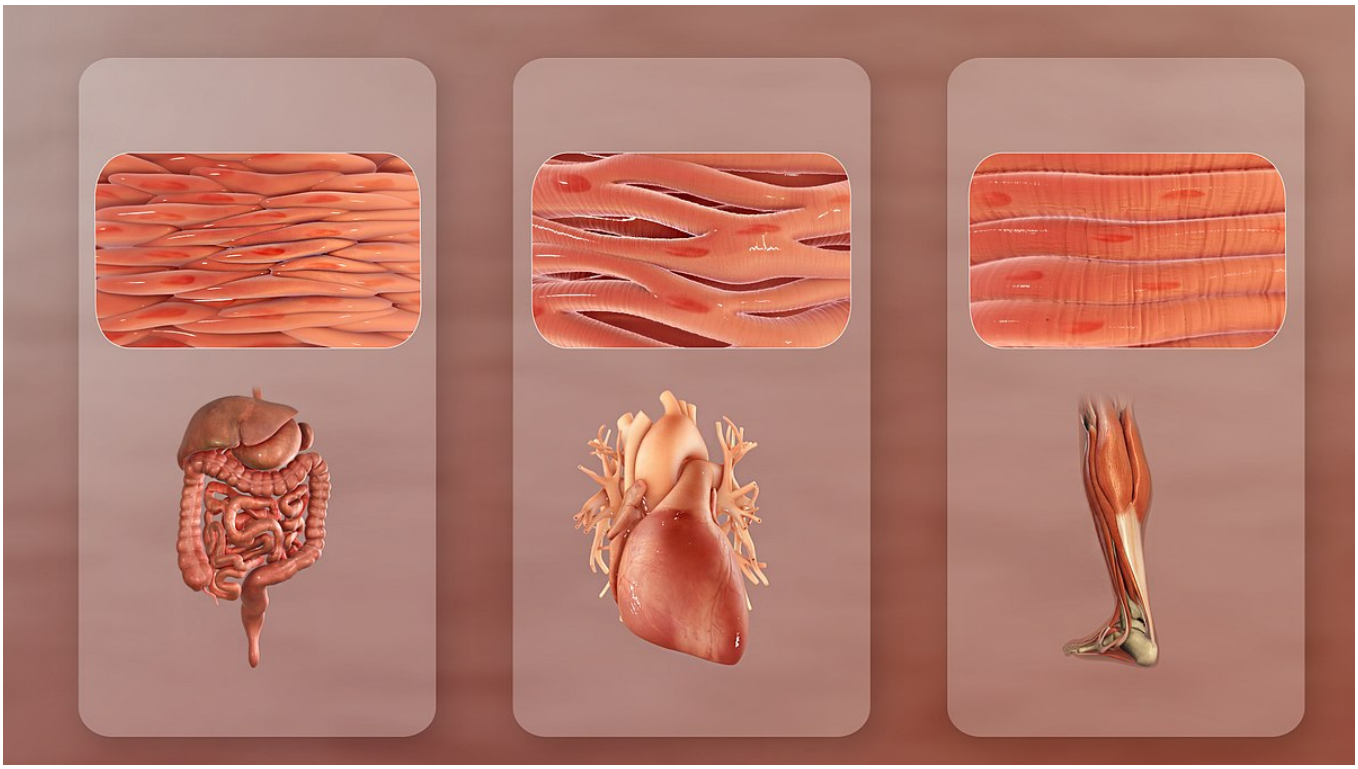


Figure 8.1.2: **Types of Muscle Tissue** (Left) Smooth muscle cells (Center) Cardiac muscle cells (Right) Skeletal muscle cells. (Copyright; Wikimedia Commons, License: CC-BY-SA-4.0)

8.1.2

8.1.2.1 Slow and Fast Twitch Skeletal Muscles

Skeletal muscle fibers can be further subdivided into slow and fast-twitch subtypes depending on their metabolism and corresponding action. Most muscles are made up of combinations of these fibers, although the relative number varies substantially.

8.1.2.1.1 **Slow Twitch**

Slow-twitch fibers are designed for endurance activities that require long-term, repeated contractions, like maintaining posture or running a long distance. These activities require the delivery of large amounts of oxygen to the muscle, which can rapidly become rate-limiting if the respiratory and circulatory systems cannot keep up.

Due to their large oxygen requirements, slow-twitch fibers are associated with large numbers of blood vessels, mitochondria, and high concentrations of myoglobin, an oxygen-binding protein found in the blood that gives muscles their reddish color. One muscle with many slow-twitch fibers is the soleus muscle in the leg (~80% slow-twitch), which plays a key role in standing.

8.1.2.1.2 **Fast Twitch**

Fast-twitch fibers are good for rapid movements like jumping or sprinting that require fast muscle contractions of short duration. As fast-twitch fibers generally do not require oxygenation, they contain fewer blood vessels and mitochondria than slow-twitch fibers and less myoglobin, resulting in a paler color. Muscles controlling eye movements contain high numbers of fast-twitch fibers (~85% fast-twitch).

8.1.3 Attributions

"Muscle Tissue: Key Properties and Classifications" and "Comparison of Structural and Functional Properties of Muscle Types" adapted by Alan Keys from J. Gordon Betts, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix, Anatomy and Physiology, OpenStax. **License:** CC BY 4.0

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8.2: Synaptic Control of Movement- Neuromuscular Junction and Motor Units

Learning Objectives

- Describe the structural and functional aspects of motor neurons and the neuromuscular junction
- Explain the key steps of electrical excitation of muscle fibers
- Apply knowledge of motor units and motor unit recruitment to functional changes in muscle strength

8.2.1 Motor Neurons

Although the neuroanatomy of the motor system will be covered in a later section, it is important to realize that a large portion of the Central and Peripheral Nervous Systems contain collections of neurons that influence motor action in some way. Many of these neurons in the CNS belong to so-called, "motor circuits" and are classified as ***motor*** neurons as opposed to sensory or interneurons. Motor neurons located in cortical and subcortical regions of the forebrain, such as motor and premotor cortex and the basal ganglia are referred to as **Upper Motor Neurons**, while those located in the medulla and spinal cord are the **Lower Motor Neurons**. The function of the Upper Motor Neurons will be addressed in later sections. The Lower Motor Neurons of the spinal cord play a direct role in both triggering voluntary movement and maintaining muscle tone. These are the **Alpha** and **Gamma** motor neurons, respectively.

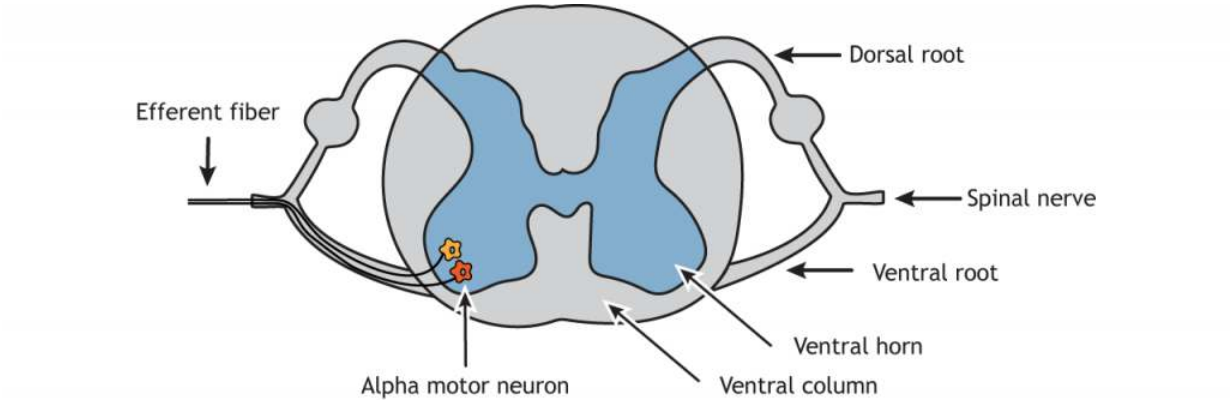


Figure 8.2.1: Alpha motor neurons are located in the ventral (anterior) horn of spinal cord. Their axons, which are efferent fibers, travel to the muscles via spinal nerves. 'Alpha Motor Neurons' by Casey Henley. License: CC BY-NC-SA 4.0 International License.

The cell bodies of the Alpha motor neurons are located in the central nervous system in the ventral (i.e. anterior) horn of the spinal cord. Their axons leave the spinal cord via the ventral roots and travel primarily to skeletal muscle via efferent (outgoing) spinal nerves to cause muscle contraction. Gamma motor neurons function to keep muscle fibers prepared for action by stimulating them in a way to maintain "tautness" or muscle tone. This resting muscle tonus allows the muscle to respond much more effectively to the alpha motor neuron stimulation, thus alpha and gamma neurons work together to maintain a muscle's sensitivity for movement. Just imagine how difficult it would be to shoot a rubber band across a room if it wasn't stretched or taut (Gamma motor neuron influence) prior to letting it go (Alpha motor neuron influence).

8.2.2 The Neuromuscular Junction

A unique specialization of the skeletal muscle is the site where a motor neuron's axon terminal meets the muscle fiber—called the **neuromuscular junction (NMJ)**. This is where the muscle fiber first responds to signaling by the motor neuron. Every skeletal muscle fiber in every skeletal muscle is innervated by a motor neuron at the NMJ. Excitation signals from the neuron are the only way to functionally activate the fiber to contract. It is important to note that one motor neuron can activate multiple muscle fibers due to axonal branching (see the Motor Units section below for more details on this topic).

8.2.2.1 Excitability of Muscle: Excitation-Contraction Coupling

All living cells have membrane potentials, or electrical gradients across their membranes. For example, in neurons which are not being stimulated the membrane potential is approximately -70 mV inside of the cell relative to the outside. This is referred to as a neuron's resting potential.

Although living cells have a cellular membrane, only some, such as neurons and muscle cells are excitable. In other words, they can shift quickly from a resting state to an excited one. Thus, neurons and muscle cells can use their membrane potentials to generate electrical signals. They do this by controlling the movement of charged particles, called ions, across their membranes to create electrical currents. This is achieved by opening and closing specialized proteins in the membrane called ion channels. Although the currents generated by ions moving through these channel proteins are very small, they form the basis of both neural signaling and muscle contraction.

Both neurons and skeletal muscle cells are electrically excitable, meaning that they are able to generate action potentials. An action potential is a special type of electrical signal that can travel along a cell membrane as a wave. This allows a signal to be transmitted quickly and faithfully over long distances.

Although the term **excitation-contraction coupling** confuses or scares some students, it comes down to this: for a skeletal muscle fiber to contract, its membrane must first be "excited"—in other words, it must be stimulated to fire an action potential. The muscle fiber action potential, which sweeps along the muscle fiber as a wave, is "coupled" to the actual contraction through the release of calcium ions (Ca^{++}) from the muscle cells. Once released, the Ca^{++} interacts with the shielding proteins, forcing them to move aside so that the actin-binding sites are available for attachment by myosin heads. The myosin then pulls the actin filaments toward the center, shortening the muscle fiber.

In skeletal muscle, this sequence begins with signals from the somatic motor division of the nervous system. In other words, the "excitation" step in skeletal muscles is always triggered by signaling from the nervous system.

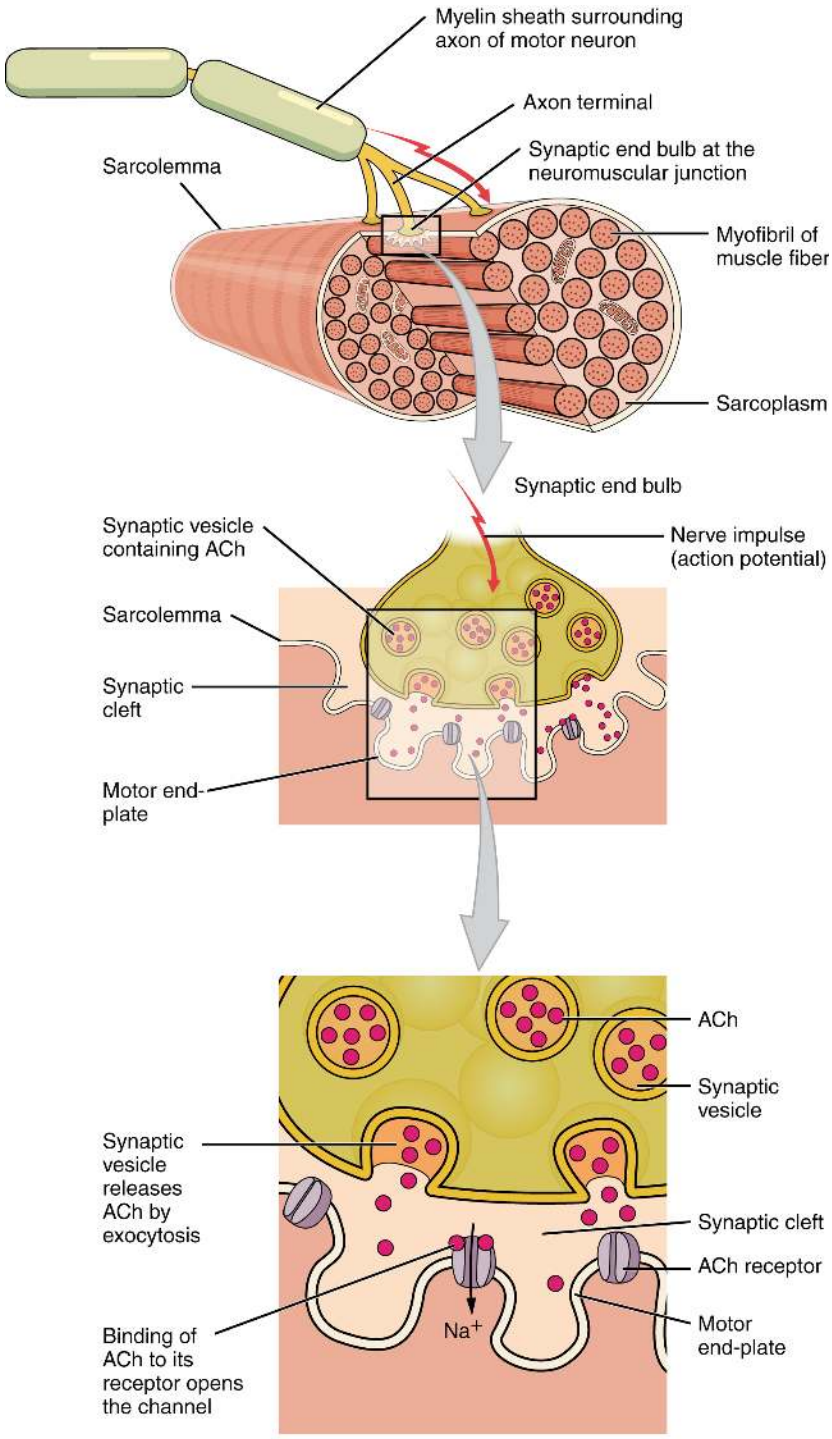


Figure 8.2.2: Motor End-Plate and Innervation at the NMJ, the axon terminal releases the neurotransmitter, Acetylcholine (ACh). The motor end-plate is the location of the ACh-receptors in the muscle fiber sarcolemma. When ACh molecules are released, they diffuse across a minute space called the synaptic cleft and bind to the receptors.

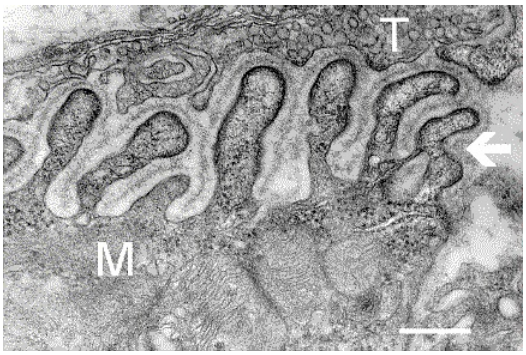


Figure 8.2.3: Electron micrograph showing a cross-section through the neuromuscular junction. T is the axon terminal, M is the muscle fiber. The arrow shows junctional folds with basal lamina. Postsynaptic densities are visible on the tips between the folds. The scale is 0.3 µm. (Wikimedia Commons) License: *Public Domain: No Known Copyright*

Although a small number of motor neurons activating the skeletal muscles of the face, head, and neck are located in the brainstem, most motor neurons originate in the spinal cord, directing skeletal muscle fibers to contract throughout the rest of the body. These neurons have long processes, called axons, which are specialized to transmit action potentials long distances— in this case, all the way from the spinal cord to the muscle itself (which may be up to three feet away). The axons of multiple neurons bundle together to form nerves, like wires bundled together in a cable.

Signaling begins when a neuronal **action potential** travels along the axon of a motor neuron, and then along the individual branches to terminate at the NMJ. At the NMJ, the axon terminal releases a chemical messenger, or **neurotransmitter**, called **acetylcholine (ACh)**. The ACh molecules diffuse across a minute space called the **synaptic cleft** and bind to ACh receptors located within the **motor end-plate** of the sarcolemma on the other side of the synapse. Once ACh binds, a channel in the ACh receptor opens and positively charged ions can pass through into the muscle fiber, causing it to **depolarize**, meaning that the membrane potential of the muscle fiber becomes less negative (closer to zero).

As the membrane depolarizes, another set of ion channels called **voltage-gated sodium channels** are triggered to open. Sodium ions enter the muscle fiber, and an action potential rapidly spreads (or "fires") along the entire membrane to initiate excitation-contraction coupling.

Things happen very quickly in the world of excitable membranes (just think about how quickly you can snap your fingers as soon as you decide to do it). Immediately following depolarization of the membrane, it repolarizes, re-establishing the negative membrane potential. Meanwhile, the ACh in the synaptic cleft is degraded by the enzyme acetylcholinesterase (AChE) so that the ACh cannot rebind to a receptor and reopen its channel, which would cause unwanted extended muscle excitation and contraction.

Propagation of an action potential along the sarcolemma is the excitation portion of excitation-contraction coupling.This excitation actually triggers the release of Calcium ions (Ca^{++}) from their storage in the cell's sacroplasmic reticulum (SR). For the action potential to reach the membrane of the SR, there are periodic invaginations in the sarcolemma, called **T-tubules** ("T" stands for "transverse"). The diameter of a muscle fiber can be up to 100 μm, so these T-tubules ensure that the membrane can get close to the SR in the sarcoplasm. The arrangement of a T-tubule with the membranes of SR on either side is called a **triad**. The triad surrounds the cylindrical structure called a **myofibril**, which contains actin and myosin.

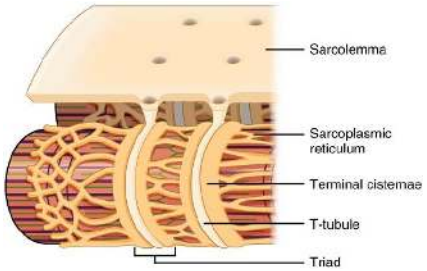


Figure 8.2.4: The T-tubule: Narrow T-tubules permit the conduction of electrical impulses. The SR functions to regulate intracellular levels of calcium. Two terminal cisternae (where enlarged SR connects to the T-tubule) and one T-tubule comprise a triad—a "threesome" of membranes, with those of SR on two sides and the T-tubule sandwiched between them.

The T-tubules carry the action potential into the interior of the cell, which triggers the opening of calcium channels in the membrane of the adjacent SR, causing Ca^{++} to diffuse out of the SR and into the sarcoplasm. It is the arrival of Ca^{++} in the sarcoplasm that initiates contraction of the muscle fiber by its contractile units, or sarcomeres.

8.2.3 Motor Units

As described in the Neuromuscular Junction section above, every skeletal muscle fiber is innervated by an axon terminal of a motor neuron in order to contract. Each muscle fiber is innervated by only one motor neuron, but each motor neuron innervates a group of muscle fibers due to the axon's ability to branch. Recall that the NMJ is the point of connection between each axon terminal and it's corresponding muscle fiber. A motor neuron and the group of muscle fibers in a muscle that it innervates is called a **motor unit**. The size of a motor unit is variable depending on the nature of the muscle.

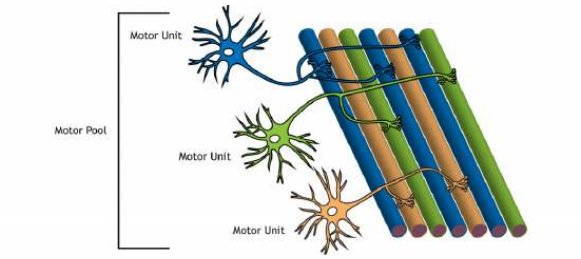


Figure 8.2.5: Motor neurons can innervate more than one muscle fiber within a muscle. The motor neuron and the fibers it innervates are a motor unit. Three motor units are shown in the image: one blue, one green, one orange. Those three motor units innervate all the muscles fibers in the muscle and are the motor pool for that muscle. 'Motor Unit and Pool'by Casey Henley. License: CC BY-NC-SA 4.0 International License.

A small motor unit is an arrangement where a single motor neuron supplies a small number of muscle fibers in a muscle. Small motor units permit very fine motor control of the muscle. The best example in humans is the small motor units of the extraocular eye muscles that move the eyeballs. There are thousands of muscle fibers in each muscle, but every six or so fibers are supplied by a single motor neuron, as the axons branch to form synaptic connections at their individual NMJs. This allows for exquisite control of eye movements so that both eyes can quickly focus on the same object. Small motor units are also involved in the many fine movements of the fingers and thumb of the hand for grasping, texting, etc.

A large motor unit is an arrangement where a single motor neuron supplies a large number of muscle fibers in a muscle. Large motor units are concerned with simple, or "gross," movements, such as powerfully extending the knee joint. The best example is the large motor units of the thigh muscles or back muscles, where a single motor neuron will supply thousands of muscle fibers in a muscle, as its axon splits into thousands of branches.

There is a wide range of motor units within many skeletal muscles, which gives the nervous system a wide range of control over the muscle. The small motor units in the muscle will have smaller, lower-threshold motor neurons that are more excitable, firing first to their skeletal muscle fibers, which also tend to be the smallest. Activation of these smaller motor units results in a relatively small degree of contractile strength (tension) generated in the muscle. As more strength is needed, larger motor units, with bigger, higher-threshold motor neurons, are enlisted to activate larger muscle fibers. This increasing activation of motor units produces an increase in muscle contraction known as **recruitment**.

As more motor units are recruited, muscle contraction grows progressively stronger. In some muscles, the largest motor units may generate a contractile force of 50 times more than the smallest motor units in the muscle. This allows a feather to be picked up using the biceps brachii arm muscle with minimal force, and a heavy weight to be lifted by the same muscle by recruiting the largest motor units.

When necessary, the maximal number of motor units in a muscle can be recruited simultaneously, producing the maximum force of contraction for that muscle, but this cannot last for very long because of the energy requirements to sustain the contraction. To prevent complete muscle fatigue, motor units are generally not all simultaneously active, but instead some motor units rest while others are active, which allows for longer muscle contractions. The nervous system uses recruitment as a mechanism to efficiently utilize a skeletal muscle.

8.2.4 Attributions

- Sections on Motor Neurons, Neuromuscular Junction, and Motor Units adapted from J. Gordon Betts, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix, Anatomy and Physiology, OpenStax. **License:** CC BY 4.0
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8.3: Spinal Reflexes

Learning Objectives

- Distinguish between the types of spinal reflexes

Spinal reflexes include the stretch reflex, the Golgi tendon reflex, the crossed extensor reflex, and the withdrawal reflex.

8.3.1 Stretch Reflex

The stretch reflex (myotatic reflex) is a muscle contraction in response to stretching within the muscle. This reflex has the shortest latency of all spinal reflexes. It is a monosynaptic reflex that provides automatic regulation of skeletal muscle length.

When a muscle lengthens, the muscle spindle is stretched and its nerve activity increases. This increases alpha motor neuron activity, causing the muscle fibers to contract and thus resist the stretching. A secondary set of neurons also causes the opposing muscle to relax. The reflex functions to maintain the muscle at a constant length.

8.3.2 Golgi Tendon Reflex

The Golgi tendon reflex is a normal component of the reflex arc of the peripheral nervous system. The tendon reflex operates as a feedback mechanism to control muscle tension by causing muscle relaxation before muscle force becomes so great that tendons might be torn.

Although the tendon reflex is less sensitive than the stretch reflex, it can override the stretch reflex when tension is great, making you drop a very heavy weight, for example. Like the stretch reflex, the tendon reflex is ipsilateral.

The sensory receptors for this reflex are called Golgi tendon receptors, and lie within a tendon near its junction with a muscle. In contrast to muscle spindles, which are sensitive to changes in muscle length, tendon organs detect and respond to changes in muscle tension that are caused by a passive stretch or muscular contraction.

8.3.3 Crossed Extensor Reflex



Jendrassik maneuver: The Jendrassik maneuver is a medical maneuver wherein the patient flexes both sets of fingers into a hook-like form and interlocks those sets of fingers together (note the hands of the patient in the chair). This maneuver is used often when testing the patellar reflex, as it forces the patient to concentrate on the interlocking of the fingers and prevents conscious inhibition or influence of the reflex.

The crossed extensor reflex is a withdrawal reflex. The reflex occurs when the flexors in the withdrawing limb contract and the extensors relax, while in the other limb, the opposite occurs. An example of this is when a person steps on a nail, the leg that is

stepping on the nail pulls away, while the other leg takes the weight of the whole body.

The crossed extensor reflex is contralateral, meaning the reflex occurs on the opposite side of the body from the stimulus. To produce this reflex, branches of the afferent nerve fibers cross from the stimulated side of the body to the contralateral side of the spinal cord. There, they synapse with interneurons, which in turn, excite or inhibit alpha motor neurons to the muscles of the contralateral limb.

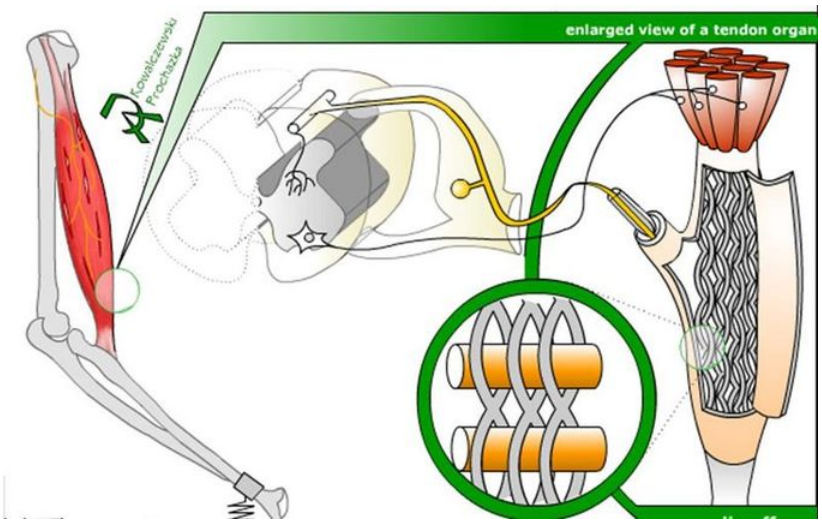
8.3.4 Withdrawal Reflex

The withdrawal reflex (nociceptive or flexor withdrawal reflex) is a spinal reflex intended to protect the body from damaging stimuli. It is polysynaptic, and causes the stimulation of sensory, association, and motor neurons.

When a person touches a hot object and withdraws his hand from it without thinking about it, the heat stimulates temperature and danger receptors in the skin, triggering a sensory impulse that travels to the central nervous system. The sensory neuron then synapses with interneurons that connect to motor neurons. Some of these send motor impulses to the flexors to allow withdrawal.

Some motor neurons send inhibitory impulses to the extensors so flexion is not inhibited—this is referred to as reciprocal innervation. Although this is a reflex, there are two interesting aspects to it:

1. The body can be trained to override that reflex.
2. An unconscious body (or even drunk or drugged bodies) will not exhibit the reflex.



Golgi tendon organ: The Golgi tendon organ, responsible for the Golgi tendon reflex, is diagrammed with its typical position in a muscle (left), neuronal connections in spinal cord (middle), and expanded schematic (right). The tendon organ is a stretch receptor that signals the amount of force on the muscle and protects the muscle from excessively heavy loads by causing the muscle to relax and drop the load.

8.3.5 Summary

- The stretch reflex is a monosynaptic reflex that regulates muscle length through neuronal stimulation at the muscle spindle. The alpha motor neurons resist stretching by causing contraction, and the gamma motor neurons control the sensitivity of the reflex.
- The stretch and Golgi tendon reflexes work in tandem to control muscle length and tension. Both are examples of ipsilateral reflexes, meaning the reflex occurs on the same side of the body as the stimulus.
- The crossed extensor reflex is a contralateral reflex that allows the body to compensate on one side for a stimulus on the other. For example, when one foot steps on a nail, the crossed extensor reflex shifts the body's weight onto the other foot, protecting and withdrawing the foot on the nail.
- The withdrawal reflex and the more-specific pain withdrawal reflex involve withdrawal in response to a stimulus (or pain). When pain receptors, called nociceptors, are stimulated, reciprocal innervations stimulate the flexors to withdraw and inhibit the extensors to ensure they are unable to prevent flexion and withdrawal.

8.3.6 ATTRIBUTIONS

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8.4: Motor Circuitry- Neural Structures and Pathways

Learning Objectives

- Identify the main structures of neural motor circuits at the cortical, subcortical, and spinal levels
- Describe the main functional roles of the basal ganglia, premotor area, and motor cortex
- Apply knowledge of functional cortical anatomy to the control of fine and gross body movements

8.4.1 Neuroanatomy of Motor Systems

The motor system controls all of our skeletal muscle movement and more. There are multiple levels of control. Within the spinal cord, simple reflexes can function without higher input from the brain. Slightly more complex spinal control occurs when central pattern generators function during repetitive movements like walking. The motor, premotor and supplementary cortices in the brain are responsible for the planning and execution of voluntary movements. And finally, the basal ganglia and cerebellum modulate the responses of the neurons in the motor cortex to help with coordination, motor learning, and balance.

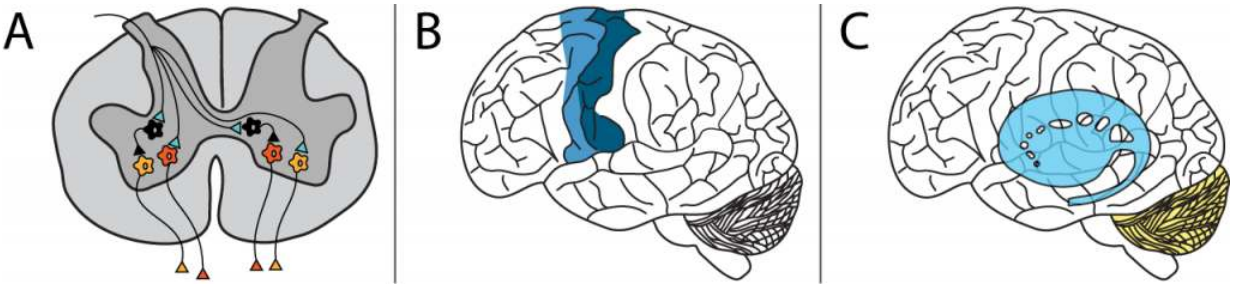


Figure 8.4.1: Motor output is controlled at multiple levels: A. Spinal cord and spinal neurons, B. Motor (dark blue) and premotor/supplementary motor cortices (light blue with supplementary motor located in top portion), C. Basal ganglia (a subcortical structure shown in light blue) and cerebellum (yellow). 'Motor Control Levels' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.

8.4.1.1 Cortical Anatomy of Movement

Much of the cortex is actually involved in the planning of voluntary movement. Sensory information, particularly the dorsal stream of the visual and somatosensory pathways, is processed in the posterior parietal cortex where visual, tactile, and proprioceptive information is integrated.

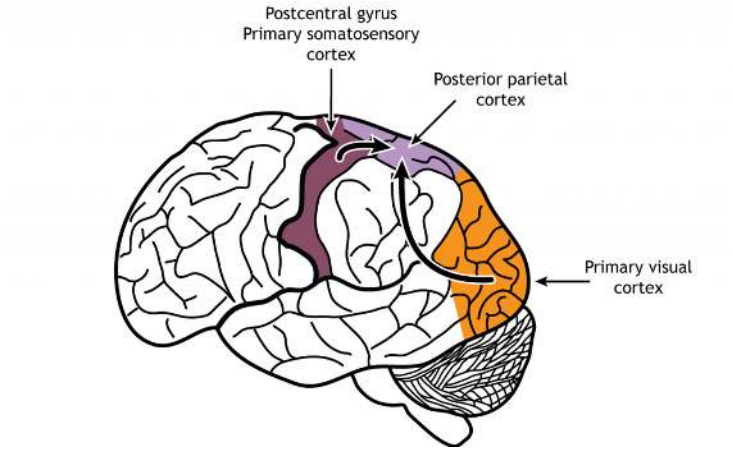


Figure 8.4.2: Information from multiple sensory systems is processed in the posterior parietal cortex. Projections are sent from the primary somatosensory and primary visual cortices. 'Posterior Parietal by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.

Connections from the posterior parietal cortex are then sent to both the premotor regions and the prefrontal cortex. The prefrontal cortex, which is located in the front of the brain in the frontal lobe, plays an important role in higher level cognitive functions like planning, critical thinking, and understanding the consequences of our behaviors. The premotor area lies just anterior to the primary

motor cortex. This region helps plan and organize movement and makes decisions about which actions should be used for a situation.

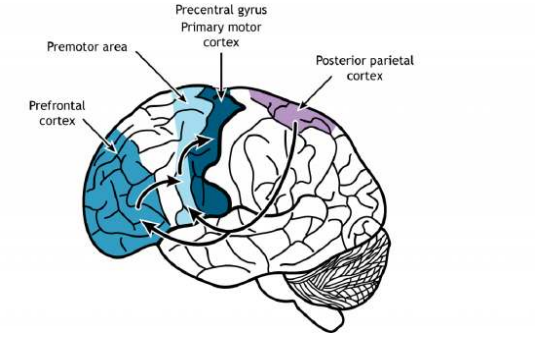


Figure 8.4.3: Sensory information from the posterior parietal cortex is processed in the prefrontal cortex and premotor area, both located in the frontal cortex. These areas then send information to the primary motor cortex located in the precentral gyrus. 'Motor Regions' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.

8.4.1.1.1 Role of Premotor Area

The premotor regions send some axons directly to lower motor neurons in the spinal cord using the same pathways as the motor cortex. However, the premotor cortex also plays an important role in the planning of movement. Two experimental designs have demonstrated this role. Monkeys were trained on a panel that had one set of lights in a row on top and one set of buttons that could also light up in a row on the bottom. The monkeys would watch for a top row light to turn on. This would indicate that within a few seconds, the button directly below would light up. When the button turned on, the monkeys were supposed to push the button.

Therefore, there were two light triggers in the experiment. The first required no motor movement from the monkey but did give the monkey information about where a motor movement would be needed in the near future. The second required the monkey to move to push the button. When brain activity was measured during this study, neurons in the premotor cortex became active when the first light trigger turned on, well before any movement actually took place (Weinrich and Wise, 1928).

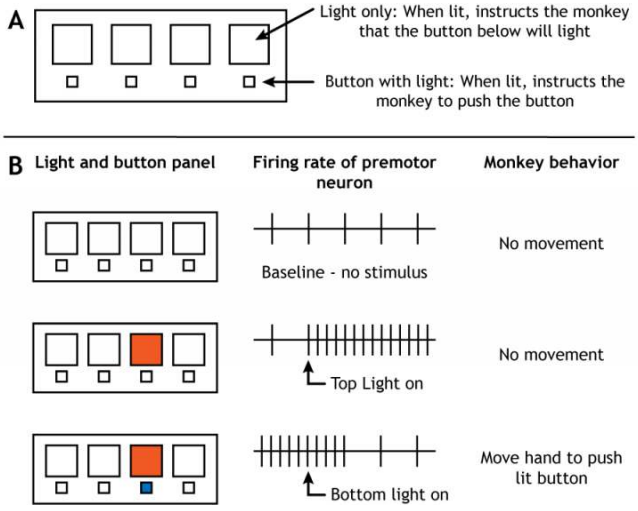


Figure 8.4.4: (A) Monkeys were trained to use a light panel. When lit, a light located in the top row informed the monkey that the button directly below would light up soon. Shortly after one of the top row lights turned on, the button directly below it would turn on, and the monkey would need to push that button for a reward. (B) When no lights are lit, premotor neurons fire at a baseline rate, and the monkey does not move. Neurons located in the premotor cortex increase action potential firing rate when the top row light turns on, even though the monkey makes no movement. The firing stops shortly after the monkey moves to push the bottom button after it turns on. (Based on Weinrich and Wise, 1928) 'Light Panel Experiment' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.

In another experiment, people were trained to move their fingers in a specific pattern. Cerebral blood flow was then measured when they repeated the finger pattern and when they only imagined repeating the finger pattern. When the movement was only imagined and not actually executed, the premotor regions along with parts of the prefrontal cortex were activated (Roland, et al, 1980).

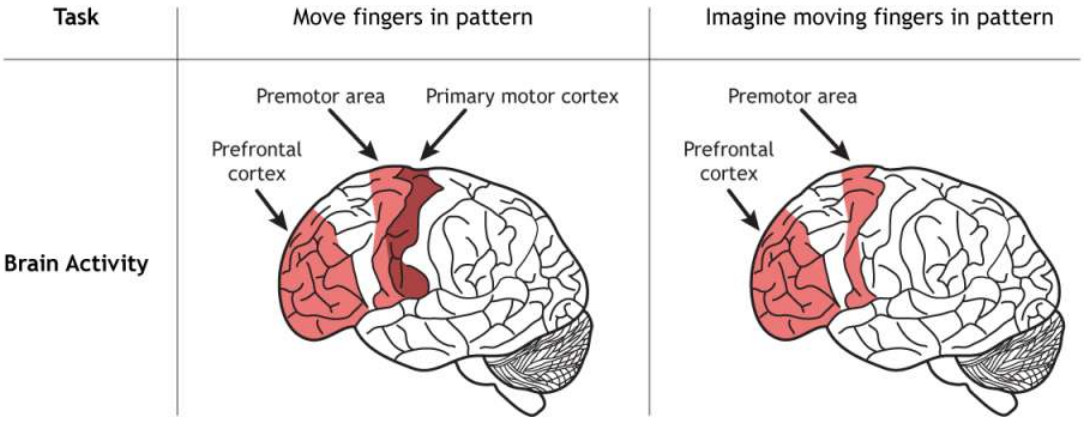


Figure 8.4.5: People were trained to move their fingers in a pattern. When the pattern was repeated, brain activity was seen in the primary motor cortex, along with the premotor area and prefrontal cortex. When the pattern was only imagined, and no finger movement took place, brain activity was seen in the premotor area and prefrontal cortex. (Based on Roland, et al, 1980) 'Finger Movement Experiment' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.

These studies show that the premotor cortex is active prior to the execution of movement, indicating that it plays an important role in the planning of movement. The posterior parietal, prefrontal, and premotor regions, though, also communicate with a subcortical region called the basal ganglia to fully construct the movement plan. The basal ganglia are covered in the next subsection.

8.4.1.1.2 Role of Motor Cortex

Once the plan for movement has been created, the primary motor cortex is responsible for the execution of that action. The primary motor cortex lies just anterior to the primary somatosensory cortex in the precentral gyrus located in the frontal lobe.

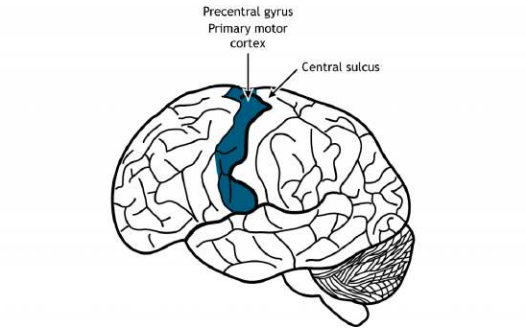


Figure 8.4.6: The primary motor cortex is located in the frontal lobe in the precentral gyrus, just anterior to the central sulcus. 'Primary Motor Cortex' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.

Like the somatosensory cortex, the motor cortex is organized by a somatotopic map in that different areas of the body are controlled by distinct areas of the motor cortex. However, the motor cortex does not map onto the body in such an exact way as does the somatosensory system. It is believed that upper motor neurons in the motor cortex control multiple lower motor neurons in the spinal cord that innervate multiple muscles. This results in activation of an upper motor neuron causing excitation or inhibition in different neurons at once, indicating that the primary motor cortex is responsible for movements and not simply activation of one muscle. Stimulation of motor neurons in monkeys can lead to complex motions like bringing the hand to the mouth or moving into a defensive position (Graziano et al, 2005).

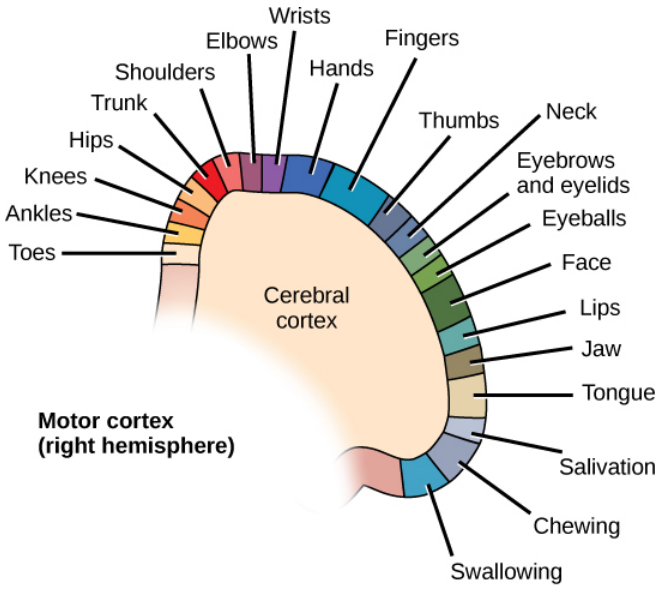


Figure 8.4.7: Different regions of the motor cortex control different muscle groups and their neighboring regions control neighboring muscle groups. Although the right hemisphere is shown, a mirror-image exists in the left hemisphere as well. Note that all areas of the body that have voluntary motor control are represented on the primary motor cortex. License: CC BY 4.0, via Wikimedia Commons

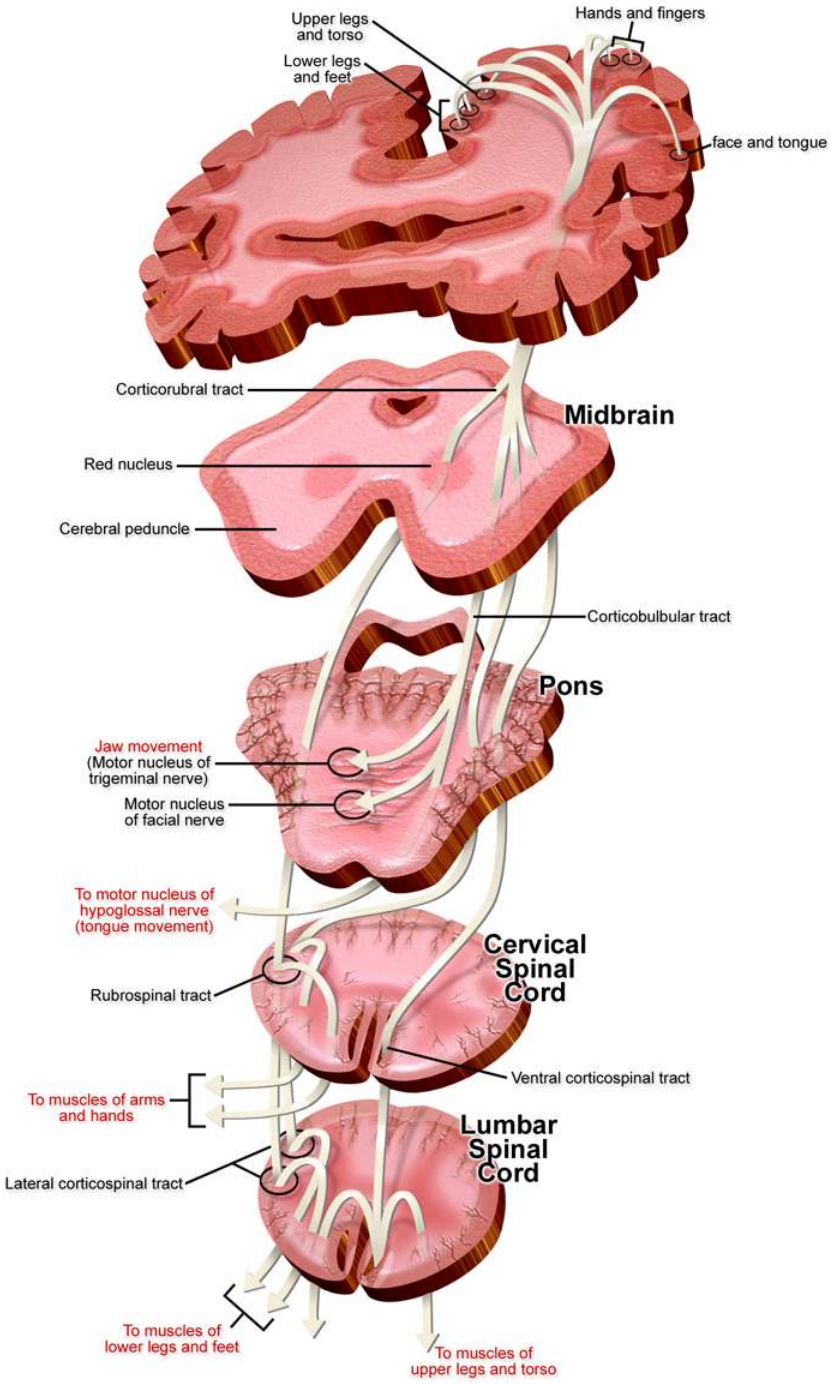


Figure 8.4.8: Descending Motor Pathways from Primary Motor Cortex to Spinal Cord. By BruceBlaus CC BY-SA 4.0, via Wikimedia Commons

8.4.1.2 Basal Ganglia

The basal ganglia are a group of subcortical nuclei, meaning groups of neurons that lie below the cerebral cortex. The basal ganglia is comprised of several nuclei including the caudate nucleus, putamen, and the globus pallidus. Another nucleus typically associated with the basal ganglia is the subthalamic nucleus. The substantia nigra of the midbrain provides dopaminergic input to these areas.

The basal ganglia are primarily associated with motor control, since motor disorders, such as Parkinson's or Huntington's diseases stem from dysfunction of neurons within the basal ganglia. For voluntary motor behavior, the basal ganglia are involved in the

initiation or suppression of behavior and can regulate movement through modulating activity in the thalamus and cortex. In addition to motor control, the basal ganglia also communicate with non-motor regions of the cerebral cortex and play a role in other behaviors such as emotional and cognitive processing.

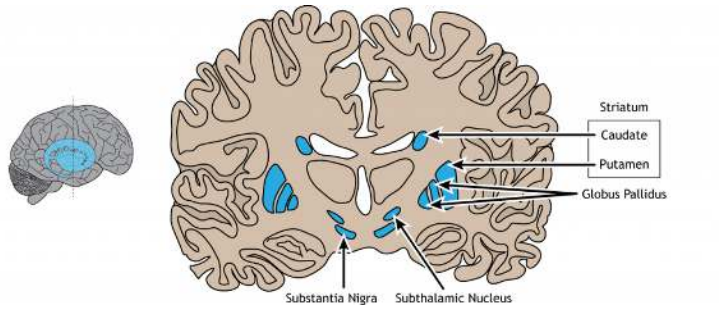


Figure 8.4.9: The basal ganglia are subcortical structures located at the base of the forebrain. They are comprised of the caudate and putamen, which both make up the striatum, as well as the globus pallidus, substantia nigra, and subthalamic nucleus. 'Basal Ganglia' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.

8.4.1.2.3 **Basal Ganglia Input**

The majority of information processed by the basal ganglia enters through the striatum. The principal source of input to the basal ganglia is from the cerebral cortex. This input is glutamatergic (i.e. uses glutamate as its neurotransmitter) and therefore, excitatory. The substantia nigra is also a region with critical projections to the striatum and is the main source of dopaminergic input. Dopamine plays an important role in basal ganglia function. Parkinson's disease results when dopamine neurons in the substantia nigra degenerate and no longer send appropriate inputs to the striatum. Dopamine projections can have either excitatory or inhibitory effects in the striatum, depending on the type of metabotropic dopamine receptor the striatal neuron expresses. Dopamine action at a neuron that expresses the D1 receptor is excitatory. Dopamine action at a neuron that expresses the D2 receptor is inhibitory.

8.4.1.2.4 **Basal Ganglia Output**

The primary output region of the basal ganglia is the internal segment of the globus pallidus. This region sends inhibitory GABAergic projections to nuclei in the thalamus. This inhibitory output has a tonic, constant firing rate, which allows the basal ganglia output to both increase and decrease depending on the situation. The thalamus then projects back out to the cerebral cortex, primarily to motor areas.

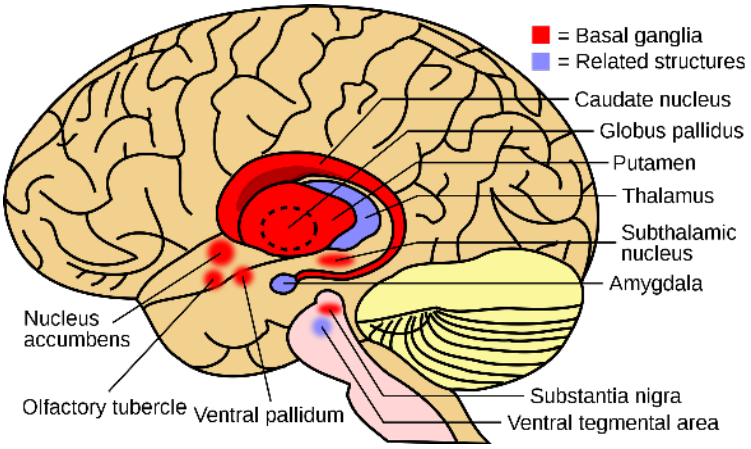


Figure 8.4.10: Basal Ganglia and Associated Structures. CC BY-SA 4.0, via Wikimedia Commons

8.4.2 Attributions:

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8.5: Impact of Disease States and Neural Damage on Motor Control

Learning Objectives

- Describe the general symptoms of the major motor disorders of the nervous system
- Categorize motor disorders based on their underlying neuroantomical or neurochemical mechanisms
- Explain some of the treatments for some of the major disorders

8.5.1 Motor Disorders and Their Neuroanatomical/Neurochemical Mechanisms

Given that motor control involves such an extensive collection of structures and circuits throughout both the central and peripheral nervous systems, it is amazing how well and, often effortlessly, these systems function every second of our lives. However, the comprehensive nature of motor systems also allows for multiple avenues of potential damage or degeneration which can lead to profound consequences in one's ability to move or even survive.

Damage or disease can occur in regions of the forebrain associated with Upper Motor Neurons in the cortex or the basal ganglia, and/or Lower Motor Neuron regions of the medulla or spinal cord. These anatomical distinctions can be critical in the diagnosis and treatment of specific motor disorders.

8.5.1.1 **Multiple Sclerosis**

Multiple sclerosis (MS) is a progressive motor disease that attacks neurons in both the central and peripheral nervous systems. The main mode of this attack is the destruction of the myelin coating around the axon which ultimately will slow down action potential conductance. As axons are demyelinated, inflammatory patches called lesions are formed. As the disease progresses, the myelin-producing oligodendrocytes and, ultimately, the axons themselves are destroyed. There is compelling evidence that the destruction is caused by selective activation of the cellular immune system and inflammatory molecules, thus supporting the idea that MS is an autoimmune disease.

Findings from MRI studies indicate that an individual with MS may have abnormalities around sites like the lateral ventricle, optic nerve, brainstem, spinal cord, cerebellum and other areas (see Figure 8.5.1 below).

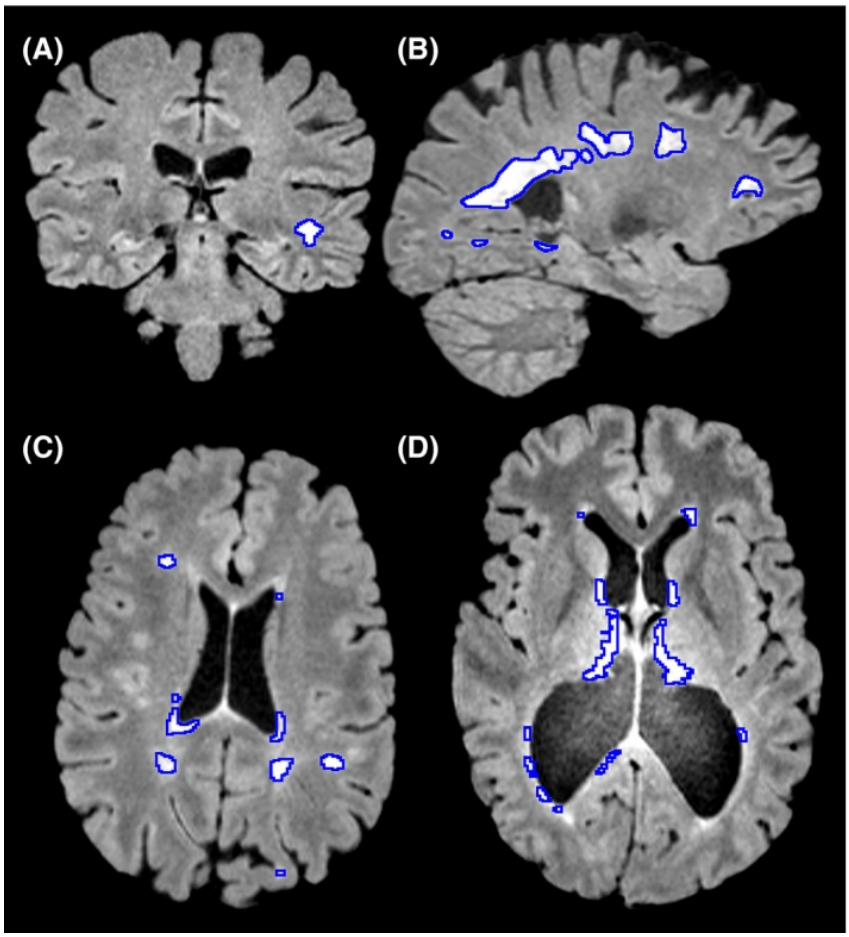


Figure 8.5.1: MRI images showing white hyperintensities in different areas of the brain of an individual experiencing symptoms of multiple sclerosis. (A) A coronal slice showing a lesion in peripheral white matter. (B) A sagittal slice showing large periventricular lesions. (C) An axial slice showing both periventricular and peripheral white matter lesions. (D) A case where severe atrophy caused midline false positives to not be removed, as they were further from midline than expected. Image from National Library of Medicine. License: CC BY 4.0.

8.5.1.1.1 Symptoms of MS

Multiple sclerosis also presents itself differently in acute and chronic phases. During the acute phase, the condition is associated with intermittent symptoms, whereas the chronic phase is associated with progressive forms of the disease and increased severity of symptoms.

Most people experience their first symptoms of MS between the ages of 20 and 40 with initial blurred or double vision, red-green color distortion, or even blindness in one eye. Most MS patients also experience muscle weakness in their extremities and difficulty with coordination and balance. These symptoms may be severe enough to impair walking or even standing. In the worst cases, MS can produce partial or complete paralysis.

Most people with MS also exhibit paresthesias, transitory abnormal sensory feelings such as numbness, prickling, or "pins and needles" sensations. Some may also experience pain. Speech impediments, tremors, and dizziness are other frequent complaints. Occasionally, people with MS have hearing loss. Approximately half of all people with MS experience cognitive impairments such as difficulties with concentration, attention, memory, and poor judgment, but such symptoms are usually mild and are frequently overlooked. Depression is another common feature of MS.

8.5.1.1.2 **Potential Causes of MS**

Currently, there is no known cause for MS although many different hypotheses have been put forward. Surprisingly, there are no known associative genes that have been implicated in causing MS, and scientists believe there might be a complex interaction between genes and environmental factors that produce demyelination. The most common theories about the cause(s) of multiple sclerosis include:

1. Viral infection resulting in an autoimmune reaction
2. Genetic factors: inherited predisposition possibly through the immune system, although a mutation in a gene has not been discovered
3. Environmental factor(s) which might work with genetics such as low vitamin D levels or smoking.

Although this is a well-characterized disorder, we still don't know much about its causes.

8.5.1.2 **Parkinson's Disease**

Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which cause unintended or uncontrollable movements of the body. The precise cause of PD is unknown, but some cases are hereditary while others are thought to occur from a combination of genetics and environmental factors that trigger the disease. In PD, brain cells become damaged or die in the substantia nigra which produces the neurotransmitter dopamine--a chemical needed to produce smooth, purposeful movement.

8.5.1.2.1 Symptoms of PD

The four primary symptoms of PD are:

- tremor--shaking that has a characteristic rhythmic back and forth motion
- rigidity--muscle stiffness or a resistance to movement, where muscles remain constantly tense and contracted
- bradykinesia--slowing of spontaneous and automatic movement that can make it difficult to perform simple tasks or rapidly perform routine movements
- postural instability--impaired balance and changes in posture that can increase the risk of falls.

Other symptoms may include difficulty swallowing, chewing, or speaking; emotional changes; urinary problems or constipation; dementia or other cognitive problems; fatigue; and problems sleeping.

PD usually affects people around the age of 70 years but can occur earlier. PD affects men more than women. Currently there are no specific tests that diagnose sporadic PD.

8.5.1.2.2 **Potential causes of PD**

The current model for most neurodegenerative conditions is that neurons die via apoptosis, a programmed form of cell death. Although this type of cell death occurs during normal development, neurodegenerative diseases such as Parkinson's Disease and Alzheimer's Disease are believed to use apoptotic pathways. This suggests that there is a component protein that is aberrantly folded to produce apoptosis. This has very important clinical implications as turning on or turning off specific genes/proteins is a method to stop or possibly reverse neurodegeneration.

Most cases of this disorder appear to be sporadic (i.e. non-genetic in origin) although a very few cases seem to have a genetic origin. Parkinson's Disease is most often associated with the loss of "pigmented" nuclei in the brain and typically involves the loss of a group of neurons found in the substantia nigra (see Figure 8.5.2). The substantia nigra neurons are dopaminergic and are pigmented because they contain the protein *melanin*.

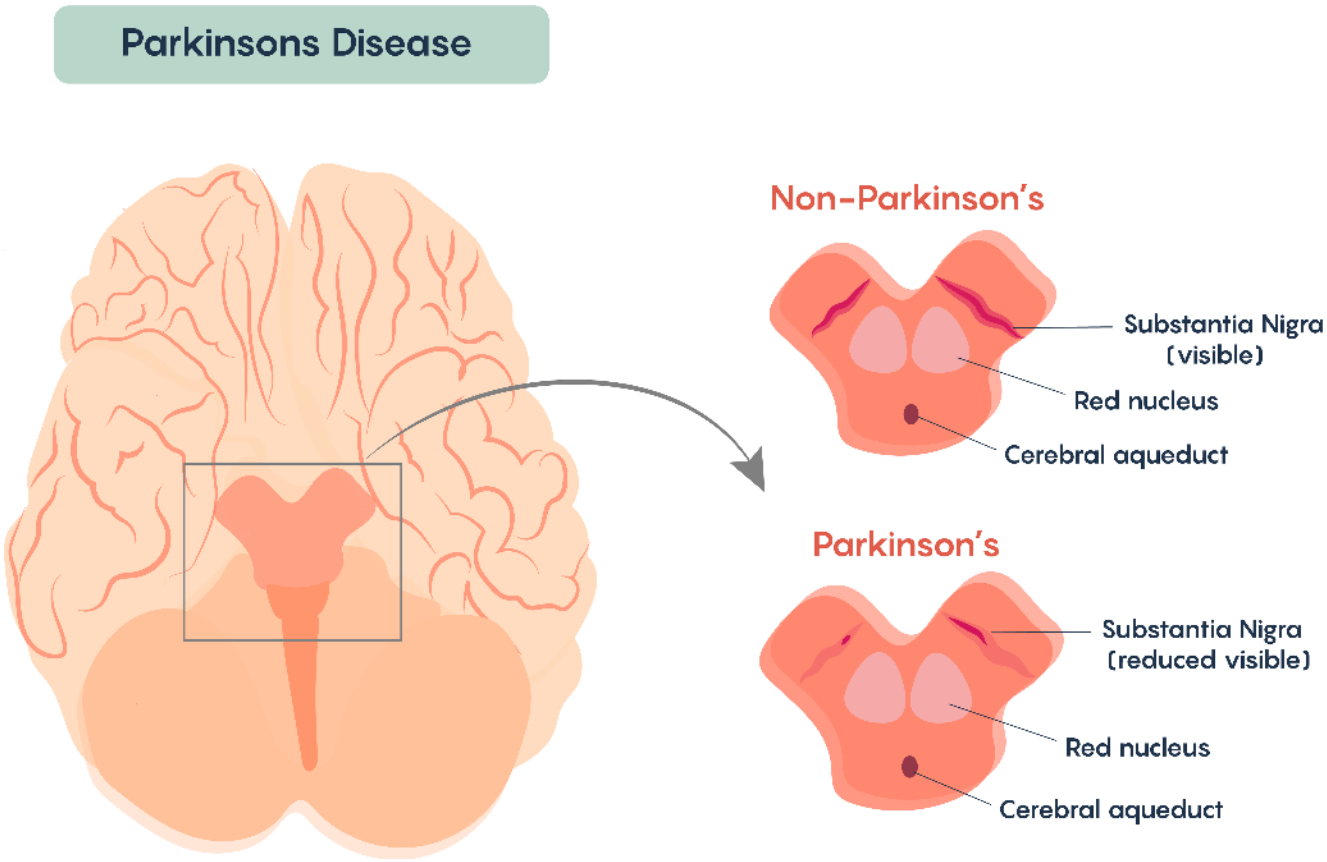


Figure 8.5.2: Loss of the pigmented dopaminergic neurons within the Substantia Nigra of individuals with Parkinson's Disease.

Loss of the substantia nigra cells affects the processing and execution of voluntary movement in individuals with Parkinson's Disease. Similar to MS, once diagnosed, the symptoms become continuous and progressive – i.e. the symptoms worsen over time. Again, there are many similarities with MS, and there is no known cure for Parkinson's Disease. The disease remains idiopathic although there are some known causes of Parkinson's Disease including loss of movement following cerebral atherosclerosis, viral encephalitis, and as the result of side effects from drugs such as phenothiazides and reserpine.

Alpha-synuclein is a naturally occurring protein within neurons. Mutations in the PARK1 and PARK4 genes which normally encodes for alpha-synuclein have been associated with Parkinson's Disease. As such, many animal models of Parkinson's Disease look for the production of the fibrillary form of alpha-synuclein as it misfolds and then accumulates within the substantia nigral neurons known as Lewy bodies (see Figure 8.5.3). The misfolding and accumulation of alpha-synuclein has been hypothesized to be the reason that neurons undergo apoptosis, although the exact mechanism for how this occurs remains to be elucidated.

Lewy bodies and alpha-synuclein – hallmark features of Parkinson's Disease

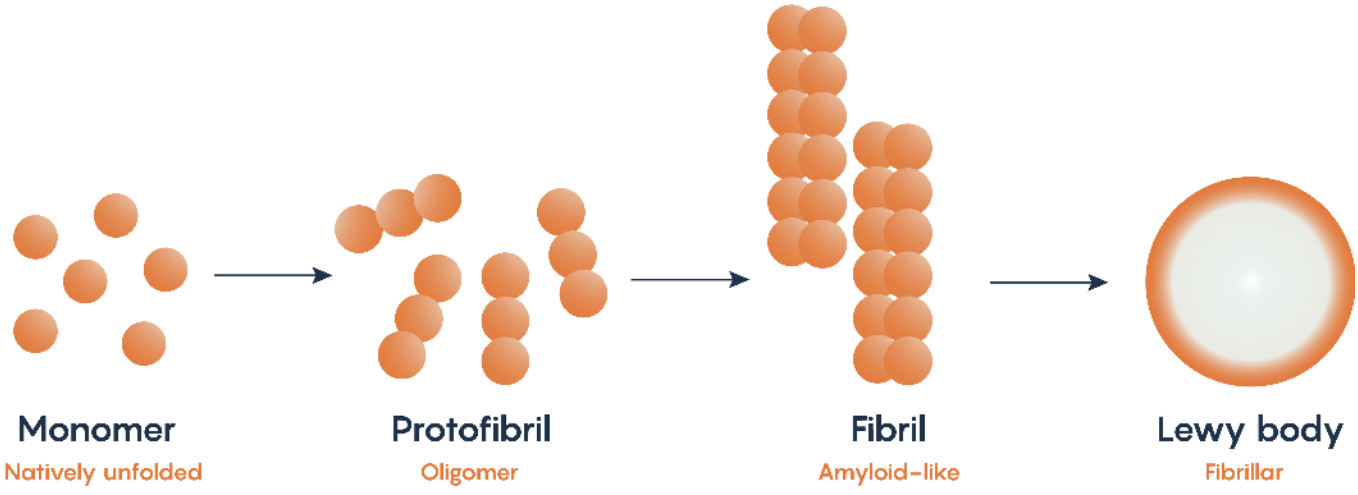


Figure 8.5.3:*Misfolding and subsequent accumulation of alpha-synuclein.*

8.5.1.2.3 Treatment of PD

At present, there is no cure for PD, but a variety of medications provide dramatic relief from the symptoms. Usually, affected individuals are given levodopa (l-dopa) combined with carbidopa. Carbidopa delays the conversion of levodopa into dopamine until it reaches the brain. Nerve cells can use levodopa to make dopamine and replenish the brain's dwindling supply. Although levodopa helps most people with PD, not everyone responds equally to the drug. The symptoms of bradykinesia and rigidity respond best, while tremor may be only marginally reduced. Problems with balance and other symptoms may not be alleviated at all.

There are a large variety of other drugs that affect the dopamine system and treat symptoms of PD. Some mimic the role of dopamine in the brain, causing the nerve cells to react as they would to dopamine, while others prolong the effects of levodopa by preventing the breakdown of dopamine in the brain. In addition to these dopaminergic drugs, anticholinergic drugs have been shown to help control symptoms of tremor and rigidity.

In some cases, surgery may be appropriate if the disease doesn't respond to drugs. One option is deep brain stimulation (DBS), in which electrodes are implanted into the brain and connected to a small electrical device called a pulse generator to painlessly stimulate the brain to block signals that cause many of the motor symptoms of PD. DBS is generally appropriate for people with levodopa-responsive PD who have developed dyskinesias or other disabling "off" symptoms despite drug therapy. However, DBS does not stop PD from progressing and some problems may gradually return.

8.5.1.3 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.

8.5.1.3.1 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.

8.5.1.3.2 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.

8.5.1.3.3 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.

8.5.1.4 Amyotrophic lateral sclerosis (Formally known as Lou Gehrig's Disease)

Amyotrophic lateral sclerosis (ALS) is a rare neurological disease that primarily affects the neurons responsible for controlling voluntary muscle movement. Voluntary muscles produce movements like chewing, walking, and talking. The disease is progressive, meaning the symptoms get worse over time. Currently, there is no cure for ALS and no effective treatment to halt or reverse the progression of the disease.

ALS belongs to a wider group of disorders known as motor neuron diseases, which are caused by gradual deterioration (degeneration) and death of motor neurons. As motor neurons degenerate, they stop sending messages to the muscles and the muscles gradually weaken, start to twitch, and waste away (atrophy). Eventually, the brain loses its ability to initiate and control voluntary movements.

Early symptoms of ALS usually include muscle weakness or stiffness. Gradually all voluntary muscles are affected, and individuals lose their strength and the ability to speak, eat, move, and even breathe. Most people with ALS die from respiratory failure, usually within three to five years from when the symptoms first appear. However, about 10 percent of people with ALS survive for 10 or more years.

Because people with ALS usually can perform higher mental processes such as reasoning, remembering, understanding, and problem solving, they are aware of their progressive loss of function and may become anxious and depressed. A small percentage of individuals may experience problems with language or decision-making, and there is growing evidence that some may even develop a form of dementia over time.

8.5.1.4.1 Possible Causes of ALS

The cause of ALS is not known, and scientists do not yet know why ALS strikes some people and not others.

Motor neuronal hyperexcitability potentially contributes to motor neuron death in ALS. Many previous studies support this hypothesis, including clinical trials of riluzole, a glutamate antagonist that delays ALS progression (Miller et al., 2012).

In addition to the possible role of motor neuron dysfunction, scientific evidence suggests that both genetics and environment play a role in motor neuron degeneration and the development of ALS.

In 1993, scientists supported by the National Institute of Neurological Disorders and Stroke (NINDS) discovered that mutations in the *SOD1* gene were associated with some cases of familial ALS. Since then, more than a dozen additional genetic mutations have been identified, many through NINDS-supported research.

Research on certain gene mutations suggests that changes in the processing of RNA molecules may lead to ALS-related motor neuron degeneration. RNA molecules are involved with the production of molecules in the cell and with gene activity.

Other gene mutations indicate there may be defects in protein recycling—a naturally occurring process in which malfunctioning proteins are broken down and used to build new working ones. Still others point to possible defects in the structure and shape of motor neurons, as well as increased susceptibility to environmental toxins.

Researchers are studying the impact of environmental factors, such as exposure to toxic or infectious agents, viruses, physical trauma, diet, and behavioral and occupational factors. For example, exposure to toxins during warfare, or strenuous physical activity, are possible reasons for why some veterans and athletes may be at increased risk of developing ALS. Ongoing research may show that some factors are involved in the development or progression of the disease.

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Miller RG, Mitchell JD, Moore DH. (2012) Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev., Mar 14;2012(3):CD001447. doi: 10.1002/14651858.CD001447.pub3.

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CHAPTER OVERVIEW

9: Learning and Memory

9.1: Learning, Genetics, and their Interaction
9.2: Types of Learning and Biological Adaptation
9.3: Introduction to Memory and the Brain
9.4: Synaptic Mechanisms of Learning and Memory
9.5: Brain Mechanisms of Memory Disorders
9.6: Supplemental Section- Detailed Review of Neuroanatomy of Memory

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9.1: Learning, Genetics, and their Interaction

Learning Objectives

1. Describe several definitions of learning which vary depending on theoretical perspective.
2. Discuss the claim that behavior is not random, but orderly and lawful.
3. Describe the fundamental law that governs the organization of behavior and the origin of that natural law.
4. Explain the similarities and differences between information in genes and learned information.
5. Discuss the nature-nurture continuum.
6. Describe examples of "biological preparedness" or biological constraints on learning.

9.1.1 Overview

In this section, we examine learning and how it contributes to the adaptive organization of mind and behavior. To understand learning within its broader biological context, it is important to compare it with genetic information, the other major source of information that organizes behavior into adaptive patterns. Learning refers to behavioral change as a result of experience, but learning is not a single, unitary phenomenon. Instead there are many types of learning which are specialized to adapt to various features of the environment and to solve a variety of adaptive problems. In other words, learning evolved in many forms to serve a range of adaptive functions. Learned and genetic sources of information interact to organize behavior into adaptive patterns. The relative contribution of each varies with the species and the behavior in question.

9.1.2 Learned and Genetic Sources of Information Shape Adaptive Behavior

Learning is defined differently by different psychologists depending upon the theoretical emphasis of the psychologist. Strict behaviorists rejected explanations of behavior that involved reference to internal mental processes. Instead, they emphasized the measurable relations between observable behaviors and observable stimuli. Consequently, behaviorists usually define learning as a change in behavior as a result of experience (excluding changes due to fatigue or other special circumstances). Cognitive psychologists, partially in reaction against strict behaviorism, are more likely to define learning as acquisition of information as a result of experience. From an evolutionary perspective, **learning** can be thought of as **the acquisition of information during the lifetime of the individual animal**. Since information often leads to changes in behavior, learning can also be thought of as **the acquisition of behaviors during the lifetime of the individual.** These last two perspectives differentiate learned information from genetic information which is acquired over the evolutionary history of the species.

Behavior is not usually random. An evolutionary perspective emphasizes the role of learning as a means of achieving successful adaptation. Certainly, the ability to learn new behaviors in response to new situations is valuable to survival and therefore increases the chances for reproduction and the transmission of one's genes into future generations, including genes for learning itself. This is important because it suggests how and why learning evolved. It also suggests why behavior is usually orderly and lawful. Behavior is organized to promote survival and reproduction. This outcome is an inevitable product of the forces of evolution, most notably, natural selection. Thus, learning itself is an evolved property of nervous systems.



Figure 9.1.1: Dusky Langur infant and mother. In the first few months the infant is constantly breast-fed. The mother must teach her infant to eat leaves, as shown in this photo. (Image and caption adapted from Wikimedia Commons; File:Dusky Langur infant learning to eat leaves.jpg; https://commons.wikimedia.org/wiki/F...eat_leaves.jpg; by: Roughdiamond21; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Behavior, and other traits of organisms, ultimately are organized by information. Just like a builder needs information in the form of structural plans to construct a building, information is required to build and operate an organism, including the guidance of its movement, its behavior. In short, behavior is not random, but orderly and lawful, because it is organized by information selected and filtered by two processes. Learning is one source of the information that organizes behavior into adaptive patterns. The second informational source for the adaptive organization of living things is in genes, as previously discussed. We know that genetic information is filtered over countless generations by natural selection and other processes of evolution so that the information transmitted across generations in genes generates traits that, in general, contribute to survival and reproduction. In short, information is required to organize living things and their functioning. This information comes from two sources: 1) genes and genetic evolution; and 2) learning and laws of learning (in those organisms that are capable of learning).

Let's briefly compare these two sources of information which organize behavior into forms which help an animal adapt to environmental demands (see Table 10.1.1 below). There are four main differences to examine.

Firstly, **genetic information is available to all living organisms on earth, but learned information is available only to species whose brains are equipped** with properties that make learning possible. Do flies learn? Do cockroaches? Do frogs? If they do, how much do they learn, how readily do they learn? How important is learning in the life of a frog compared to how important learning is in the life of a dog, a chimpanzee, or a human? In general, learning is more characteristic of the brains of the more complex animals, especially the mammals. Nevertheless, learning does occur even in many invertebrates (animals without backbones, such as insects or squid and octopus). Usually, however, the more complex the animal's brain, the more likely it is that the animal has well developed capacities for learning--capacities for the acquisition of information during its individual lifetime.

Secondly, ***genetic information*** **has been acquired and transmitted over the entire genetic history of the species, whereas** ***learned information*** **is acquired during the short lifetime of the individual animal.** For example, think of flies, or pelicans, both of whom are very good at flying. They ride the air currents perfectly and skim the ocean only inches above it, their paths rising and falling with the tops of breaking waves. How do these birds (and flies) know how to fly at all, and to fly and dive so well?



Figure 9.1.2: Brown pelican tucking its wings as it dives for a fish. Genetic information controls the complex, precisely timed movements involved (Image from Wikimedia Commons; File:Brown pelican (Pelecanus occidentalis occidentalis) diving.jpg; https://commons.wikimedia.org/wiki/F...is)_diving.jpg; By Charles J. Sharp, Sharp Photography; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Over the evolutionary history of these diverse species (one an insect, the other a large bird), natural selection has preserved the genetic information that allows flies and pelicans to fly (they don't learn it); and it is the "correct" information needed to organize the complex movements of flight in these two very different species. How did the correct information that so perfectly organizes the movements required for flight, get into fly DNA and pelican DNA? The primary mechanism for acquisition of the correct (i.e., adaptive) genetic information, is natural selection. Its method of transmission is heredity.

By contrast, learned information is useful because some changes in the environment may be temporary or unique to the experience of only one or a few individuals and may impact chances for survival and reproduction (successful adaptation) . Such changes are far too rapid and too specific to one or a few individuals for the relatively slow processes of natural selection to operate. For example, learning where the local water holes are would certainly be very useful to a lion during the dry season. Dependence upon genetics for this type of information isn't likely to work very well. Learning mechanisms are required.



Figure 9.1.3: Lioness drinking from small water hole on the African savannah. Information about location of water on the savannah changes too rapidly to be incorporated into genes and therefore must be learned (Image from Wikimedia Commons; File:Lioness drinking.jpg; https://commons.wikimedia.org/wiki/F...s_drinking.jpg; By James Wagner; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Thirdly, **the mode of coding and storage is different for genetic information compared to learned information**. Remember, DNA forms a molecular code for coding and storage of genetic information. Learned information is coded and stored in memory systems in brains. This storage of learned information is complicated and takes many forms. Current research suggests that in general, changes in existing synapses, making them more or less responsive, and/or formation of new synapses, stores learned information in memory. More on this process will be covered in subsequent sections of this chapter.

Lastly, **genetic information is transmitted across generations by genetic transmission (heredity).** By contrast**, learned information, in a few species including us, can also be transmitted across generations--not by genetic transmission, but instead by what is known as cultural transmission** (tradition, imitation of the old by the younger members of the social group, books, teaching and learning, storytelling, and so forth). Cultural transmission occurs in relatively few species. We can do it; chimpanzees can do it to a limited degree; Japanese macaque (ma-cack) monkeys can do it to a limited degree. However, rats, and most other species, can't do cultural transmission, and certainly no other species comes close to using cultural transmission to the extent that humans do.



Figure 9.1.4: Macaque monkey feeding. Learned behaviors can be transmitted across generations by cultural transmission by humans and a limited number of other species including macaques (Image from Wikimedia Commons; File:Artis Dining Japanese macaque (6807832054).jpg; https://commons.wikimedia.org/wiki/F...807832054).jpg; By Kitty Terwolbeck; licensed under the Creative Commons Attribution 2.0 Generic license).

Cultural transmission takes a special kind of brain but most species don't have the kind of brain circuit organization required for cultural transmission (the transmission of learned information from generation to generation). Language in humans, of course, plays a crucial role in human cultural transmission, but so do technological and social inventions such as writing, the printing press, film, video, formal education, research institutions, computers, and the internet. All have magnified human cultural transmission and played an enormous role in recent human adaptation (Koenigshofer, 2011). Just as swimming can be considered a defining adaptation of fish, cultural transmission is an adaptive specialty of humans.

Period of Acquisition Laws of Acquisition Mechanisms of Encoding/Storage Transmission Mechanism

Genetic information	acquired over generations (slow information acquisition process), producing species-wide, innate adaptations	acquired by the laws of evolution, primarily by natural selection, over the evolutionary history of the species	encoded and stored in a molecular code in DNA in the genes and chromosomes of the nucleus of cells	transmitted across generations by genetic transmission (heredity, inheritance)

Learned information	acquired during an individual's lifetime (fast information acquisition process) producing rapid and individualized adaptation	acquired by the laws of learning such as the law of effect and association by occurrence of events close in time	encoded and stored in changes in neural circuits probably involving changes in synaptic connections between neurons	transmitted across generations by cultural transmission

Table 10.1.1. Comparisons between genetic and learned information organizing behavior into adaptive patterns. Adaptations, including behavioral adaptations, are not random, but highly structured. This structure requires information. Two sources of information organize behavioral adaptations--genetics and learning, nature and nurture, in interaction (table and caption by Kenneth A. Koenigshofer, PhD; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

9.1.3 Types of Biological Adaptation

At this point it is useful to note that biological adaptations can be loosely categorized into three (overlapping) general types:

1. **Anatomical adaptations** (structural features of the organism such as having fur, or wings, or fins, or hands, or bones, or a liver, or a large brain with a well developed cerebral cortex). These are organized by genetic information and change (evolve) only relatively slowly (although small changes, for example, in beak size and thickness of finches in the Galapagos, can occur much more rapidly; Grant & Grant, 1993).
2. **Physiological adaptations** (internal dynamic processes of the organism such as photosynthesis in plants, digestive processes in animals, the immune system's operations, shivering in response to cold, sweating in response to excess heat, the circulatory system's operations, etc.). These are organized by genetic information and change (evolve) only relatively slowly, although the immune system shows significant plasticity during the individual lifetime to deal with newly encountered pathogens.
3. **Behavioral adaptations** (the goal-directed movements of the organism and the mental processes such as thoughts, plans, emotions, perceptions, reasoning processes, imagination, etc. that underlie and control these movements). As implied above, behavioral adaptations can be organized by genetic information (genetically preprogrammed, "instinct" and reflexes; flying in flies; swimming in fish; feeding in frogs; sex drive in humans) or by learned information (acquired during the lifetime of the animal), or by a combination of both of these sources. It is important to be aware that *the abilities for learning* in any species are themselves genetically evolved. Species that can learn can do so only because learning, and the properties of the nervous system that make learning possible, evolved in those species, including humans, as a result of natural selection.



Figure 9.1.5: Human sex drive is inborn. It can be thought of as a psychological adaptation involving intense emotions leading to reproductive behavior within the context of a pair-bond, increasing likelihood of surviving offspring. Learned cultural practices influence courtship practices and the expression of innate sex drive. (Image from Wikipedia Commons; File:Family love wiki008.jpg; https://commons.wikimedia.org/wiki/F...ve_wiki008.jpg; By Shagil Kannur; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

The behaviors of various animal species can be thought of as falling on a **nature-nurture continuum**, with some behaviors in some species (flies, roaches) being almost completely at the nature (innate) end of the continuum (i.e. behavior determined by genes and genetic evolution), while at the other end, the nurture end of the continuum, are behaviors which are dependent primarily on information acquired during the lifetime of the individual (i.e. learned information) See Figure 9.1.6: below.



Figure 9.1.6: Web construction by spiders is a complex set of movements directed by circuits in the spider nervous system constructed by information in the spider's DNA. The spider's behavior is so stereotyped that experts who study spiders can identify the species of spider from the structure of its web alone, even if the spider is not present. No learned information is required by the

spider to construct its species-typical web. By contrast, human construction of structures is highly dependent upon learned information that has been culturally transmitted across generations. The human brain evolved mechanisms for learning, cultural transmission, comprehension of three-dimensional space, and the ability to visualize in imagination forms like the one depicted here. (Images from Wikipedia Commons; Source of image of spider and web: File:Spider weaving it's web.jpg; https://commons.wikimedia.org/wiki/F...it%27s_web.jpg; by Varun V Vasista; licensed under the Creative Commons Attribution-Share Alike 4.0 International license. Source of image of palace in Spain: File:Dawn Charles V Palace Alhambra Granada Andalusia Spain.jpg; https://commons.wikimedia.org/wiki/F...usia_Spain.jpg; by Jebulon; made available under the Creative Commons CC0 1.0 Universal Public Domain Dedication license).

9.1.4 Slow (Genetics) vs. Fast (Learning) Mechanisms of Behavioral Change

Genetically organized behavioral adaptations (such as web-building in spiders), like anatomical and physiological adaptations, are organized by genetic information and therefore they change (evolve) only relatively slowly, over many generations by natural selection and other mechanisms of evolution. However, for many genes in the organism's phenotype, the gene's *expression* can be affected by multiple environmental factors. The study of this kind of gene-environment interaction is called epigenetics.

By contrast, learned behavioral adaptations can change moment to moment and, as discussed above, may be transmitted (in some species) to future generations by cultural transmission to the benefit of those future generations. For example, the agricultural practices--learned behavioral adaptations or "adjustments"--upon which we have come to depend for our food supply, were invented by people who died generations ago. However, the death of those who invented these behaviors did not result in the loss of the successful behavioral adaptations upon which we depend for our food supply. Instead, these learned behavioral adaptations have been passed on, and refined, over many generations, to our current generation to its adaptive advantage--not by genetic transmission, but by cultural transmission. All would impossible were we, humans, not so powerfully equipped by our brain evolution for efficient cultural transmission of learned behavioral adaptations across generations. By this means, the learning of prior generations is not lost, but remains over generations for each new generation to build upon. Just like flying is a specialty of birds, or swimming is a specialty of fish, cultural transmission is the specialty of the human species.

9.1.5 Summary

In short, learning describes processes whereby information is acquired during the lifetime of an individual animal. Learned information, along with genetic information, helps organize the animal's behavior into adaptive patterns, especially in response to short-term environmental changes where specific, frequently changing details are adaptively significant and therefore must be captured by the organism and put to adaptive use. For example, learning and remembering where a temporary water hole is located on the open savannah is essential to survival for innumerable species that live on the African plains. Because many short-term event details do not regularly recur over generations, such non-recurrent environmental details cannot drive natural selection for genetically evolved instinctual or reflexive adaptations. Instead adaptation to such novel idiosyncratic event details favors the evolution of learning mechanisms (Koenigshofer, 2017). Usually this learned information supplements hereditary (genetic) sources of information in the organization of successful behavioral adaptations--behavioral solutions to the problems of survival and reproduction. As noted above, behavior is one way that organisms (at least animals) adapt. Behavior becomes organized into adaptive patterns by information (i.e. behavior is not random, but guided by laws of nature which govern chances of survival and reproduction--laws of evolution and the laws of learning). The information that organizes behavior comes from the genes after having been perfected by eons of genetic evolution by natural selection. That organizing information can also come from learning by an individual animal during its lifetime (laws which govern learning are also organized to enhance survival and reproduction--see sections below).

Adaptive behaviors can be transmitted to future generations. If the behavior is organized by information in the genes, then that behavior can be transmitted by genetic transmission (heredity). If the information for a particular behavior comes from learning (and is stored in memory), then the behavior can be transmitted to future generations, not by genetic transmission, but instead by cultural transmission (in some species, as noted above). Thus behavioral adaptations in species capable of cultural transmission can undergo not only genetic evolution (true for behaviors organized by genetic information contained in DNA, and also true of anatomical and physiological adaptations) but also cultural evolution (examples of cultural evolution are the development of human technology, modern medical practices, agricultural practices, economies, science, governmental systems and so on, leading over time to generally improved human adaptation). Cultural transmission and the resulting cultural evolution gives our species great survival advantage. Cultural transmission accounts for the success of the human species more than any other single factor.

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9.1.7 Attributions

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9.2: Types of Learning and Biological Adaptation

Learning Objectives

- Describe the various types of learning and how each contributes to adaptation
- Compare and contrast classical (Pavlovian) conditioning and instrumental (operant) conditioning
- Discuss how classical and operant conditioning involve the learning of predictive relations between different types of events in the world
- Explain the concept of adaptively specialized learning and give examples
- Discuss the key aspects of observational learning according to Social Learning Theory.
- Describe the function of habituation
- Describe the general elements from research on cognitive learning in animals

9.2.1 Overview

Learning brings to mind school, memorization, tests, and study. But these associations are related to a single type of learning only, human verbal learning. Actually, learning, as you may already know, is a much broader phenomenon. First of all, learning of various sorts occurs in a wide range of animal species from humans to honey bees. Furthermore, across species, a wide range of behaviors can be acquired or modified by learning, giving behavior in many species a great deal of plasticity. In addition, we now know that learning is not a single unitary capacity, but instead there are many different, but related, processes, ranging from imprinting to cognitive learning. In this module, we examine several types of learning and how they interact with genetic information to serve adaptation. Both forms of conditioning, classical and operant, will be examined. In every kind of learning, learning fills in informational details that are too variable, short-term, and individually experienced to be captured by natural selection and thereby encoded into genes. By contrast, more abstract and general features, common to particular learning situations or problem types across generations, *are* captured by natural selection, genetically encoded, and provide innate, genetic information about the problem type (problem domain) that guides and facilitates the learning.

9.2.2 Habituation, Sensitization, and Adaptation

Habituation is a simple form of learning that produces **a *decrease* in response to a repeated stimulus** that has no adaptive significance. In other words, as an adaptively unimportant stimulus is repeatedly presented to an animal, it will gradually cease responding to the stimulus as it learns that the stimulus holds no information that might impact its biological fitness (survival and reproduction). For example, prairie dogs typically sound an alarm call when threatened by a predator, but they become habituated to the sound of human footsteps when no harm is associated with this sound; therefore, they no longer respond to the sound of human footsteps with an alarm call. Thus, habituation is a form of **non-associative learning** given that the stimulus is not associated with any punishment or reward.

Habituation occurs when your brain has already extracted all the adaptive information that a stimulus or an event holds. However, what happens when, after habituation, a change in the stimulus or situation occurs? Stimulus change might signal that something important has happened. If so, the animal must reengage the processing capacity of its brain, its attentional resources, to evaluate whether the stimulus change might signal something that is adaptively important that may require a behavioral response. This recovery of responding to a habituated stimulus is called **dishabituation** (the undoing of habituation as the organism now responds to the stimulus situation it had previously stopped responding to).



Figure 9.2.1: Habituation is adaptive. Birds feeding along a road eventually habituate to passing traffic preventing them from wasting time and energy by flying away (escape behavior) unnecessarily in the absence of real threat, thereby increasing time and energy available for feeding (Image from Wikimedia Commons; File:Birds feeding on newly ploughed land with Ballymagreehan Hill in the background - geograph.org.uk - 2202208.jpg; https://commons.wikimedia.org/wiki/F..._-_2202208.jpg; by Eric Jones; licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license.).



Figure 9.2.2: After habituation to the loud sound of their submarine's engines, sailors sleep through the noise, but are awakened by the silence if the engines stop. Stimulus change reverses habituation. This is called dishabituation and is highly adaptive; see text (Image from Wikimedia Commons; File:Vladivostok Submarine S-56 Forward torpedo room P8050522 2475.jpg; https://commons.wikimedia.org/wiki/F...50522_2475.jpg; by Alexxx1979; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Sensitization is a similar, form of non-associative learning, however it produces **an *increase* in response to a repeated stimulus over time**.In this case, the first occurrence of this stimulus is more intense than those that follow, thus priming or sensitizing the individual to these future, less-intense stimuli.

Sensitization is a useful model in studying the underlying causes of pathologies such as asthma, substance dependence, allergies, pain-related illnesses, psychological disorders, etc. Now, there are different types of sensitization therapies not only utilized for

medical purposes (allergies, cancer and other tumors) but also for marriage counseling and family psychotherapy (Sarah Mae Sincero (Jul 15, 2011). Sensitization. Retrieved Jun 30, 2023 from Explorable.com: https://explorable.com/sensitization)

One lesson is clear with both habituation and sensitization: stimulus change is very potent in causing the brain to become alert and responsive. This implies that the brain must hold an ongoing representation or neural model of a current situation and must respond to any mismatch between that ongoing memory and the current stimulus situation This is a very adaptive property of the brain's functioning. For example, imagine you are studying psychology late at night. Your window is open and a breeze gently bangs the blinds against the window frame as you read. You will probably habituate to the sound, and thus pay no attention to it, to the point where you don't even hear it as you continue to study. But then, if the lights in your house suddenly go out, you probably will dishabituate and pay attention to every little sound, including the sounds coming from the blinds. In other words, you are now sensitized to any little sound. Your brain is programmed to respond to stimulus change, to novelty, because in stimulus change there may be information important for survival and reproduction, demanding an adaptive response.

9.2.3 **Conditioning and Biological Adaptation**

Basic principles of learning are always operating and always influencing human and animal behavior. This section continues by discussing two fundamental forms of associative learning: classical (Pavlovian) and operant (instrumental) conditioning. Both classical and operant conditioning involve the learning of predictive relationships between events (if event A occurs, then event B is likely to follow) and how this contributes to adaptation. Through them, we respectively learn to associate 1) stimuli in the environment, or 2) our own behaviors, with adaptively significant events, such as rewards and punishments or other stimuli. The two types of learning have been intensively studied because they have powerful effects on behavior. They also allow scientists to rigorously analyze learning processes in detail and the physical basis of learning and memory in the brain.

9.2.4 Classical Conditioning

Many people are familiar with the classic study of “Pavlov’s dog,” but rarely do they understand the significance of Pavlov's discovery. In fact, Pavlov’s work helps explain why some people get anxious just looking at a crowded bus, why the sound of a morning alarm is so hated, and even why we swear off certain foods we’ve only tried once. Classical (or Pavlovian) conditioning is one of the fundamental ways we learn about the world, specifically its predictive relationships between events. This involves learning *what leads to what* in an organism's environment. This is extremely valuable adaptive information that animals and humans appear to incorporate into brain-mediated cognitive models of how the world works--information which allows prediction and therefore improved organization of behavior into adaptive patterns. But classical conditioning is far more than just a theory of learning; it is also arguably a theory of identity. Your favorite music, clothes, even political candidate, might all be a result of the same process that makes a dog drool at the sound of bell.

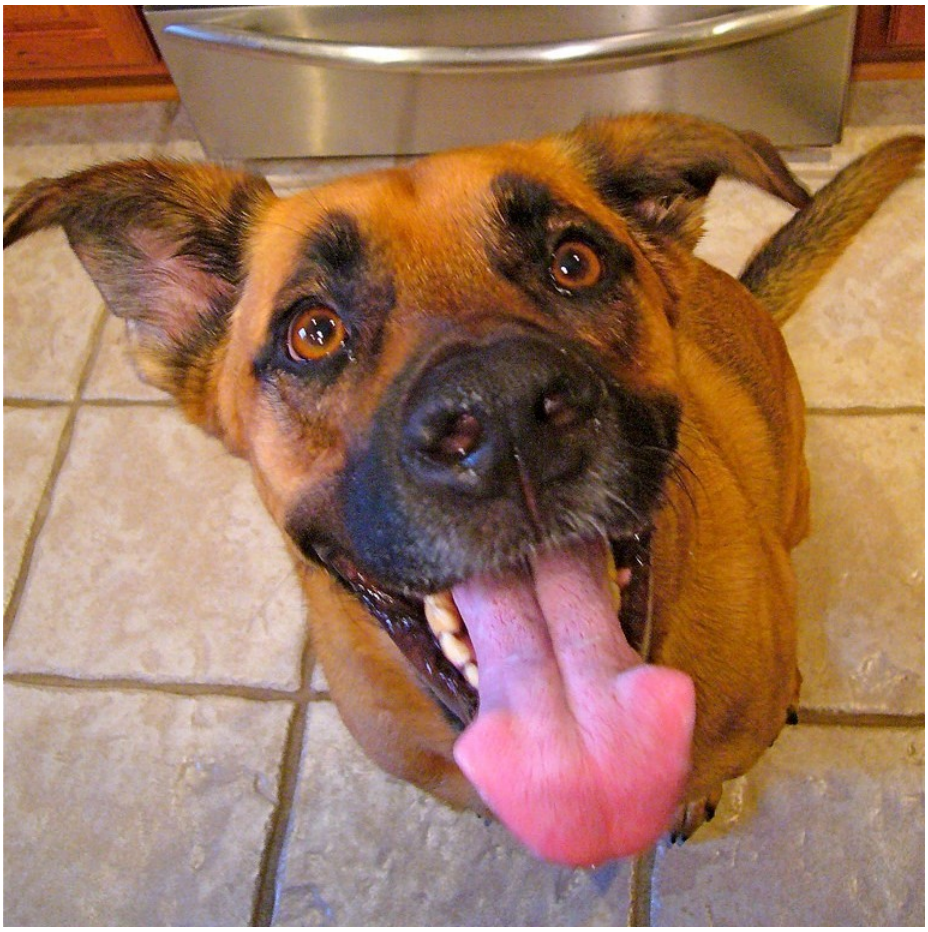


Figure 9.2.3: Does your dog learn to beg for food because you reinforce her by feeding her from the table? Classical conditioning signals to your dog when food reward may be available and operant conditioning (see below) occurs when begging is reinforced by a food reward [Image: David Mease, https://nobaproject.com/modules/cond...g-and-learning, CC BY-NC 2.0]

In his famous experiment, Pavlov rang a bell and then gave a dog some food. After repeating this pairing multiple times, the dog eventually treated the bell as a signal for food, and began salivating in anticipation of the treat. This kind of result has been reproduced in the lab using a wide range of signals (e.g., tones, light, tastes, settings) paired with many different events besides food (e.g., drugs, shocks, illness; see below).

We now believe that this same learning process, **classical conditioning**, is engaged, for example, when humans associate a drug they've taken with the environment in which they've taken it; when they associate a stimulus (e.g., a symbol for vacation, like a big beach towel) with an emotional event (like a burst of happiness); and when a cat associates the sound of an electric can opener with feeding time. Classical conditioning is strongest if at least some of the stimuli are intense or particularly meaningful to the individual. It is also best if at least some of the stimuli involved are relatively new to the individual. And it is especially strong if the organism's biology (its genetic evolution) has prepared it to associate a particular stimuli together. For example, rats, coyotes, and humans are naturally inclined by natural selection to associate an illness with a flavor, rather than with a light or tone. Although classical conditioning may seem "old" or "too simple" a theory, it is still widely studied today because it is a straightforward test of associative learning that can be used to study other, more complex behaviors. Also, biological psychologists can use it to study how at least some forms of learning occur in the brain.

9.2.5 Conditioning Involves Learning Predictive Relations

Pavlov was studying the salivation reflex, reflexive drooling in response to food placed in the mouth. A **reflex** is an innate, adaptive, genetically built-in stimulus-response (S-R) relationship; in this case, the stimulus is the food in the mouth and the respons is the salivation. Specifically, the food stimulus is referred to as an **unconditional stimulus or US** (i.e. it is *not* dependent upon prior learning), and the salivation is referred to as the **unconditional response** or **UR** (i.e. it is *not* dependent upon prior learning).

Recall that Pavlov found that if he rang a bell just before feeding his dogs, the dogs came to associate the sound of the bell with the coming presentation of food. Thus, after this classical conditioning had occurred, the bell alone caused the dog to salivate, before the presentation of food. The bell stimulus became known as the **conditioned stimulus** or **CS** (i.e. it's action *is* dependent on prior learning). The CS is a signal that has little or no importance to the organism until it is paired with something that does have adaptive significance, in this case, food. Reliable pairing of CS and US close together in time (**temporal contiguity**) is important to the processes of classical conditioning. However, temporal contiguity alone is not sufficient for classical conditioning. The pairing of stimuli must be reliable so that a **predictive relationship** is maintained between CS and US. This usually requires the CS and US to be paired repeatedly. Predictiveness between CS and US determines whether or not an association is formed. If the CS does not predict occurrence of the US, no conditioning occurs (Gallistel, et al., 1991).

Pavlov also discovered **extinction**. Recall from Introductory Psychology that if the CS is not followed by the US at least some of the time, then eventually the CR will no longer occur in response to the presentation of the CS. When the animal stops producing the CR in response to the CS, we say that extinction of the CR has occurred.

Research findings emphasize that conditioning is about *learning to predict what leads to what* in the environment. Classical conditioning is the **learning of predictive relations between stimuli**, leading to the learned emission of responses that **prepare for** the coming US. A classical CS (e.g., the bell) does not merely elicit a simple, unitary reflex. In Pavlov's experiments, his bell almost certainly elicited a whole *system* of responses that functioned to get the organism ready for the upcoming US (food). For example, in addition to salivation, the bell most likely caused changes in attention, excitement, and the secretion of gastric acid, pancreatic enzymes, and insulin (which gets blood glucose into cells). All of these responses anticipate coming food and prepare the body and mind for it's arrival.

Modern studies of classical conditioning use a very wide range of CSs and USs and measure a wide range of conditioned responses including emotional responses. If an experimenter sounds a tone just before applying a mild shock to a rat’s feet, the tone will elicit fear or anxiety after one or two pairings. This is an example of **fear conditioning,** which plays a role in creating many anxiety disorders in humans, such as phobias and panic disorders (Mineka & Zinbarg, 2006). Here, rather than a response like salivation, the CS triggers an emotion. Have you experienced conditioned emotional responses to formerly emotionally neutral stimuli? How about the emotional response you might have to a particular song, or a particular place, that once was your and your ex-partner's favorite song or the place you would go to meet one another? Or after you break up with someone, you seem to see their car (or cars like theirs) everywhere and you have a brief moment of anticipation that you might see them. Classical conditioning plays a large role in our emotional lives, and in the emotional lives of other animals as well.



Figure 9.2.5: Intense emotions can be classically conditioned to originally neutral stimuli such as places or songs associated with a special person. (Image from Wikimedia Commons; File:A couple looking at the sea.jpg;

https://commons.wikimedia.org/wiki/F...at_the_sea.jpg; by Joydip dutt; https://commons.wikimedia.org/wiki/F...at_the_sea.jpg; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Where classical conditioning takes place in the nervous systems varies with the nature of the stimuli involved. For example, clearly an auditory CS such as a bell will involve auditory pathways including the auditory system's medial geniculate nucleus of the thalamus (Fanselow & Poulos, 2005) and auditory cortex in the temporal lobe, while a visual CS will involve visual pathways. A US such as food will involve taste pathways, whereas presentation of a painful shock US will involve pain and fear pathways. Researchers have identified a number of brain areas that become active during fear conditioning.

In response to a painful shock during conditioning, there is increased neural activity in a variety of areas but most notably in the **amygdala** and parts of the **anterior cingulate cortices** (Linnman, et al., 2011). Other biological psychologists found that the **cerebellum** has a special role in simpler forms such as the conditioning of the eye blink reflex in rabbits (Thompson & Steinmetz, 2009), whereas more complex conditioning involves the **hippocampus** and **hippocampal-cerebellar interactions** (Schmajuk & DiCarlo, 1991). More on this anatomy and other models of conditioning at the synatic level will be presented later in this chapter.

9.2.6 Operant Conditioning

Operant conditioning is another kind of conditioning in which the organism actively operates on the environment. Like classical conditioning, it also involves learning a predictive relationship between events, but the events are different than in classical conditioning. In operant or instrumental conditioning, the animal or human learns a **predictive relationship between its own voluntary behavior and the outcome or effect of that behavior**. In other words, individuals learn the association between their behavior (i.e. **responses**) and the **consequences** of that behavior.

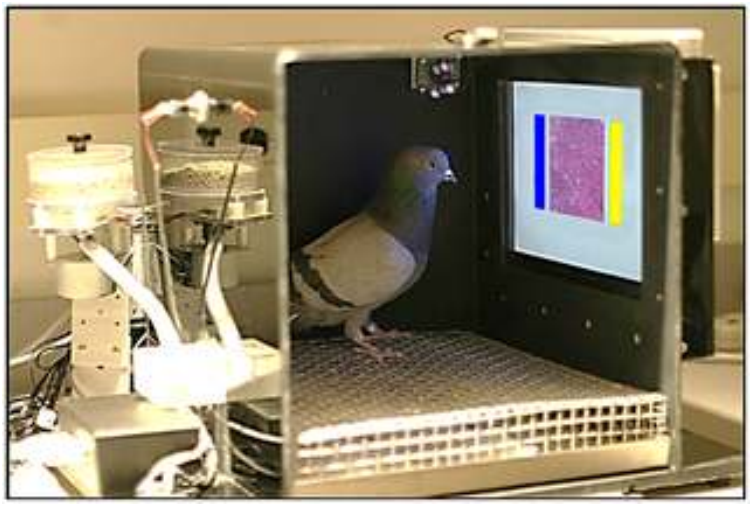


Figure 9.2.6: An operant conditioning chamber. Pecking on the correct color will deliver food reinforcement to the pigeon (Image from Wikimedia Commons; File:The pigeons' training environment.png; https://commons.wikimedia.org/wiki/F...nvironment.png; Creative Commons CC0 1.0 Universal Public Domain Dedication).

Operant conditioning research studies how the effects of a behavior influence the probability that it will occur again. For example, the effects of the rat's lever-pressing behavior (i.e., receiving a food pellet) influences the probability that it will keep pressing the lever. According to Thorndike's **law of effect**, when a behavior has a positive (satisfying) effect or consequence, it is likely to be repeated in the future. However, when a behavior has a negative (painful/unpleasant) consequence, it is *less* likely to be repeated in the future. In other words, the **effect of a response, determines its future probability**. Effects that increase the frequency of behaviors are referred to as **reinforcers**, and effects that decrease their frequency are referred to as **punishers**.

In general, operant conditioning involves an animal or human **tracking the reinforcement contingencies** or dependencies in its environment and exploiting them to its advantage. Clearly, operant conditioning is highly adaptive. Operant conditioning shapes the voluntary behavior of the organism to maximize reinforcement and minimize punishment, just as we would expect from the law of effect. The law of effect in turn depends upon **reward circuits** in the **mesolimbic system** (see Chapter on Psychoactive Drugs) and on circuits for **pain and the emotional response to pain** which are distributed in many regions of the brain including the **somatosensory cortex, insula, amygdala, anterior cingulate cortex, and the prefrontal cortex** (see chapter on Sensory processes). **Reinforcers activate mesolimbic pleasure circuitry** in the brain or reduce activity in pain circuits. This gives the

organism feedback about its actions. Reinforcers and activation of pleasure circuits tend to be **associated with enhanced adaptation** (food, a reinforcer to an animal deprived of food, enhances chances of survival). **Punishers activate circuitry for physical or emotional pain** and tend to be **associated with reduced adaptation and biological fitness** (i.e. reduced chances of survival and reproduction; physical pain is associated with potential tissue damage, while emotional pain is often associated with loss of things or persons upon which one depends or highly values, including romantic partners, financial or social status, etc.). Voluntary behaviors by the animal which lead to positive consequences (and increased pleasure; reinforcement) for the animal tend to be repeated (increase in probability in the future). Voluntary behaviors which the animal produces that lead to nothing or lead to negative outcomes for the animal (a reduction in pleasure or the occurrence of pain) tend not to be repeated, but avoided by the animal in the future.



Figure 9.2.7: Receiving a reward can condition you toward certain behaviors. For example, when you were a child, your mother may have offered you this deal: "Don't make a fuss when we're in the supermarket and you'll get a candy treat on the way out." [Image: Oliver Hammond, https://nobaproject.com/modules/cond...g-and-learning; CC BY-NC-SA 2.0]

This is a wonderful mechanism for assuring the adaptive organization of behavior in species which have behavioral capacities beyond rigidly genetically programmed behavior. In species such as fish, reptiles, amphibians, and many invertebrate species, the larger portion of behavioral adaptation is organized by information in the genes, honed over millions of years of evolution by natural selection. These reflexes and "instincts" generally do not rely very much, if at all, upon information acquired during the lifetime of the individual animal (i.e. learning), but instead upon information acquired over the evolutionary history of the species and stored in DNA.

Learned voluntary behavior is flexible but must also be directed into adaptive patterns by some principle, and that principle is the law of effect. The law of effect allows behavioral flexibility but also provides a mechanism for assuring that the animal (or human) learns adaptive behavior, behavior good for it and its genes, most of the time. "Voluntary" behaviors are not rigidly pre-formed by genetic information, but are organized in a more general way which allows for their modification by information gathered from the animal's current environment (experienced day to day and even moment to moment).

Like classical conditioning, operant conditioning is part of the way an animal forms a **mental model or neural representation** of its environment and the predictive relationships among events in that environment. In classical conditioning, it is the predictive relationships between two stimulus events that is learned. In operant conditioning, it is the predictive relationships between a voluntary response and its outcome or consequence that is learned. Prediction allows preparation for future, even if the future is moments away, and preparation for what is coming next improves chances of survival and reproduction.

When we examine operant conditioning, we see that it bears some similarities to evolution by natural selection. In operant conditioning, voluntary responses by an animal that are successful usually are reproduced (repeated) and those that are unsuccessful (not reinforced) get weeded out (they are not repeated). In evolution by natural selection, genetic alternatives that are successful (lead to better adaptation) get reproduced (and appear in future generations) and those that are unsuccessful (do not lead to improved adaptation or are maladaptive) get weeded out (they are not replicated in future generations). In each case, a selection mechanism (natural selection or the law of effect) preserves some alternatives (genetic or behavioral, respectively) into the future, while eliminating others. In both cases, the result is improved adaptation.

9.2.7 Cognition and Operant Conditioning

Modern research also indicates that reinforcers do more than merely strengthen or "stamp in" the behaviors they are a consequence of. Instead, animals learn about the specific consequences of each behavior, and will perform a behavior depending on how much they currently want—or "value"—its consequence. This idea is best illustrated by a phenomenon called the **reinforcer devaluation effect** (see Colwill & Rescorla, 1986). A rat is first trained to perform two instrumental actions (e.g., pressing a lever on the left, and on the right), each paired with a different reinforcer (e.g., a sweet sucrose solution, and a food pellet). At the end of this training, the rat tends to press both levers, alternating between the sucrose solution and the food pellet. In a second phase, one of the reinforcers (e.g., the sucrose) is then separately paired with illness. This conditions a taste aversion to the sucrose. In a final test, the rat is returned to the Skinner box and allowed to press either lever freely. No reinforcers are presented during this test (i.e., no sucrose or food comes from pressing the levers), so behavior during testing can only result from the rat's memory of what it has learned earlier. Importantly here, the rat chooses *not* to perform the response that once produced the reinforcer that it now has an aversion to (e.g., it won't press the sucrose lever). This means that the rat has learned and remembered the reinforcer associated with each response, and can combine that knowledge with the knowledge that the reinforcer is now "bad." Reinforcers do not merely stamp in responses; response varies with how much the rat wants/doesn't want a reinforcer. As described above, in operant conditioning, the animal tracks the changing reinforcement and punishment contingencies in its environment, as part of a dynamic mental model or neural representation of its world, and it adjusts its behavior accordingly.

Habituation, sensitization, classical conditioning, and operant conditioning are just a few types of learning. Each contributes to adaptation and increases biological fitness (chances of solving the problems associated with survival and reproduction). There are many other types of learning as well, often quite specialized to perform a particular biological function. These specialized forms of learning, also known as adaptive specializations of learning, have been studied mostly by ethologists and behavioral biologists, but biological psychologists are becoming increasingly interested in such forms of learning and their importance. For instance, psychologists have studied one of these specialized forms of learning, taste aversion learning, extensively. In addition to this form, we will now also examine adaptive specializations of learning involved in bird navigation by the stars during migration, bee navigation by the sun, and acquisition of bird song, which some researchers have compared to human language acquisition.

9.2.8 Specialized Forms of Learning

> "Biological mechanisms are adapted to the exigencies of the functions they serve. The function of memory is to carry information forward in time. The function of learning is to extract from experience properties of the environment likely to be useful in the determination of future behavior." (Gallistel, 2003, p. 259).
>
> "One cannot use a hemoglobin molecule as the first stage in light transduction and one cannot use a rhodopsin molecule as an oxygen carrier, any more than one can see with an ear or hear with an eye. Adaptive specialization of mechanism is so ubiquitous and so obvious in biology, . . . it is odd but true that most past and contemporary theorizing about learning does not assume that learning mechanisms are adaptively specialized for the solution of particular kinds of problems. Most theorizing assumes that there is a general purpose learning process in the brain, a process adapted only to solving the problem of learning. . . . , this is equivalent to assuming that there is a general purpose sensory organ, which solves the problem of sensing." (Gallistel, 2000, p. 1179).

As the quotes above imply, learning, the acquisition of information during the lifetime of the individual animal, comes in many different forms. Many specialized forms of learning are highly specific for the solution of specific adaptive problems (problem domains) often found in only one or a few species. These types of learning probably involve specialized neural circuits, organized for their particular specialized form of learning by natural selection.

A familiar sight is ducklings walking or swimming after their mothers. Hatchling ducks recognize the first adult they see, usually their mother, and make a bond with her which induces them to follow her. This type of non-associative learning is known as imprinting. Imprinting is a form of learning occurring at a particular age or a particular life stage that is very important in the

maturation process of these animals as it encourages them to stay near their mother in order to be protected, greatly increasing their chances of survival. Imprinting provides a powerful example of **biologically prepared learning** in response to particular genetically determined cues. In the case of imprinting, the duckling becomes imprinted on the first moving object larger than itself that it sees after hatching. Because of this, if newborn ducks see a human before they see their mother, they will imprint on the human and follow him or her in just the same manner as they would follow their real mother. Because this form of learning is biologically prepared, some cues that trigger the duckling to learn to follow its mother (or a person) are innately programmed into the duckling's genetically controlled brain circuitry while the details of the imprinting object (usually their real mother) are learned from the duckling's initial experience with a moving object larger than itself (again, most likely its real mother). Though this learning is very rapid because it is genetically (biologically) facilitated, it is also very resilient, its effects on behavior lasting well into adulthood. This form of learning illustrates well the general principle that all learning relies upon an underpinning of genetic information about some features of the learning situation while details are filled in by learning through experience. For example, genetic information programs the duckling's brain to follow the first moving thing it sees after hatching that is larger than itself, the details about what that object looks like are added into the bird's memory by learning during imprinting.



Figure 9.2.10: Imprinting is the learned attachment of ducklings to their mother or, under rare circumstances, to the first moving object larger than themselves that they see after hatching (Image from LibreTexts, Book: General Biology (Boundless), Learned Animal Behavior 45.7A; caption by Kenneth A. Koenigshofer, Ph.D.; licensed under

9.2.9 Taste Aversion Learning

Taste aversion learning is a specialized form of learning that helps omnivorous animals (those that eat a wide range of foods) to quickly learn to avoid eating substances that might be poisonous. In rats, coyotes, and humans, for example, eating a new food that is later followed by sickness causes avoidance of that food in the future. With food poisoning, although having fish for dinner may not normally be something to be concerned about (i.e., a “neutral stimulus”), if it causes you to get sick, you will now likely associate that neutral stimulus (the fish) with the adaptively significant event of getting sick.

This specialized form of learning is genetically or **"biologically prepared"** so that taste-illness associations are easily formed by a single pairing of a taste with illness, even if taste and illness are separated by extended periods of time from 10-15 minutes up to several hours. Colors of food, or sounds present when the food is consumed, cannot be associated with illness, only taste and illness can be associated. This is known as "belongingness," an example of "biological preparedness," in which learning has specialized properties as a result of genetic evolution--in this case, only taste and illness can be readily associated, not visual or auditory stimuli and illness (Garcia and Koelling, 1966; Seligman, 1971). A second difference is that taste aversion learning requires only a single pairing of taste and illness, whereas classical conditioning usually requires many pairings of the CS and US. The usual requirements for multiple pairings and close temporal contiguity between stimuli don't apply in learned taste aversion. This makes adaptive sense, because in the wild, sickness from a new food which is toxic won't occur immediately, but only after it has had time to pass into the digestive system and be absorbed. And when it comes to poisons, you may not get a second chance to learn to avoid that substance in the future.

This genetically prepared form of learning evolved over generations of natural selection in omnivorous species which consume a large variety of foods. Species that are very specialized feeders, such as Koala bears which eat eucalyptus leaves exclusively or baleen whales which filter ocean water for microscopic organisms, have not evolved taste aversion learning. They simply don't need it because they never experience novel foods that could possibly pose a threat.

9.2.10 Adaptively Specialized Learning for Navigation and Song Acquisition

Two other examples of specialized forms of learning are of interest here. **Bees learn to navigate by** the position of the **sun** which changes with the date, time, and place on the Earth's surface. When moved to a new location, they learn to update their navigation to compensate for the change in location. This learning is strongly guided by innate, genetically evolved information stored in the bee brain (Dyer & Dickson, 1994; Towne, 2008).

One other example is of special interest, **song learning in song birds**. Birds of a specific species can only learn the song of their own species illustrating genetic constraints on what songs they can learn (Gallistel, et al., 1991, p. 21). White-crowned sparrows show variations in their song depending upon their geographical location, akin to dialects in human language. Experiments have shown that young white-crowned sparrows learn the specific dialect by exposure to it during a critical period for song learning in the species. A critical period during which learning must occur indicates another genetic constraint on learning and is similar to critical periods evident in imprinting, learning the night sky by Indigo Buntings, and a sensitive period in humans prior to adolescence for language acquisition.

The learning involved in the above examples is not classical or operant conditioning, but each is a very specialized form of learning in one particular species for solution to a specific adaptive problem (a specific domain). Note that the learned information supplements and interacts with information in the genes, guiding the animal to attend to and to readily learn highly specific information. In the case of the buntings, in a sense, the birds "imprint" on the correct stars for navigation later in life.

9.2.11 Observation learning

Observation learning is learning by watching the behavior of others. It is obviously an extremely important form of learning in us, but it is also "an ability common to primates, birds, rodents, and insects" (Dawson et al., 2013). It plays a crucial role in human social learning. Imagine a child walking up to a group of children playing a game on the playground. The game looks fun, but it is new and unfamiliar. Rather than joining the game immediately, the child opts to sit back and watch the other children play a round or two. Observing the others, the child takes note of the ways in which they behave while playing the game. By watching the behavior of the other kids, the child can figure out the rules of the game and even some strategies for doing well at the game.



Figure 9.2.11: Children observing a social model (an experienced chess player) to learn the rules and strategies of the game of chess. [Image: David R. Tribble, https://nobaproject.com/modules/cond...g-and-learning, NOBA, Conditioning and Learning; CC BY-SA 3.0]

Observational learning is a component of Albert Bandura's **Social Learning Theory** (Bandura, 1977), which posits that individuals can learn novel responses via observation of key others' behaviors. Observational learning does not necessarily require reinforcement, but instead hinges on the presence of others, referred to as **social models**. Social models in humans are typically of higher status or authority compared to the observer, examples of which include parents, teachers, and older siblings. In the example above, the children who already know how to play the game could be thought of as being authorities—and are therefore social models—even though they are the same age as the observer. By observing how the social models behave, an individual is able to learn how to act in a certain situation. Other examples of observational learning might include a child learning to place her napkin in her lap by watching her parents at the dinner table, or a customer learning where to find the ketchup and mustard after observing other customers at a hot dog stand.

Bandura theorizes that the observational learning process consists of four parts. The first is *attention*—as, quite simply, one must pay attention to what s/he is observing in order to learn. The second part is *retention*: to learn one must be able to retain the behavior s/he is observing in memory. The third part of observational learning, *initiation*, acknowledges that the learner must be able to execute (or initiate) the learned behavior. Lastly, the observer must possess the *motivation* to engage in observational learning. In our vignette, the child must want to learn how to play the game in order to properly engage in observational learning. Bandura, Ross, & Ross (1963) demonstrated that children who observed aggression in adults showed less aggressive behavior if they witnessed the adult model receive punishment for their aggression. Bandura referred to this process as **vicarious reinforcement**, as the children did not experience the reinforcement or punishment directly, yet were still influenced by observing it.

9.2.12 Observation Learning and Cultural Transmission Improve Biological Fitness in Non-human Animals

Orangutans in protected preserves have been seen copying humans washing clothes in a river. After watching humans engage in this behavior, one of the animals took pieces of clothing from a pile of clothes to be washed and engaged in clothes washing behavior in the river, imitating behavior it had recently observed in humans. Orangutans also use observation learning to copy behaviors of other orangutans. Observation learning has also been reported in wild and captive chimpanzees and in other primates such as Japanese macaque monkeys. One of the most thoroughly studied examples of observation learning in animals is in Japanese macaques.

There is a large troop of macaques (Old World monkeys; see Chapter 3) which lives near the beaches on an island in Japan, Koshima Island. Researchers were interested to see how these animals would respond if the researchers scattered novel foods such as wheat grain on the sand. The animals meticulously picked out the grain from the sand one grain at a time, laboriously cleaning it a grain at a time. However, researchers reported that after a while one Japanese macaque in the troop invented an efficient method for cleaning the grain by scooping up handfuls of wheat grain and sand and throwing the mixture into the water. The wheat grains floated while the sand sank. This macaque monkey then scooped up quantities of clean grain floating on the surface of the water and ate its fill, repeating its novel grain cleaning behavior again and again. Although this showed impressive intelligence and inventiveness on the part of this monkey, just as significant was the fact that **other members of the troop observed this behavior and copied it**. By observation learning, most of the troop learned this innovative method of cleaning and separating grain from sand. As time passed, youngsters observed older members engaging in this **learned behavior** and copied it so that the behavior was **passed over several generations** (Schofield et al., 2018). This example of observation learning illustrates one of its most important biological functions--observation learning is a primary mechanism of **cultural transmission of learned behavior across generations**, not only in animals like the macaques, but even more so in humans. The effect of the cultural transmission of learned behavioral adaptations from generation to generation produces "cumulative culture . . . characterized as a ‘ratchet,’ yielding progressive innovation and improvement over generations (Tomasello et al. 1993). The process can be seen as repeated inventiveness that leads to incrementally better adaptation; that is, more efficient, secure, . . . survival and reproduction" (Schofield et al., 2018, p. 113). Efficient cultural transmission of successful learned behavior is **enormously powerful in boosting biological fitness**, and it accounts for those features of human life, such as science, technology, governments, and so on, that distinguish us most from all other species on the planet (Koenigshofer, 2011, 2016).

9.2.13 **Cognitive Learning**

Classical and operant conditioning are only two of the ways for humans and other intelligent animals to learn. Some primates, including humans, are able to learn by imitating the behavior of others and by taking instructions. The development of complex language by humans has made **cognitive learning**, a change in knowledge as a result of experience or mental manipulation of existing knowledge, the most prominent method of human learning. In fact, that is how you are learning right now by reading this information, you are experiencing a change in your knowledge. Humans, and probably some non-human animals, can make mental images of objects or organisms, imagining changes to them or behaviors by them as they anticipate the consequences. Cognitive learning is so powerful that it can be used to understand conditioning (discussed in the previous modules). In the reverse scenario, conditioning cannot help someone learn about cognition.

Classic work on cognitive learning was done by Wolfgang Köhler with chimpanzees. He demonstrated that these animals were capable of abstract thought by showing that they could learn how to solve a puzzle. When a banana was hung in their cage too high for them to reach, along with several boxes placed randomly on the floor, some of the chimps were able to stack the boxes one on top of the other, climb on top of them, and get the banana. This implies that they could visualize the result of stacking the boxes even before they had performed the action. This type of learning is much more powerful and versatile than conditioning.

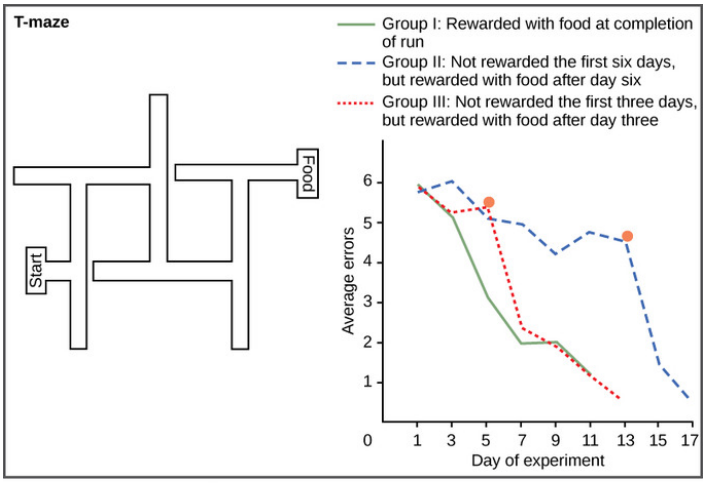
Cognitive learning is not limited to primates, although they are the most efficient in using it. Maze-running experiments done with rats in the 1920s were the first to show cognitive skills in a simple mammal, the rat. The motivation for the animals to work their way through the maze was the presence of a piece of food at its end.

In these studies, the animals in Group I were run in one trial per day and had food available to them each day on completion of the run. Group II rats were not fed in the maze for the first six days and then subsequent runs were done with food for several days after. Group III rats had food available on the third day and every day thereafter. The results were that the control rats, Group I, learned quickly, figuring out how to run the maze in seven days. Group III did not learn much during the three days without food, but rapidly caught up to the control group when given the food reward. Group II learned very slowly for the six days with no

reward to motivate them. They did not begin to catch up to the control group until the day food was given; it then took two days longer to learn the maze. Results suggested that although there was no reward for the rats in groups II and III during several days at the beginning of the experiment, the rats were still learning. This is evidenced particularly by the performance of group III. Although not given any food reward in the maze for the first three days of the experiment, nevertheless, once food reward was added on day 4, the maze learning performance of rats in this group rapidly caught up with the control group (Group I) that had received food reward in the maze every day from the start of the experiment.

These results showed that even in the absence of food reward, the rats were learning about the maze. This was important because at that time many psychologists believed that learning can only occur in the presence of reinforcement. This experiment showed that learning information about a maze, gaining knowledge about it, can occur even in the absence of reinforcement. Some have referred to this as "**latent learning**." The learning that has taken place remains hidden or latent in behavior until a motivating factor such as food reward stimulates action that reveals the learning that had previously not been apparent in observable behavior.

Cognitive learning involves acquisition of knowledge, in this case, about a maze; in this example, it took place in rats without food reward, as evidenced by their performance in the maze once food reward was presented as a motivator. This procedure revealed the learning that had taken place in the first few days of the experiment.



Redrawn after H. C. Blodgett, The effect of the introduction of reward upon the maze performance of rats. Univ. Calif. Publ. Psychol., 1929, 4, No. 8, pages 117 and 120.

Figure 9.2.12: **Cognitive learning**: Group I (the green solid line) found food at the end of each trial; group II (the blue dashed line) did not find food for the first 6 days; and group III (the red dotted line) did not find food during runs on the first three days. Notice that rats given food earlier learned faster and eventually caught up to the control group. The orange dots on the group II and III lines show the days when food rewards were added to the mazes. (Image from: **Book: General Biology (Boundless)**. Learned Animal Behavior 45.7C Unless otherwise noted, LibreTexts content is licensed by CC BY-NC-SA 3.0. Legal. https://bio.libretexts.org/Bookshelv...d_Sociobiology

Clearly this type of learning is different from conditioning. Although one might be tempted to believe that the rats simply learned how to find their way through a conditioned series of right and left turns, Edward C. Tolman proved a decade later that the rats were making **a representation** of the maze **in their minds**, which he called a “cognitive map.” This was an early demonstration of the power of cognitive learning and how these abilities were not limited just to humans.

Research discussed more fully in the Cognition and Intelligence chapter will demonstrate the involvement of a variety of cortical areas as well as the hippocampus in the ability to form **cognitive maps** and engage in many types of cognitive learning.

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9.2.15 Attributions

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9.3: Introduction to Memory and the Brain

Learning Objectives

- Explain the basic differences between learning and memory
- Describe the different types of memory and the brain structures involved in each
- Explain the three stage model of memory
- Compare and contrast implicit and explicit memory
- Describe types of declarative memory and their features
- Discuss the case of H.M. and what it tells us about the role of the medial temporal lobes in declarative memory
- Describe the concept of the "engram"

9.3.1 Overview

There are a number of different types and stages of memory, involving different brain areas and processes. In this section, we briefly outline the different types of memory and some of what is known about the localization of where they are processed in the brain. We discuss the intriguing case of H.M. whose profound loss of ability to form new long-term memory of facts and events led to much of what we know about declarative memory and the involvement of the medial temporal lobes in memory formation. Formation of memories about how to do things, procedural or motor memory involves different brain areas, in particular, the cerebellum and the basal ganglia.

9.3.2 Memory and the Brain

Learning can be defined as the acquisition of information during the lifetime of the individual organism. This information is typically stored in memory systems of the brain of the animal. By contrast, genetic information, which is acquired over the evolutionary history of the species, is stored in DNA. Remember that behavioral adaptations can be organized by information from both sources. The relative contribution of each source of information to the organization of any particular behavior varies with the type of behavior and the species. Typically, learning is more important to organization of behavior in animal species with larger, more complex nervous systems. However, evidence of memory is even found in honey bees and other invertebrates.

9.3.3 Types of Memory

Memory refers to the processes of storage and retrieval of learned information. Just as there are different types of learning, there are also different types of memory. The most common distinction is between **short-term** and **long-term** memory processes. Each of these major processes have distinctions in terms of various subtypes and the brain areas involved with them.

Another major distinction is between **verbal memory** and **visuospatial** memories. Verbal memories are in the form of words and ideas stated in words,whereas, visuospatial memories are in the form of visual images. Memories can be in the form of other sensory modalities as well. For example, when you try to recall talking to a friend on the phone, you may be able to "hear" your friend's voice in your mind (i.e. an auditory "image"). Verbal memories themselves can often involve auditory "images" in the form of the sounds of the words you are thinking about. Also, thinking about what a lemon tastes like can trigger a "taste" of it in your mind (i.e. a taste "image").

Yet another important way to differentiate between forms of memory is memory for facts and events versus procedural and conditioned responses. Memory for facts is **explicit or declarative memory**, which is of two types, **episodic** (memory of episodes in your life) and **semantic** memory (memory for facts and knowledge). A second type, **implicit memory**, is also of two types, **procedural memory** (memory for how to do things, such as skills like riding a bike, **sometimes called motor memory**), and memory for **classically conditioned** responses and priming effects.

It is difficult to keep all of these distinctions straight, especially since there is overlap between them, as we will see. Perhaps the best way to approach this is to start with examining a basic model of the stages of memory and then explore the brain mechanisms behind them.

9.3.4 The Three Stage Model of Memory and the Brain

One simple and influential model of memory proposes three stages (Baddeley, 1982): Sensory memory--Short-term or working memory (STM)--Long-term memory (LTM)

Sensory memory is of very short duration but very high capacity. To illustrate, just close your eyes at this moment and you will probably "see" a **mental image** of what it was you were just looking at. That is visual sensory memory and likely involves the visual cortex in **occipital lobe**. Notice it is nearly a replica of what you were just looking at; the mental image is very detailed and information dense, suggesting a high capacity form of storage. But the image quickly fades--that is, this stage of memory is of very brief duration, not more than a few seconds. Because sensory memories usually involve more than just visual input, **multiple brain areas** are used to processes this rapid form of memory.

Short-term memory (**STM** (**STM**) is a bit longer in duration, up to a few minutes, but could be as short as 20 seconds if the information is not rehearsed or worked with in some way. On the other hand, the capacity of STM is not nearly as large as sensory memory. It is usually said that STM has the capacity to store 7 plus or minus 2 separate items of information at a time (Miller, 1956). This is a limited storage capacity compared to the other stages of memory. Short term memory is also called **working memory.** This is because when you use information from your memory to do some task you are actively using or working with it. As will be discussed in later sections, STM relies heavily on the function of the **prefrontal cortex** of the frontal lobe.

Long term memory (**LTM**) has a very large capacity and very long duration. The capacity is so large it is difficult to quantify and the duration may last a lifetime. According to the three-stage model, information typically moves from STM (working memory) into LTM. However, sometimes this movement can be very fast without requiring much work, but other times it can take a great deal of time and effort.

The movement or **"consolidation"** of declarative and some other types of information from STM to LTM appears to involve the **hippocampus** (Squire, et al., 2015), located in the **medial temporal lobes** (see Figure 9.3.1:). For example, when you are studying for an exam, you are trying to get information encoded into long-term memory. Consolidation of the new semantic memory by your hippocampus, and the surrounding medial temporal lobe, is essential to this process. More on the roles of the hippocampus and temporal lobe is presented in later sections.

Information can also move from LTM back into STM or working memory. For example, if you were asked to name the capital of your home state (e.g. California), you could probably say it fairly quickly ("Sacramento!"). However, this information was not in your conscious awareness before you were asked the question. The information had to be pulled from your long term memory into your conscious awareness. This movement of information from LTM to your conscious awareness (into your "working memory") is **memory retrieval**.

How does your brain do it? How can it locate and pull into your conscious working memory a piece of information from among the countless pieces of information stored in your long term memory over your lifetime? Apparently, there are **associative networks** formed in long term memory that help facilitate an efficient search when you are trying to locate a particular piece of information for retrieval into conscious working memory. The formation and action of these networks are quite complicated and have been under active study for quite some time and will most likely continue to be. What is clear is that many distinct brain areas and circuits are involved in the types of memory that make up the three stages described above.

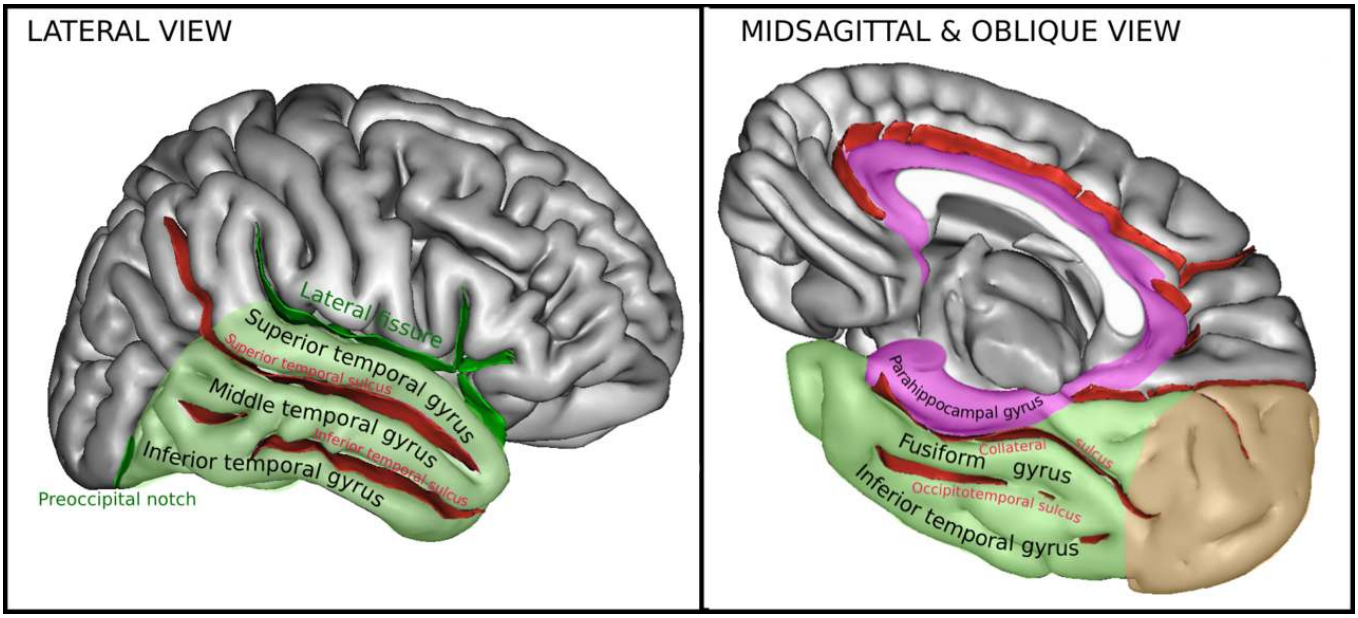


Figure 9.3.1: Right human cerebral hemisphere highlighting temporal lobe (green) showing locations of major cortical gyri and fissures of temporal lobe. The hippocampus (not shown) is buried within medial temporal cortex important in declarative memory. (Image from Wikimedia Commons; Medial temporal cortex; TempCapts.png; by Sebastian023; https://commons.wikimedia.org/wiki/F...:TempCapts.png; licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. Caption by Kenneth A. Koenigshofer, PhD.).

9.3.4.1 Brain Areas Involved with Sensory Memory

The brain areas and circuits involved with sensory memory are incredibly varied. Remember, just about all of your senses are sending information to your brain regarding the current state of both the external environment and internal sensations coming from within your own body. This compilation of information is constantly refreshing itself on a second-by-second basis. Due to the varied nature of this input, **many areas of the cortex** from all the lobes are involved in creating these sensory **"snapshots"** of your perceptual world.

9.3.4.2 Brain Areas Involved with Short-term/Working Memory

A large body of evidence indicates that the **dorsolateral prefrontal cortex** plays an important role in certain forms of memory work (Barbey, et al., 2013), in particular those that involve alternating between two memory tasks and exploring various possibilities before making a choice (Hunt et al., 2015). It seems fairly certain that dorsolateral prefrontal cortex holds information required for reasoning processes that are in progress.

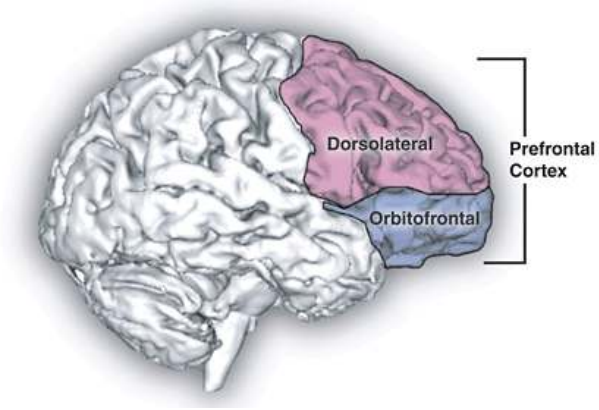


Figure 9.3.2: Divisions of Human Prefrontal Cortex (Image from Wikimedia Commons; File:Prefrontal cortex.png; https://commons.wikimedia.org/wiki/F...tal_cortex.png; by Natalie M. Zahr, Ph.D., and Edith V. Sullivan, Ph.D.; image is a work of the National Institutes of Health and is in the public domain).

The **prefrontal cortex** is the main integrative area in the frontal lobe which plays a major role in short-term and working memory, along with it's extensive contributions to higher cognitive function, such as planning and decision-making. These roles are clearly interrelated in that most decisions require the juggling of both current, short-term information and information from past experiences. Similarly, most plans for both the immediate and long-term future benefit from at least some input from current circumstances. The prefrontal cortex is well-situated to play this role since it receives input from brain areas involved with a variety of functions from sensory processing to emotion and motivational regulation.

A number of classic studies have shown that the short-term/working memory can handle the simultaneous processing of 7 +/- 2 "chunks" of information for a relatively short-period of time (~20 seconds) without rehearsal. If the information is worked with on a regular basis, it can be held for a longer time until it is either lost or committed to long-term memory.

9.3.4.3 Brain Areas Involved with Explicit Long-term Memory

The **hippocampus** has been implicated in the **"consolidation"** or fixing of **new declarative and episodic long-term memories** into permanent storage (see Bird & Burgess, 2008). It has also been shown to be involved with the **encoding of the temporal sequencing** of events (Ranganath & Hsieh, 2016), **spatial memory** (Bird & Burgess, 2008; Voss, et al., 2017), and **retrieval of memories** by reactivating cortical representations of them (Tanaka, et al., 2014). See Figure 9.3.1: and the section below for more details on these functions and the associated hippocampal and temporal lobe anatomy.

9.3.4.4 Brain Areas Involved with Implicit Long-term Memory

The **basal ganglia** is a collection of subcortical nuclei that have a variety of functions from an extensive influence on motor control to a powerful mechanism involved with many types of motivation. Some of the areas here are also collectively referred to as the striatum and include the caudate and putamen. Due to it's role in motor function, it is suited to play a significant role in the development and implementation of memories related to habits. Habitual behaviors help us preserve cognitive bandwidth, reducing the “mental energy” that is used during repetitive task performance. The downside of habits is that reliance on habitual responding can limit behavioral flexibility, and cause a person to act in a suboptimal manner, perhaps behaving in a way that led to a positive outcome in a previous set of circumstances without incorporating and evaluating the present circumstances (Lim, A. OER Neuroscience Initiative, https://oercommons.org/courses/open-...nce-initiative).

The **cerebellum**, located in the hindbrain, is also involved in formation and storage of implicit memories. In this case it plays a role in the control of motor programs for learned skilled movements (**procedural or motor memory**) and is also the source of learning and memory of simple **conditioned reflexes,** such classical conditioning of the eye blink reflex (Kim & Thompson, 1997; Christian & Thompson, 2003). Due to these roles, it has been extensively studied in the learning areas of classical conditioning and it's contribution to implicit forms of memory.

9.3.5 The Medial Temporal Lobes and Declarative Memory

Research has led to a consensus that the **medial temporal lobes** have an essential function in **declarative memory**. As Squire et al. (2004, p. 279) summarize: "The medial temporal lobe includes a system of anatomically related structures that are essential for declarative memory (conscious memory for facts and events). The system consists of the **hippocampal region** (CA fields, dentate gyrus, and subicular complex) and the adjacent **perirhinal, entorhinal, and parahippocampal cortices**." See Figure 9.3.3:.

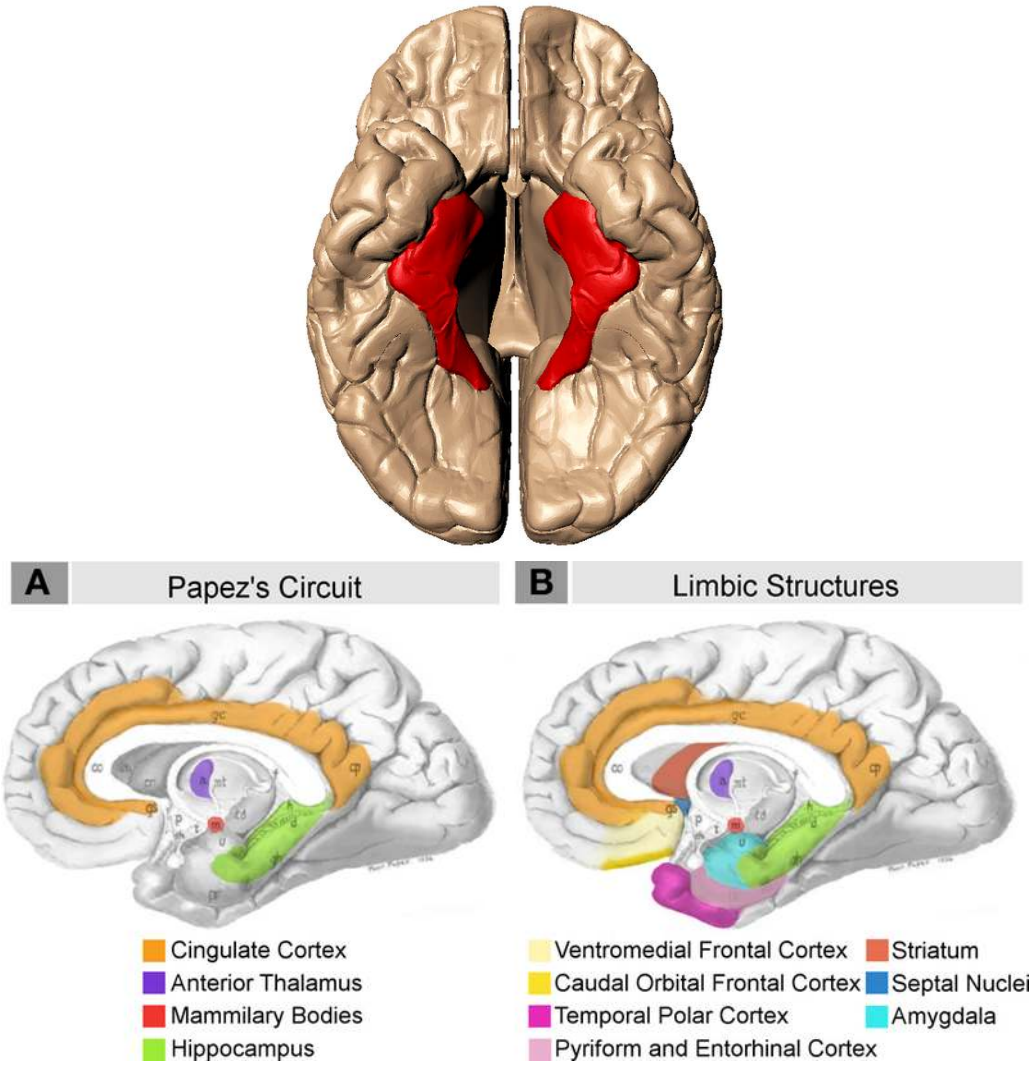


Figure \(\PageIndex{3}\): Parahippocampal cortex (Left). Papez Circuit and Limbic system structures (Middle and Right) . Some are within the medial temporal lobe and are involved in memory. Many limbic structures are also involved in emotion. (Images from Wikimedia Commons; (Left) Parahippocampal gyrus; https://commons.wikimedia.org/wiki/F...riror_view.png; by Polygon data generated by Database Center for Life Science (DBCLS)[2]; licensed under Creative Commons Attribution-Share Alike 2.1 jp; (Middle and Right) File:Neural systems proposed to process emotion.png; https://commons.wikimedia.org/wiki/F...ss_emotion.png; by Barger N, Hanson KL, Teffer K, Schenker-Ahmed NM and Semendeferi K; licensed under the Creative Commons Attribution 3.0 Unported license. Caption by Kenneth A. Koenigshofer, PhD).

9.3.5.1 Patient H.M, the Temporal Lobe, and Declarative Memory

A fascinating research enterprise contributing greatly to our understanding of memory is the case of **H.M**. (e.g. Henry Molianson). In an attempt to control his major epileptic seizures, H.M. had **bilateral removal** of much of his **medial temporal lobes** including both of his hippocampi. Up until his death in December of 2008 of natural causes at age 82, H.M. still believed that Eisenhower was President of the United States. He knew almost nothing about anything that had happened after his brain surgery. According to a researcher working with H.M., whenever he was asked to describe his physical appearance, even years after his surgery, H.M. continued to describe himself as a young man with a thick head of wavy black hair, even though, at his age, he had almost no hair at all. After the surgical removal of much of his medial temporal lobes, H.M. could remember most things that happened before his surgery, but he **could not remember any new facts or events** for more than a few minutes. His **old long-term episodic and semantic memory was fine**. His **short-term memory** was also **normal**. What he could not do was to consolidate or **fix any new information about facts or events into** his **long-term memory**. Yet, his **implicit memory and his ability to consolidate new procedural memories into permanent storage was normal.** He learned to play computer games with great skill, but never was able to remember having learned them, and he was often puzzled about why he was so good when he couldn't even remember having seen computers or computer games before.

It is interesting to speculate about what it must have been like for H.M. when he got up in the morning and looked in the mirror, expecting to see himself as a young man and finding an old man instead. Or what he thought when he awoke in the morning and looked over at his wife lying next to him. He can only remember her as she looked as a much younger woman. What must he have experienced when he saw the older woman asleep next to him? Did he know who she was? He must have been puzzled about what could have happened to her overnight. Soon, however, he would forget what he had just seen minutes before. The life of H.M. must have been truly extraordinary. Studies of H.M. for many decades and others like him revealed much that we know about memory and the brain today, in particular the role of the **medial temporal lobe** structures in declarative (conscious) memory formation.

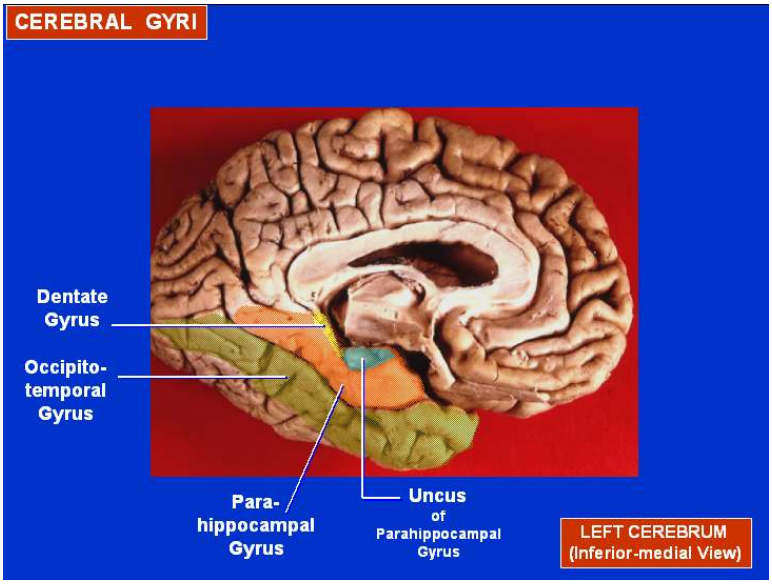




Figure 9.3.4: (Left) Medial view, left human cerebral hemisphere highlighting Dentate (yellow) and Parahippocampal gyri (orange) within medial temporal lobe important in declarative memory. (Right) Hippocampus (red). (Images from Wikimedia Commons; (Left) Dentate gyrus; File:Cerebral Gyri - Medial Surface2.png; https://commons.wikimedia.org/wiki/F...l_Surface2.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. (Right) Hippocampus; File:Hippocampus image.png; https://commons.wikimedia.org/wiki/F...mpus_image.png; by Life Science Databases(LSDB); licensed under the Creative Commons Attribution-Share Alike 2.1 Japan license. Caption by Kenneth A. Koenigshofer, PhD.).

9.3.6 The Engram

In the mid 20th centure, Karl Lashley, a pioneering physiological psychologist, now well known in the history of psychology, investigated the physical basis of memory in the brain. One of the famous (or infamous) techniques he used was to teach rats to navigate a maze and then destroy various parts and amounts of their brain tissue to see which areas were critical to memory. He was searching for the physical representation of memory in the brain. He referred to the physical changes in the brain, which occur when we learn and remember something, the **"engram," or "memory trace**."

Ulitmately, his results were inconclusive, but he did find that the more cortex he destroyed the greater the disruption of memory. He called this the **"principle of mass action."** Today memory research continues and new insights have been discovered about the nature of the "engram," which appears to involve the **modification of synapses** (Howland & Wang, 2008), the **growth of new synapses**, and even the growth of **new neurons** (Deng et al., 2010; Ranganath & Hsieh, 2016). We discuss more about the physical changes in the brain that appear to be involved in learning and memory in later sections of this chapter.

9.3.7 Summary

Different types of memory have been designated by researchers as explicit and implicit, declarative, semantic and episodic, procedural or motor memory, and some forms of memory involve three stages, sensory, short-term, and long-term. Different types of memory and different stages involve different brain areas and processes. The case of H.M. led researchers to recognize the essential role of the hippocampus and other regions of the medial temporal lobes in the formation of long-term declarative memories, while the cerebellum stores motor programs of learned skilled movements and memory of at least some reflexes such as the eye-blink reflex. Mechanisms that seem to be the basis for learning and memory at the more microscopic level appear to depend on synaptic changes.

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9.3.8.1 Attributions

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9.4: Synaptic Mechanisms of Learning and Memory

Learning Objectives

- Describe Hebb's theory of the engram
- Define Hebb's rule and Hebb synapses
- Describe the synaptic changes mediating habituation and sensitization in the sea slug
- Explain the dual-trace theory of memory
- Describe the role of the hippocampus in learning and memory
- Describe the role of the cerebellum, basal ganglia, and amygdala in learning and memory
- Explain the concepts and associated neural changes of Long-term Potentiation (LTP) and Long-term depression

9.4.1 Overview

Donald Hebb's (1949) **dual-trace theory** of the physical basis of memory focused on changes at the synapse as the basis for learning and memory. This influential theory led to the discovery of changes in transmitter release associated with learning in the invertebrate nervous system of the sea slug. Other researchers found sustained increases in synaptic strength caused by high frequency stimulation of the pre-synaptic neuron (**Long-term Potentiation, LTP**) as well as sustained decrease in synaptic strength known as **Long-term Depression (LTD)**. Researchers have also discovered anatomical changes in dendritic spines associated with LTP and learning and memory, suggesting anatomical changes at synapses as a possible mechanism for learning and long-term memory. Although early studies in search of the "engram", the physical basis for learning and memory, concluded that these functions were widely distributed throughout the brain, later research found that the hippocampus is critical for formation of long-term explicit memories and that the cerebellum is involved in implicit memory, while the amygdala plays an essential role in emotional memories.

9.4.2 **The** Search for Learning and Memory in the Synapse

Just as information is stored digitally in "the cloud" or on hard drives and flash drives, the information in our long-term memory must be physically stored in the brain. According to current theory, the ability to maintain information in **long-term memory** involves a gradual **strengthening of the synaptic connections** among neurons. When pathways in these neural networks are frequently and repeatedly activated, the synapses become more efficient permitting enhanced communication among neurons in the network, and these changes create memory (Saylor Foundation, 2012). As we will see, this view of the physical basis of memory was heavily influenced by the ideas of a Harvard biological psychologist named Donald Hebb.

Over a century ago a Russian physiologist named **Ivan Pavlov** proposed a theory of how learning occurred in the brain. As you recall, Pavlov discovered classical conditioning when he observed that repeated pairings of a bell and food eventually led dogs to salivate at the sound of the bell, even when food was not present. To explain this phenomenon, Pavlov hypothesized that the conditioned stimulus (CS), a bell in this case, generated a **locus of neural activity** in sensory cortex (auditory cortex in this experiment) which radiated outward over the cortical surface. This was followed by a similar locus of cortical neural activity generated by the unconditioned stimulus (US) (meat powder in Pavlov's classic experiments) which also set up **waves of radiating neural activity**. Pavlov proposed that these two expanding fields of neural activity, originating from different areas of cortex, would intersect one another. According to Pavlov, this intersection of the cortical fields of neural activity, generated by the CS and US, formed the neurological basis for the association between CS and US.

This early theory of the physical basis of learning and memory was put to the test by experimental psychologist, **Karl Lashley** in the mid 20th century. Lashley made cuts throughout the cerebral cortex of rats and then attempted to condition them. He did this to disrupt any radiating neural activity in the cortex that might be present during conditioning, as Pavlov had proposed. Lashley found that the rats still could be conditioned and that they retained the conditioned response later in spite of the crisscross cuts over their entire cerebral cortex. This disproved Pavlov's theory that the physical basis of learning an association by classical conditioning was the intersection of waves of neural activity radiating outward from cortical loci.

Lashley, like Pavlov, was interested in finding the "**engram**." This term refers to the physical memory trace, the neural representation of memory in the brain. Toward this end, Lashley performed additional experiments in which he trained rats to navigate a maze and then destroyed different parts of their brains. He found that no matter where the brain damage was located, rats still retained some memory of the maze (Lashley, 1929, 1943, 1950). Lashley interpreted these results as evidence that it was the

amount of cortical tissue removed, not its location, that determined the degree of impairment in learning and memory. He also hypothesized that memories were widely distributed throughout the brain and that therefore there was no particular area of the brain that was especially critical for memory formation.

Lashley proposed two principles derived from his research on the physical basis of learning and memory: 1) **mass action** (the amount of cortex destroyed determines degree of impairment in learning and memory) and 2) **equipotentiality** (any part of cortex within a functional area can take over the functions of any other part of that same functional area).

Lashley's conclusions had two primary impacts. First, his analysis "tended to discredit, or at least deemphasize, the role of the interior [subcortical] parts of the brain in learning and memory and, on the other, tended to localize the mechanisms of learning and memory within the confines of the cerebral cortex" (Thompson, 1974). Second, Lashley's principles of mass action and equipotentiality led to an **anti-localization bias** in the study of learning and memory, which discouraged attempts to find specific brain structures involved in these functions. However, consistent with current views, and **contradicting Lashley's findings**, Kaada, Rasmussen, and Kveim (1961) reported that **lesions of the hippocampo-fornix system impaired maze performance.** This was an early study that confirms what we know today, that a subcortical structure, the **hippocampus**, is critical to many forms of learning and memory.

9.4.2.1 Hebb's Rule, Cell Assemblies, and the Engram

After receiving his doctorate from Harvard in 1936, one of Lashley's graduate students, Donald Hebb, published *The Organization of Behavior: A Neuropsychological Theory*. In this influential book, Hebb proposed that the **"engram"** consisted of **changes at synapses** during learning and memory formation. A quote from the book (Hebb, 1949, p. 62) explains **Hebb's central principle** of synaptic change in learning and memory:

> “When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased."

Here Hebb is proposing an **increase in the strength of synaptic connections between neurons that consistently fire together** and that this involves growth or metabolic events in one or both of the cells.

More simply stated: "Neurons that fire together, wire together." This is known as "**Hebb's rule**" (retrieved from https://can-acn.org/donald-olding-hebb/ August 8, 2021).

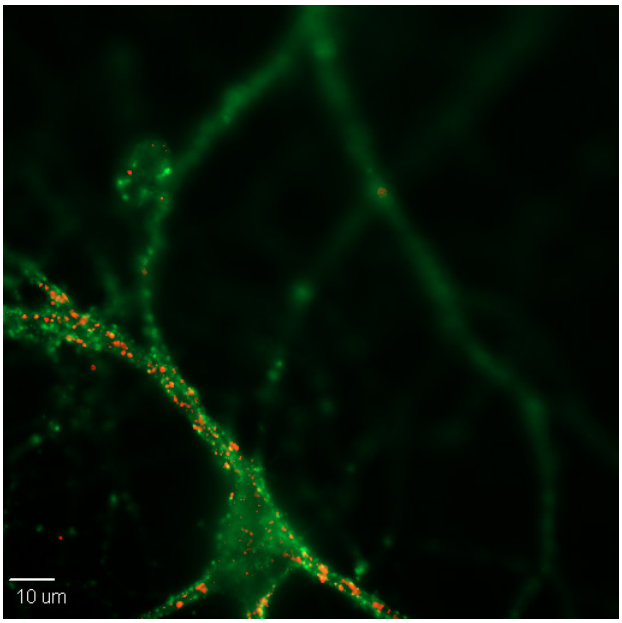


Figure 9.4.1: A 20X image of a cultured mouse cortical neuron in cell culture. Synapses are labeled for pre- (green) and post-synaptic (red) proteins, synaptophysin and PSD-95, respectively. (Image and caption from Wikimedia, Synapse; https://commons.wikimedia.org/wiki/F...n_Synapses.jpg; author, Dchordpdx; licensed under the Creative Commons Attribution 4.0 International license).

Neuroscientists use the term, **Hebbian synapses**, to refer to synapses that follow this principle. Hebb also proposed the idea of "cell assemblies." Hebb hypothesized that when cells repeatedly firing together, wired together, eventually they would form larger structures, "**cell assemblies**," which would form neural representations of whole, complex perceptions, ideas, memories, and other cognitive structures, such as schemas, and highly abstract categories and concepts. All of this could be built from changes in the efficiency of synaptic transmission at specific synapses, following Hebb's principle that "neurons that fire together, wire together." One can imagine that *entire cell assemblies* that fire together might also wire together, creating much larger and much more complex neural representations in the brain of complex, abstract ideas including such things as scientific theories and mathematical formulations.

9.4.2.1 Non-Association Learning in Aplysia

These ideas have inspired the hunt by neuroscientists for changes at synapses and in pre- or post-synaptic neurons, during and after learning--changes which might be the physical basis in the nervous system for learning and memory (Lashley's "engram," which, by the way, has nothing to do with the non-scientific use of the term by Scientology). Much of the pioneering scientific work on the search for the "engram" has involved looking for these physical changes associated with learning in the simple nervous system of a marine species, Aplysia californica, a type of sea slug. A major reason for the selection of this species for study, aside from the simplicity of its nervous system (just 20,000 neurons), is the large size of its neurons which makes the work and the observations easier.

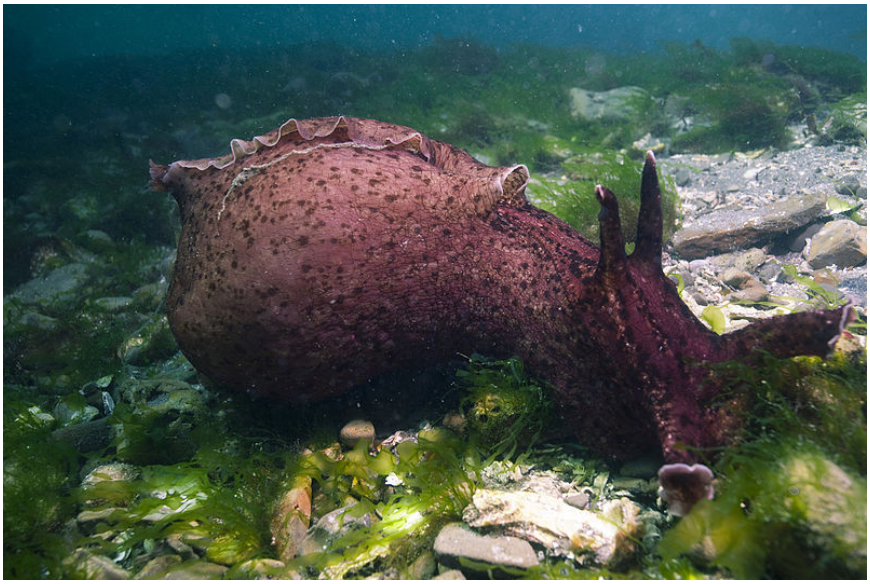


Figure 9.4.2: Aplysia californica. (Image from Wikimedia, Aplysia californica; https://commons.wikimedia.org/wiki/F...,_Monterey.jpg; Chad King / NOAA MBNMS; this image is in the ***public domain*** because it contains materials that originally came from the U.S. *National Oceanic and Atmospheric Administration*, taken or made as part of an employee's official duties).

Eric Kandel (1976) and his colleagues did pioneering work which showed synaptic changes that mediate habituation (see sections above) of the Aplysia's siphon and gill defensive withdrawal reflex. A **decrease in conductivity** was found at synapses involved in the siphon and gill withdrawal reflex in Aplysia after **habituation** to a repeated presentation of a harmless novel stimulus. Kandel and co-workers showed that the **pre-synaptic sensory neuron released less neurotransmitter onto the post-synaptic motor neuron** as a result of repeated presentation of the novel stimulus leading to habituation of the reflex. The opposite was found for increased responsiveness.

Sensitization refers to enhancement of responsiveness to a familiar stimulus. A single small electric shock to the tail of Aplysia heightens its gill withdrawal response for minutes to hours. Kandel and colleagues found that **sensitization** was mediated by an **increase** in release of **neurotransmitter from the pre-synaptic sensory neuron onto the post-synaptic motor neuron** serving the gill muscle. Thus, sensitization is the opposite of habituation both behaviorally and at the level of transmitter release (Kolb and Whishaw, 2001). Later studies showed synaptic changes involving **modified transmitter release** during **classical conditioning** as well (Kandel and Schwartz, 1982).

9.4.2.1 The Special Roles of the Hippocampus, Cerebellum, and Amygdala

As discussed above, research since Lashley has revealed that his speculation that all areas of brain were equally involved in learning and memory was incorrect. Now we know that one of the most important brain regions in **explicit memory** is the **hippocampus**, which serves as a preprocessor and elaborator of information (Squire, 1992). The hippocampus helps us encode information about **spatial relationships**, the **context** in which events were experienced, and the associations among memories (Eichenbaum, 1999). The hippocampus also serves in part as a switching point that **holds the memory for a short time and then directs** the information **to other parts of the brain**, such as the **cortex**, to actually do the rehearsing, elaboration, and **long-term storage** (Jonides, Lacey, & Nee, 2005; Saylor Foundation, 2015). We also now know that different parts of the brain are involved in different kinds of memory.

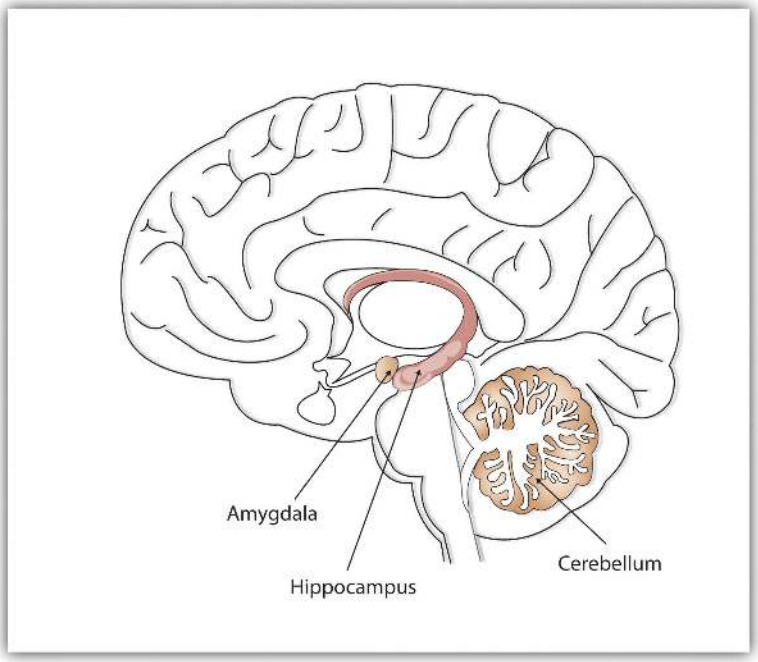


Figure 9.4.3: Different brain structures help us remember different types of information. The hippocampus is particularly important in explicit memories, the cerebellum in implicit memories, and the amygdala in emotional memories (Image and caption from the Saylor Foundation, 2015; Remembering and Judging; https://learn.umgc.edu/d2l/le/conten.../25917628/View; licensed under a Creative Commons Attribution 3.0 Unported License.).

While the hippocampus is handling explicit memory, the **cerebellum** and the **amygdala** are critically involved in **implicit and emotional memories, respectively**. Research shows that the cerebellum is more active when we are learning associations and in priming tasks (based on implicit memory), and animals and humans with damage to the cerebellum are impaired in classical conditioning (Krupa, Thompson, & Thompson, 1993; Woodruff-Pak, Goldenberg, Downey-Lamb, Boyko, & Lemieux, 2000). The storage of many of our most important emotional memories, and particularly those related to fear, is initiated and controlled by the amygdala (Sigurdsson, Doyère, Cain, & LeDoux, 2007).

9.4.3 Changes at the Synapse Correlated with Learning and Memory

Hebb's theory that long-term memory was stored by physical changes at the synapse has been so influential that research on the neural basis of learning and memory has focused primarily on synaptic events. Focus on the synapse was reinforced by the discovery in 1973 in rabbit hippocampus that a **long-lasting increase in synaptic conductivity (synaptic strength)** could be produced **by high frequency stimulation of** the **pre-synaptic neuron** (Bliss and Lomo, 1973). This finding that synaptic strength can be increased for an extended period of time following high frequency pre-synaptic stimulation is now referred to as **Long-Term Potentiation (LTP)**. LTP has been found in many species and in many parts of the brain. However, it has been studied most in the hippocampus of the rat. Since this early research, additional forms of synaptic change have also been discovered.

9.4.4 Synaptic Plasticity

Synaptic plasticity is the strengthening or weakening of synapses over time in response to increases or decreases in their activity. Plastic change also results from the alteration of the number of receptors located at a synapse. Synaptic plasticity is the basis of learning and memory, enabling a flexible, functioning nervous system. Synaptic plasticity can be either short-term (synaptic enhancement or synaptic depression) or long-term. Two processes in particular, **long-term potentiation (LTP) and long-term depression (LTD)**, are important forms of synaptic plasticity that occur in **synapses in the hippocampus**.

9.4.4.1 Long-term Potentiation (LTP)

Long-term potentiation (LTP) is a persistent strengthening of a synaptic connection, which can last for minutes or hours or even weeks. LTP is based on the Hebbian principle: “cells that fire together wire together.” There are various mechanisms, none of which are fully understood, behind the synaptic strengthening seen with LTP.

One known mechanism involves a type of postsynaptic glutamate receptor: **NMDA** (N-Methyl-D-aspartate) receptors. These receptors are normally blocked by magnesium ions. However, when the postsynaptic neuron is depolarized by multiple presynaptic inputs in quick succession (either from one neuron or multiple neurons), the magnesium ions are forced out and Ca^{2+} ions pass into the postsynaptic cell. Next, Ca^{2+} ions entering the cell initiate a signaling cascade that causes a different type of glutamate receptor, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, to be inserted into the postsynaptic membrane. Activated **AMPA** receptors allow positive ions to enter the cell.

Therefore, the next time glutamate is released from the presynaptic membrane, it will have a larger excitatory effect (EPSP) on the postsynaptic cell because the binding of glutamate to these AMPA receptors will allow more positive ions into the cell. The insertion of additional AMPA receptors strengthens the synapse so that the postsynaptic neuron is more likely to fire in response to presynaptic neurotransmitter release.

LTP has many similarities with the synaptic changes Hebb proposed as basis for long-term memory, including two key features. First, LTP is long lasting, up to a year with repeated trials. Second, many forms of LTP require simultaneous activation in pre-synaptic and post-synaptic neurons at the synapse where LTP takes place ("neurons that fire together, wire together"); this is because NMDA (N-methyl-d-aspartate) receptors for glutamate (the most common excitatory transmitter in the brain), which are prominent at synapses where LTP occurs, have the same requirement for simultaneous activity in both pre- and post-synaptic neurons in order for these receptors to become activated. Research showing that many features of LTP are similar to features of long-term memory provides strong circumstantial evidence that LTP is related to the mechanisms of learning and memory. For example, LTP can be stimulated by low intensity stimulation similar to that produced in single neurons; LTP is most prominent in structures associated with learning; LTP is produced in the hippocampus by learning; drugs that enhance or impair learning also enhance or impair LTP; and LTP occurs in the nervous system of simple invertebrates (see discussion of Aplysia above) at the specific synapses involved in the learning (Pinel & Barnes, 2021).

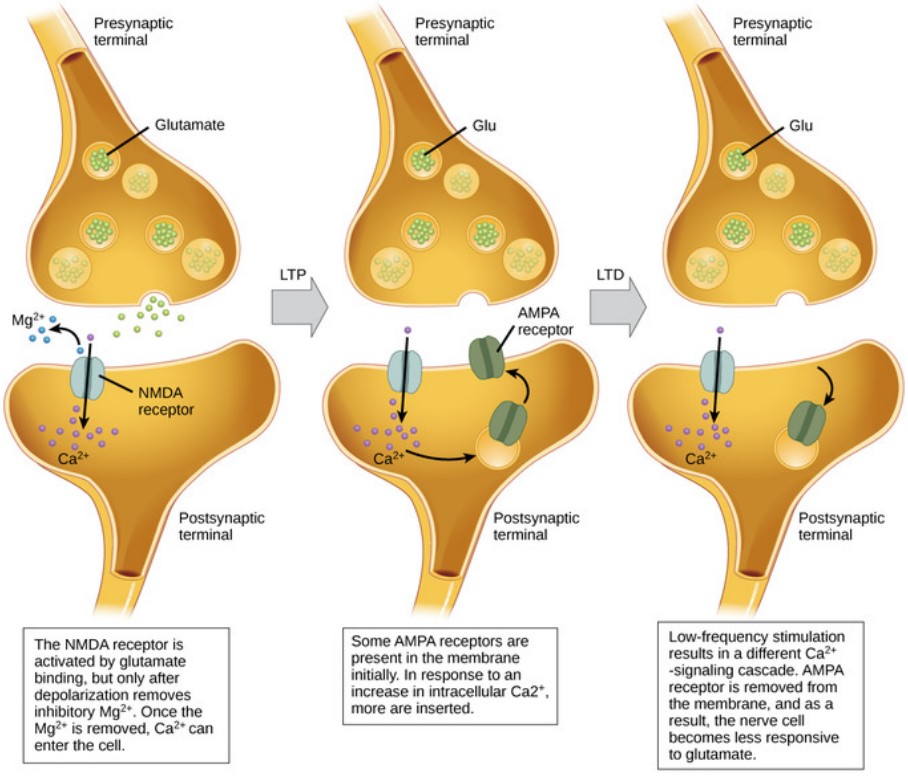


Figure 9.4.4: **Long-term potentiation and depression**: Calcium entry through postsynaptic NMDA receptors can initiate two different forms of synaptic plasticity: long-term potentiation (LTP) and long-term depression (LTD). LTP arises when a single synapse is repeatedly stimulated. This stimulation 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. (Image and caption from Lumen Boundless Biology, How Neurons Communicate; https://courses.lumenlearning.com/bo...s-communicate/; curation and Revision. Provided by: Boundless.com. License: ***CC BY-SA: Attribution-ShareAlike***.)

9.4.4.2 Long-term Depression (LTD)

Another related phenomenon is **long-term depression (LTD)**, associated with decreases in synaptic conductivity. LTD might be part of the processes involved in creating and modifying patterns of excitation and inhibition in large populations of neurons for the coding of learned movements, sensory experience, and perhaps the mental representations of complex cognitive structures such as perceptions, whole memories, concepts, and even abstract ideas (Churchland, 2013). A related possibility is the pruning away of some synapses to form permanent changes in neural circuitry. Long-term depression (LTD) is essentially the reverse of LTP: it is a long-term weakening of a synaptic connection. One mechanism known to cause LTD 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. With the decrease in AMPA receptors in the membrane, the postsynaptic neuron is less responsive to the glutamate released from the presynaptic neuron. While it may seem counterintuitive, LTD may be just as important for learning and memory as LTP. The weakening and pruning of unused synapses trims unimportant connections, leaving only the salient connections strengthened by long-term potentiation.

9.4.4.3 Changes at the Synapse Correlated with Learning and Memory: Anatomical Changes in Dendritic Spines

Modifications in synaptic strengths in excitatory synapses in the hippocampus appear to play a critical role in storage and recall of information in mammals. In humans at least, the role of the hippocampus is especially critical in explicit episodic

(autobiographical) memory. As noted above, it is also crucially involved in spatial memory for many mammal species, including humans. Changes in synaptic strength throughout much of the brain may be important in learning and memory.

9.4.4.4 Dendritic Spines

Dendritic spines are tiny protruding structures located on the shaft of dendrites and are associated with synaptic connections. These spines "are present in large numbers on the surface of dendrites. For example, a single pyramidal neuron in the hippocampal CA1 region possesses as many as 30,000 dendritic spines. A majority of excitatory synapses are formed on the surface of these dendritic spines" (Irie & Yamaguchi, 2009, p. 1141). The primary sites of excitatory synaptic interaction in the mammalian central nervous system appear to be at dendritic spines.

Changes in spines play a significant role during brain development. "In a developing brain, spines exhibit a high degree of structural and functional plasticity, reflecting the formation and elimination of synapses during the maturation of neuronal circuits. The morphology of spines in developing neurons is affected by synaptic activity, hence contributing to the experience-dependent refinement of neuronal circuits, learning, and memory. Thus, understanding spine dynamics and its regulation is of central importance to studies of synaptic plasticity in the brain" (Bertling, et al., 2012, p. 391). During brain development synapses are formed, modified and sometimes eliminated as a function of input to them.

As discussed above, LTP has been shown to lead to functional changes at synapses where it is induced. These changes due to LTP are increased synaptic conductivity and enhanced responsiveness of the post-synaptic neuron. It appears that anatomical changes in spines accompany these changes in synaptic strength which occur during LTP and learning and memory. Changes in synaptic strength, associated with LTP, are accompanied by LTP-induced alterations of the shape and size of dendritic spines (Chidambaram, et al., 2019; Harris, et al., 2003). This is in line with the anatomical changes at the synapse that Hebb predicted.

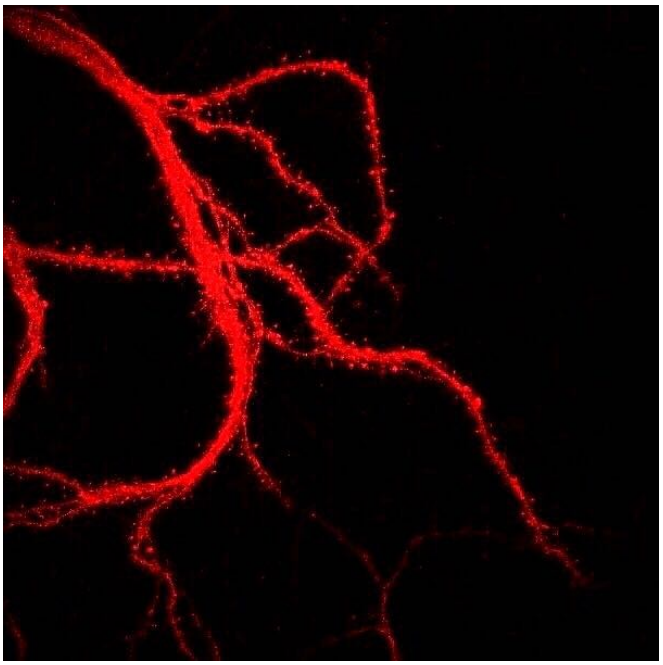


Figure 9.4.5: Branching dendrites of a neuron showing dendritic spines (tiny bristle-like projections lining each dendritic branch). The photograph was obtained with a laser scanning microscope. Dendritic spines can rapidly change in size and shape and numbers, and are important in learning and memory. (Caption by Kenneth A. Koenigshofer, PhD. Image from Wikimedia Commons; File:Нейрональные отростки с шипиками.jpg; https://commons.wikimedia.org/wiki/F...0%BC%D0%B8.jpg; by Sergb95; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

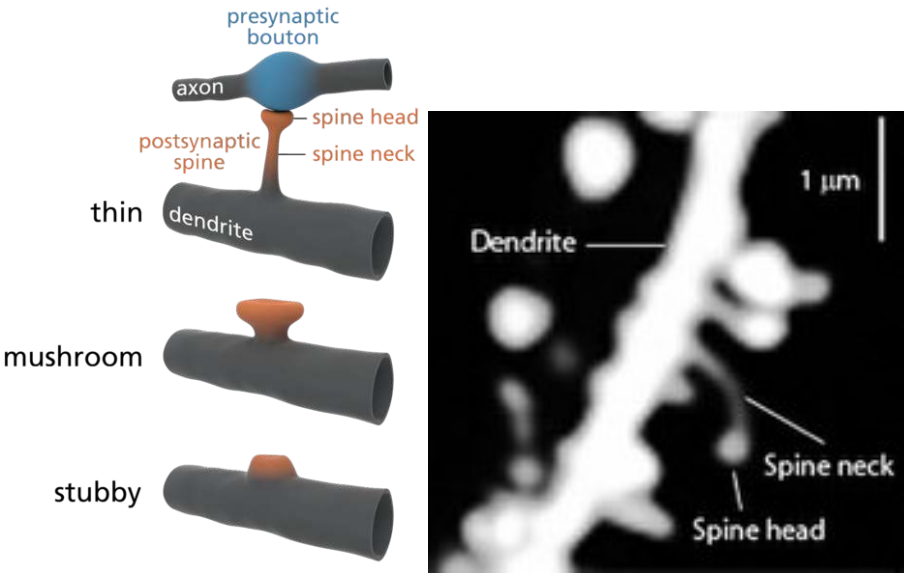


Figure 9.4.6: (Left) Varying morphology of types of dendritic spines. Changes in their shape and size are associated with LTP and learning and memory. (Right) Spines on the dendrite of a medium spiny striatal neuron. The image was obtained by expressing Enhanced Green Fluorescent Protein (EGFP) in the neurons and imaging them using a laser scanning two photon microscope. (Caption for image on left by Kenneth A. Koenigshofer, PhD; Image on left from Wikimedia Commons, Dendritic spines; https://commons.wikimedia.org/wiki/F...e_types_3D.png; original work of Thomas Splettstoesser (www.scistyle.com); licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. Image on right and its caption from Wikimedia Commons, Dendritic spines; https://commons.wikimedia.org/w/inde...=Go&type=image; Released into Public Domain by the image author).

Chidambaram, et al. (2019, p.161) summarize the relationship of changes in synaptic conductivity to changes in dendritic spines: "During synaptic plasticity the number and shapes of dendritic spines undergo radical reorganizations. Long-term potentiation (LTP) induction promotes spine head enlargement and the formation and stabilization of new spines. Long-term depression (LTD) results in their shrinkage and retraction."

Hebb's theory has proven to be impressively predictive of discoveries made many years after his book was published in 1949. Findings like those described in this module continue to confirm many aspects of Hebb's theory.

9.4.4.5 Additional Mechanisms of LTP

"Silent synapses" are another mechanism that was discovered in the mid-1990s and that may contribute to long-term potentiation (LTP). These synapses are physically present, but under normal conditions do not contribute to synaptic transmission.

Some of these silent synapses have been found in the hippocampus. They appear to have receptors for NMDA but not for AMPA. It is thought that these synapses may be activated during LTP and thus help to strengthen the synaptic response. The discovery that after LTP, these synapses do display an electrical current associated with AMPA channels suggests that some newly synthesized AMPA receptors may be inserted into the post-synaptic membrane.

In addition to all of the post-synaptic mechanisms involved in the **establishment of LTP**, it has long been postulated that some pre-synaptic modifications occur during the ensuing **maintenance phase**. But certain modifications, such as an increase in the amount of glutamate released by the pre-synaptic neuron, would imply the presence of a retrograde messenger that goes back to this neuron and modifies it. Because nitric oxide (**NO**) is a gas in its natural state, and can thus diffuse through cell membranes, it would be an ideal candidate for this role. But its involvement is still the subject of much debate and controversy.

The following videos provide a useful animated review of the key elements of LTP:

https://www.youtube.com/watch?v=KyQUBukwwO8

https://www.youtube.com/watch?v=-mHgPfXHzJE

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9.4.7 Attributions

"Learning Objectives," "Overview," "The Search for Learning and Memory in the Synapse," "Changes at the Synapse Correlated with Learning and Memory," "Changes at the Synapse Correlated with Learning and Memory: Anatomical Changes in Dendritic Spines," "LTP, Neurochemical Cascades, and Stages of Memory," original material written by Kenneth A. Koenigshofer, Ph.D., is licensed under CC BY 4.0. Modified by Alan Keys, Ph.D., Sacramento City College, Sacramento, CA.

"Synaptic Plasticity," "Synaptic Plasticity: short-term enhancement, long-term potentiation and long-term depression," "Short-term Synaptic Enhancement and Depression," "Long-term Potentiation (LTP)," and "Long-term Depression (LTD)," adapted by Kenneth A. Koenigshofer, Ph.D., from Lumen Boundless Biology, How Neurons Communicate; https://courses.lumenlearning.com/bo...s-communicate/; curation and Revision. Provided by: Boundless.com. License: ***CC BY-SA: Attribution-ShareAlike.***

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9.5: Brain Mechanisms of Memory Disorders

Learning Objectives

- Explain the roles of the hippocampus and medial temporal lobes in memory.
- Describe the case of H.M. and how it contributed to our understanding of the brain mechanisms in memory.
- Describe global amnesic syndrome.
- Discuss retrograde and anterograde amnesias including temporally graded amnesia.
- Describe amnesia of the frontal lobes.
- Discuss specific amnesias due to specific and circumscribed cortical damage.

9.5.0.1 Overview

We now examine the roles of the hippocampus and medial temporal lobes in memory and memory loss, focusing on amnesic syndromes associated with Korsakoff's Syndrome and Alzheimer's Disease. We also consider frontal lobe amnesia and highly specific forms of amnesia for highly specific types of information due to localized cortical damage. Damage to the amygdala disrupts emotional memories including memories of traumatic events. Diseases or other causes of cellular loss in the hippocampi can produce amnesia.

9.5.0.1 **Amnesia, Hippocampus, and Medial Temporal Lobes**

The Russian psychologist A. R. Luria (1968) has described the abilities of a man known as “S,” who seems to have unlimited memory. S remembers strings of hundreds of random letters for years at a time, and seems in fact to never forget anything. But what would this be like?

Shereshevsky, or “S,” the mnemonist studied by Luria was a man who almost never forgot. His memory appeared to be virtually limitless. He could memorize a table of 50 numbers in under 3 minutes and recall the numbers in rows, columns, or diagonals with ease. He could recall lists of words and passages that he had memorized over a decade before. Yet Shereshevsky found it difficult to function in his everyday life because he was constantly distracted by a flood of details and associations that sprung to mind. His case history suggests that remembering everything is not always a good thing. You may occasionally have trouble remembering where you parked your car, but imagine if every time you had to find your car, every single former parking space came to mind. The task would become impossibly difficult to sort through all of those irrelevant memories. Thus, forgetting is adaptive in that it makes us more efficient. The price of that efficiency is those moments when our memories seem to fail us (Schacter, 1999).

Clearly, remembering everything would be maladaptive, but what would it be like to remember nothing? We will now consider a profound form of forgetting called amnesia that is distinct from more ordinary forms of forgetting. Most of us have had exposure to the concept of amnesia through popular movies and television. Typically, in these fictionalized portrayals of amnesia, a character suffers some type of blow to the head and suddenly has no idea who they are and can no longer recognize their family or remember any events from their past. After some period of time (or another blow to the head), their memories come flooding back to them. Unfortunately, this portrayal of amnesia is not very accurate. What does amnesia typically look like?

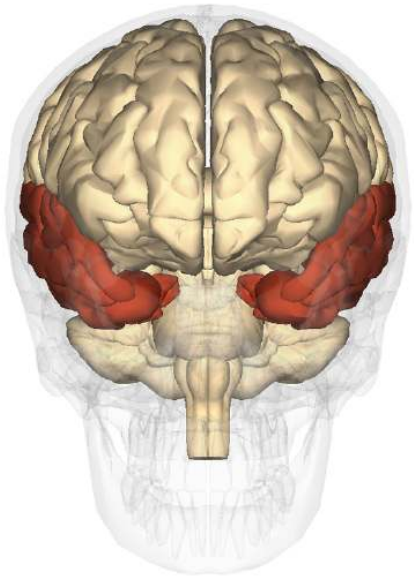


Figure 9.5.1: Patients with damage to the temporal lobes may experience anterograde amnesia and/or retrograde amnesia. [Image from Wikimedia Commons; File:Temporal lobe - anterior view.png; https://commons.wikimedia.org/wiki/F...erior_view.png; by Anatomography; licensed under the Creative Commons Attribution-Share Alike 2.1 Japan license; CC BY-SA 2.1 JP, https://goo.gl/BDF2Z4]

As previously discussed, the most widely studied amnesic patient was known by his initials H. M. (Scoville & Milner, 1957). H.M.'s disorder is an example of **global amnesic syndrome** characterized by severe anterograde amnesia and more moderate retrograde amnesia (see below). This syndrome results from bilateral lesions of the medial portion of the temporal lobe, and more specifically, of the hippocampus and its neighboring structures (the parahippocampal, entorhinal, and perirhinal cortices). These lesions can be due to surgical ablation, as in the case of H.M., or to other causes such as tumors, ischemic episodes, head traumas, and various forms of encephalitis.

As a teenager, H. M. suffered from severe epilepsy, and in 1953, he underwent surgery to have both of his medial temporal lobes removed to relieve his epileptic seizures. The **medial temporal lobes** encompass the hippocampus and surrounding cortical tissue. Although the surgery was successful in reducing H. M.'s seizures and his general intelligence was preserved, the surgery left H. M. with a profound and permanent memory deficit. From the time of his surgery until his death in 2008, H. M. was unable to learn new information, a memory impairment called **anterograde amnesia**. H. M. could not remember any event that occurred since his surgery, including highly significant ones, such as the death of his father. He could not remember a conversation he had a few minutes prior or recognize the face of someone who had visited him that same day. He could keep information in his short-term, or working, memory, but when his attention turned to something else, that information was lost for good. It is important to note that H. M.'s memory impairment was restricted to **declarative memory**, or conscious (explicit) memory for facts and events. H. M. could learn new motor skills and showed improvement on motor tasks even in the absence of any memory for having performed the task before (Corkin, 2002).

In addition to anterograde amnesia, H. M. also suffered from **temporally graded retrograde amnesia**. **Retrograde amnesia** refers to an inability to retrieve old memories that occurred before the onset of amnesia. Extensive retrograde amnesia in the absence of anterograde amnesia is very rare (Kopelman, 2000). More commonly, retrograde amnesia co-occurs with anterograde amnesia and shows a temporal gradient, in which memories closest in time to the onset of amnesia are lost, but more remote memories are retained (Hodges, 1994). In the case of H. M., he could remember events from his childhood, but he could not remember events that occurred a few years before the surgery.

Amnesiac patients with damage to the **hippocampus and surrounding medial temporal lobes** typically manifest a similar clinical profile as H. M. The degree of anterograde amnesia and retrograde amnesia depend on the extent of the **medial temporal lobe damage**, with greater damage associated with a more extensive impairment (Reed & Squire, 1998). Anterograde amnesia provides evidence for the role of the **hippocampus** in the formation of long-lasting declarative memories, as damage to the hippocampus results in an inability to create or consolidate this type of new long-term memory. Similarly, temporally graded retrograde amnesia can be seen as providing evidence for the importance of **memory consolidation** (Squire & Alvarez, 1995). A memory depends on

the hippocampus until it is consolidated (or "fixed") and transferred into a more durable form that is **stored in the cortex**. According to this theory, an amnesiac patient like H. M. could remember events from his remote past because those memories were fully consolidated and no longer depended on the hippocampus, but instead had been transferred to other brain areas, primarily to particular areas of the cerebral cortex.

The classic amnesiac syndrome we have considered here is sometimes referred to as **organic amnesia**, and it is distinct from functional, or dissociative, amnesia. Functional amnesia involves a loss of memory that cannot be attributed to brain injury or any obvious brain disease and is typically classified as a mental disorder rather than a neurological disorder (Kihlstrom, 2005). The clinical profile of dissociative amnesia is very different from that of patients who suffer from amnesia due to brain damage or deterioration. Individuals who experience **dissociative amnesia** often have a history of trauma. Their amnesia is retrograde, encompassing autobiographical memories from a portion of their past. In an extreme version of this disorder, people enter a dissociative fugue state, in which they lose most or all of their autobiographical memories and their sense of personal identity. They may be found wandering in a new location, unaware of who they are and how they got there. Dissociative amnesia is controversial among research psychologists, as both the causes and existence of it have been called into question. The memory loss associated with dissociative amnesia is much less likely to be permanent than it is in organic amnesia.

9.5.0.1 Korsakoff's Amnesia

Another well-known form of amnesia is **Korsakoff's syndrome**, encountered for the first time in chronic alcoholics. Korsakoff's syndrome is similar to global amnesic syndrome, except that people with Korsakoff's are more prone to confabulation to cover up gaps in their memories of their own past. Korsakoff's syndrome is also known as **diencephalic amnesia** (or Wernicke-Korsakoff syndrome), because the vitamin B1 deficiency that results from alcoholism causes bilateral damage to the **mammillary bodies of the hypothalamus**. Similar symptoms are also produced by damage to the **dorsomedial thalamic nuclei, the mammillothalamic tract, and the upper portion of the brainstem**. Once again, other etiologies, such as strokes and tumors, can affect the same structures and produce the same results.



Figure 9.5.2: Brain affected by Wernicke-Korsakoff syndrome. Note the pigmentation of the grey matter around the third ventricle. (Image Source: University of Texas (Houston); https://thebrain.mcgill.ca/flash/a/a...07_cr_oub.html; The Brain from Top to Bottom; Copyleft license).

9.5.0.1 Alzheimer's Disease

In Alzheimer's disease, beta-amyloid, an insoluble toxic substance, forms clumps known as "senile plaques" around the neurons. These plaques release free radicals that strip atoms from organic molecules that are vital to the neurons, including molecules in their cell membranes. Holes thus develop in these membranes, allowing large amounts of harmful substances to enter and kill the neurons. The memory circuits that depend on them, especially those in the hippocampus, are thus permanently damaged.

The National Institute on Aging reports on research indicating that the brains of Alzheimer's patients also contain neurofibrillary tangles which consist of a protein called tau. This protein normally plays a role in healthy microtubules inside neurons that assist with the transport of vital substances within the neuron cell body to the axon and dendrites. In Alzheimer's they form clumps that disrupt the neuron's transport system interfering with synaptic transmission. Complex interactions between beta-amyloid and tangles and other factors may then result in Alzheimer's. "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" (https://www.nia.nih.gov/health/what-...eimers-disease).

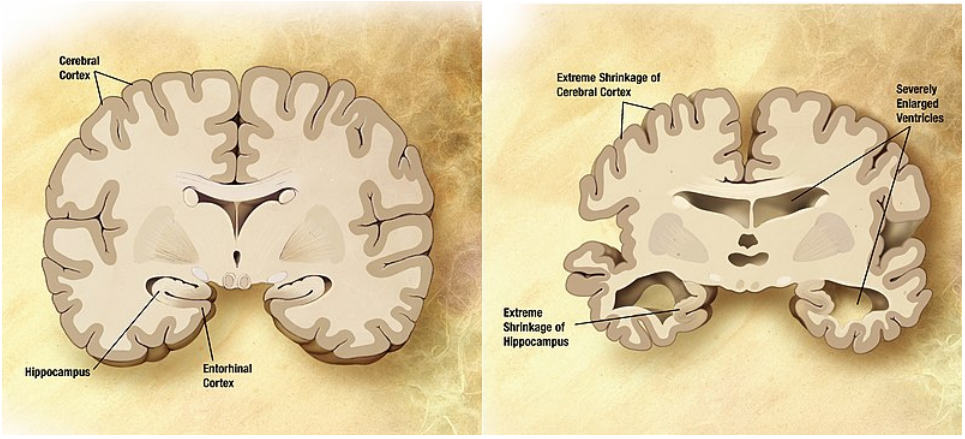


Figure 9.5.3: Diagram showing changes of the brain caused by Alzheimer's disease. Note extreme shrinkage of cerebral cortex and hippocampus, and extensive deterioration and loss of brain tissue resulting in extremely enlarged cerebral ventricles (Image and caption from Wikimedia Commons; File:Alzheimer's disease brain comparison.jpg; https://commons.wikimedia.org/wiki/F...comparison.jpg; by SEVERESLICE_HIGH.JPG: ADEAR: "Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging," modifications by Garrondo; this work is in the **public domain**. This applies worldwide).

According to the National Institute on Aging, "at first, Alzheimer's disease typically destroys neurons and their connections in parts of the brain involved in memory, including the entorhinal cortex and hippocampus. It later affects areas in the cerebral cortex responsible for language, reasoning, and social behavior. Eventually, many other areas of the brain are damaged. Over time, a person with Alzheimer's gradually loses his or her ability to live and function independently. Ultimately, the disease is fatal" (https://www.nia.nih.gov/health/what-...eimers-disease; retrieved 5/11/2022).

9.5.0.1 Specific Cortical Damage and Memory Loss

There is also an **amnesia of the frontal lobe** due to damage at this site. People with this disorder do not suffer from global amnesia, but do show a memory deficit in tasks involving temporal planning of sequences of events. These people also have problems with the sources of newly acquired knowledge and have deficient meta-memory (they cannot make judgments about their memory's contents).

Other types of damage to the cortex can cause forms of amnesia that are **sometimes highly specific**. For example, if the part of the cortex that perceives colors is damaged, people can lose their knowledge of color. And since the memory of colours is reconstructed at this same location, this memory disappears as well.

Other localized cortical lesions can prevent people from accessing certain items in their semantic memory and thus cause all sorts of specialized aphasias (language disorders).

9.5.0.1 Other Specific Forms of Memory Loss

A specific injury to the amygdala can prevent people from recording memories of traumatic events. In normal people, such memories are formed when particularly stressful conditions make certain details of a scene practically unforgettable.

Certain encephalopathies due to anoxias, ischemias, hypoglycemias, carbon monoxide poisoning, or prolonged epileptic attacks can cause the **loss of large numbers of neurons in both hippocampi.**

The pyramidal neurons of hippocampal area CA1, as well as the cortical neurons of layers 3, 5 and 6, the Purkinje cells, and the striate neurons are especially sensitive to lack of oxygen and energy.

Since these neurons are involved in various memory systems, malfunctions in their circuits inevitably lead to memory problems.

Thus, damage to the temporal lobes of the cortex can cause severe, permanent anterograde amnesia, as well as retrograde amnesia extending back from three to ten years before the accident.

When selective neuronal losses occur in area CA1 of the hippocampus, the resulting anterograde amnesia is just as severe, but the resulting retrograde amnesia generally remains slight (extending only one to two years before the accident).

Lastly, certain **transitory global amnesias** can be triggered suddenly, causing people to completely lose their memory for a few hours. Though these transitory amnesic episodes are frightening, they are brief and do not cause any permanent damage to the

brain. They seem to be due to a temporary vascular insufficiency in the brain tissue.

9.5.1 Summary

Amnesiac patients show us what a life without memory would be like. Amnesiac patients suggest a special role for the hippocampus and surrounding medial temporal lobe structures in memory. Korsakoff's Syndrome is caused by vitamin B1 deficiency due to long term use of alcohol. Alzheimer's disease is associated with damage to neurons caused by plaques and tangles. Damage to specific cortical areas can cause very specific forms of memory loss including specific aphasias.

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9.5.3 Attributions

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9.6: Supplemental Section- Detailed Review of Neuroanatomy of Memory

Learning Objectives

- Explain the role of the dorsolateral prefrontal cortex in memory, problem-solving and reasoning.
- Discuss working memory and its various components including the central executive, the phonological loop, episodic buffer, and visuospatial sketch pad
- Describe the region of brain associated with the operation of the central executive
- Describe the brain structures involved in consolidation of new memories into long-term storage
- Explain the different types of memory, three stages of memory, and the brain areas associated with each as discussed below
- Describe the role of place cells in the formation of spatial maps in the hippocampus
- Explain the trisynaptic circuit of the hippocampus and its role in memory

9.6.1 Overview

IMPORTANT NOTE: This section is supplemental and contains a great deal of overlap with previous sections of this chapter.

Here we examine memory from the standpoint of its different types focusing on the role of the hippocampus and other medial temporal lobe structures and circuits in the consolidation of new declarative memories. The hippocampal/mammillothalamic tract, also called Papez's circuit, plays an essential role in this process. After consolidation, long-term memories are stored in the cerebral cortex and become independent of the hippocampus. We also consider the role of the prefrontal cortex in working memory, important for the retention of information during problem-solving and reasoning. In addition, we discuss the role of the hippocampus in spatial memory and in the formation of cognitive maps or mental models of space.

9.6.2 **Types and Stages of Memory Localized in Different Brain Regions**

A large body of evidence indicates that the **dorsolateral prefrontal cortex** plays an important role in certain forms of memory work (Barbey, et al., 2013), in particular those that involve alternating between two memory tasks and exploring various possibilities before making a choice (Hunt et al., 2015). It seems fairly certain that dorsolateral prefrontal cortex holds information required for reasoning processes that are in progress.

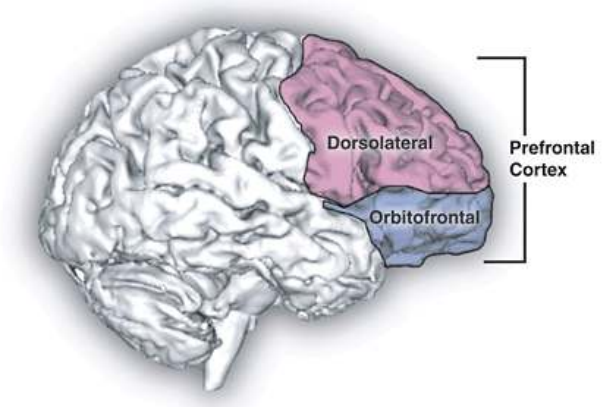


Figure 9.6.1: Divisions of Human Prefrontal Cortex (Image from Wikimedia Commons; File:Prefrontal cortex.png; https://commons.wikimedia.org/wiki/F...tal_cortex.png; by Natalie M. Zahr, Ph.D., and Edith V. Sullivan, Ph.D.; image is a work of the National Institutes of Health and is in the public domain).

9.6.2.1 Short-term Memory

Short-term memory depends on the attention paid to the elements of sensory memory. Short-term memory lets you retain a piece of information for less than a minute and retrieve it during this time. One typical example of its use is the task of repeating a list of items that has just been read to you, in their original order. In general, you can retain 5 to 9 items (or, as it is often put, 7±2 items) in short-term memory. It is clear that **short-term memory does not depend on** the **medial temporal cortex including the hippocampus and surrounding structures**. We know this because H.M. who had bilateral removal of his medial temporal lobe still retained his short-term explicit memory. If someone came into the room, he could remember the visit for a short time. Of

course, as you have learned, if we checked his recollection a few minutes later, without ability to consolidate the memory into a long-term form, he would have no recollection of the visit that occurred just minutes before. This suggests that the **dorsolateral prefrontal cortex**, left intact in H.M., may be at least **one of the structures capable of retaining information for a brief period, particularly when engaged in reasoning and decision-making.** But its precise role remains the subject of much debate.

9.6.2.2 Working Memory

Working memory is a more recent extension of the concept of short-term memory. As techniques for studying memory have become more refined, it has become increasingly apparent that the original conception of short-term memory as a mere temporary receptacle for long-term memory is too simplistic. In fact, it is becoming increasingly clear that there is no strict line of demarcation between memories and thoughts. In order to test some hypotheses that may provide a better understanding of this complex phenomenon, the concept of working memory has therefore been advanced.

Working memory is used to perform cognitive processes on the items that are temporarily stored in it. It would therefore be heavily involved in processes that require reasoning, such as reading, or writing, or performing computations. One typical example of the use of working memory is the task of repeating a list of items that has just been read to you, but in the reverse of their original order. Another good example is the task of simultaneous language interpretation, where the interpreter must store information in one language while orally translating it into another. In the course of a day, there are many times when you need to keep some piece of information in your head for just a few seconds. Maybe it is a number that you are “carrying over” to do a subtraction, or a persuasive argument that you are going to make as soon as the other person finishes talking. These are good examples of why you usually hold information in your short-term/working memory: to accomplish something that you have planned to do. Perhaps the most extreme example of working memory is a chess master who can explore several possible solutions mentally before choosing the one that will lead to checkmate.

Working memory appears to be composed of several independent systems, which would imply that we are not aware of all the information that is stored in it at any given time. For example, when you drive a car, you are performing several complex tasks simultaneously. It is unlikely that all of the various types of information involved are being handled by a single short-term memory system.

Baddeley & Hitch (1974) proposed a model of **working memory** with **several components**: a certain number of auxiliary “slave” systems and a **central executive** that supervises and controls the flow of information to and from the "slave systems," which are short-term storage repositories for particular types or domains of information. One of these slave systems, the **phonological or articulatory loop**, specializes in processing linguistic information, while another, the **visuospatial sketchpad**, specializes in processing visual-spatial information. The **episodic buffer** is a third storage system, **dedicated to linking information across domains to form integrated units of visual, spatial, and verbal information** (e.g., the memory of a story, a movie scene, or an integrated autobiographical memory). The episodic buffer is also assumed to have **links to long-term memory**.

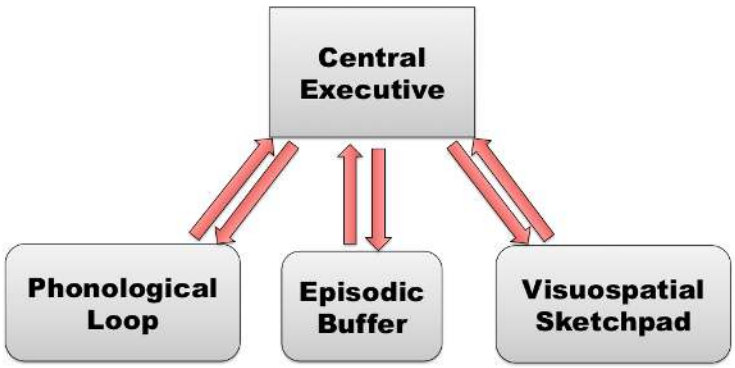


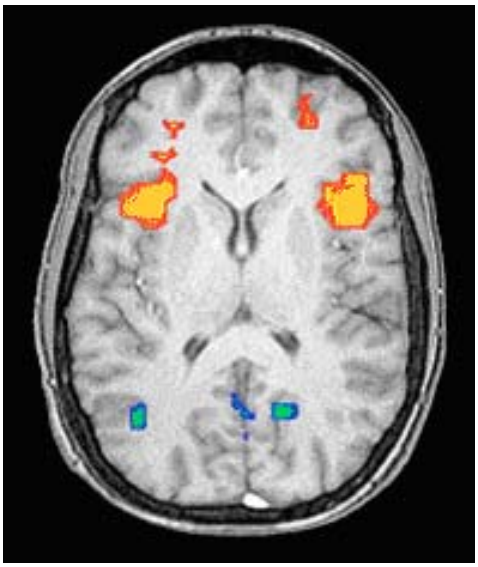
Figure 9.6.2: Baddeley's Model of Working Memory. (Image from Wikimedia Commons; Baddeley's Model of Working Memory; https://commons.wikimedia.org/wiki/F...ing_Memory.png; author, AmandaSilver15; permission is granted to copy, distribute and/or modify this document under the terms of the **GNU Free Documentation License**, Version 1.2 or any later version published by the Free Software Foundation).

The phonological or articulatory loop plays an important role in everyday life. For example, when you repeat a phone number to yourself in your head, you are activating this loop. This loop is also heavily involved in reading and writing. The presence **in**

working memory of another slave system that can manipulate mental images of visual objects is suggested by tests where subjects are asked to rotate such images.

Perhaps the most important but least understood component in Baddeley's model of working memory is the **central processor or central executive**, whose job would be to select, initiate, and halt the routines performed by its slave systems.

Baddeley's model of **working memory** has proven especially fruitful for research on the brain areas involved in problem solving. This model posits a **central executive** or **central processor** that coordinates the activity of two sub-systems. Many brain-imaging studies show high activity in the frontal lobe, in particular the **prefrontal lobe,** when this central executive is working. For example, the image shown below (see Figure 10.5.3.2) was produced by **functional magnetic resonance imaging (fMRI)**. As you have learned in a previous chapter, fMRI is a technique based on the increased blood flow to the most active areas of the brain. In this image, taken while the subject was holding an image of a face in his memory, the yellow area in the **prefrontal cortex** is very active, confirming the role of these prefrontal cortical areas in working memory.



9.6.2.3

Figure 9.6.3: fMRI images of brain showing increased activity in the frontal lobes while the subject is keeping an image of a face in his memory (Image from NIMH Laboratory of Brain and Cognition. Published in *Nature*, Vol 386, April 10, 1997, p. 610, Courtney et al., 1997).

As you have learned in an earlier chapter, this region, at the very front of the brain, is highly developed in humans. It appears that the **prefrontal cortex**, by holding information in storage during **working memory**, may play a significant role in functions related to **attention, problem-solving, and intelligence** (Conway et al., 2003; Engle et al., 1999; Kane & Engle, 2002; Matzel and Kolata, 2010; Barbey et al., 2014; Waltz et al., 1999).

Recall that Baddeley's model also postulates the existence of a **phonological** (acoustic and linguistic) memory and a **visual/spatial** memory (containing mental images). Brain imaging studies have also revealed distinct neuroanatomical bases for both of these forms of short-term working memory.

The **phonological loop** activates certain areas in the **left hemisphere** that are associated with the production of language, such as **Wernicke's area in the temporal lobe** and **Broca's area in the frontal lobe**. **Visual/spatial memory** seems to be associated with a region of the **occipital cortex** generally associated with visual processing. This is consistent with the hypothesis that visual imagination in which humans can manipulate visual images in the "mind's eye" to mentally test out and anticipate future consequences of action involves parts of the visual system "recruited" into this new function during evolution (Koenigshofer, 2017).

Meanwhile, certain sub-regions of the **prefrontal cortex** are activated only if the memorization exercise is somewhat difficult for the subject, thus confirming the coordinating role of the **central executive**.

The phenomenon of working memory is made all the more complex by the fact that it takes place over time. For example, the experimental results illustrated below show how various areas of the subjects' brains alter their activity levels as the subjects are presented with various visual stimuli. When the subjects are shown a blurred image, the activity level (represented by the blue bars

in the graph) becomes highest in area 1, the visual part of the brain. When the subjects are shown an image of a face, brain activity (black bars) becomes highest in the **associative and frontal regions** (4, 5, and 6). Lastly, when the subjects are retaining an image of a **face** in their working memory, brain activity (red bars) is highest in the **frontal** regions, while the **visual areas are scarcely stimulated at all**.

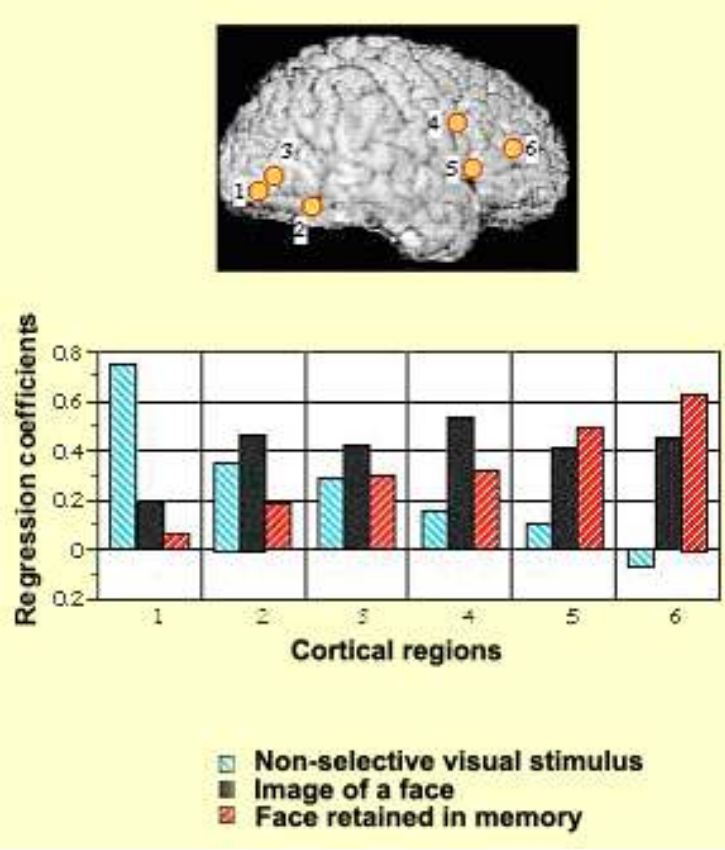


Figure 9.6.4: Activity in cortical areas (labeled 1-6 in image of cortical surface) primarily in occipital lobe with presentation of blurred image (blue bars, tallest in area 1), in frontal and association cortical areas with presentation of a photo of a face (black bars), and in frontal areas (areas 5 and 6), with little activity in visual areas (red bars in cortical areas 1 and 2), when subject retains memory of a face in working memory (red bars). (Image source: NIMH Laboratory of Brain and Cognition. Published in *Nature*, Vol. 386, April 1997, p. 610, Courtney et al., 1997).

It has also been observed that distinct processes appear to be involved in the storage and recall of items memorized with the phonological loop and the visual/spatial sketchpad. One thing is certain: the **prefrontal cortex** plays a fundamental role in **working memory**. It enables people to keep information available that they need for their current reasoning processes. For this purpose, the prefrontal cortex must cooperate with other parts of the cortex from which it extracts information for brief periods. For this information to eventually pass into longer-term memory, the limbic system has to be brought into play.

9.6.2.4 Long-Term Memory

Recent research has provided a complex, highly intricate picture of memory functions and their loci in the brain. The **hippocampus, the temporal lobes, and the structures of the limbic system that are connected to them** are essential for the **consolidation of long-term declarative memory**. The **hippocampus receives** connections **from** the **cortex's primary sensory areas, unimodal associative areas** (those that involve only one sensory modality), and **multimodal associative areas**, as well as from the **rhinal and entorhinal cortexes.** While these anterograde connections converge at the hippocampus, other, retrograde **pathways emerge from it**, returning **to** the **primary cortexes**, **where** they record in the cortical synapses the **associations facilitated by the hippocampus**. Thus, in the mechanism of memorization, we find **feedback loops among these various brain structures.**

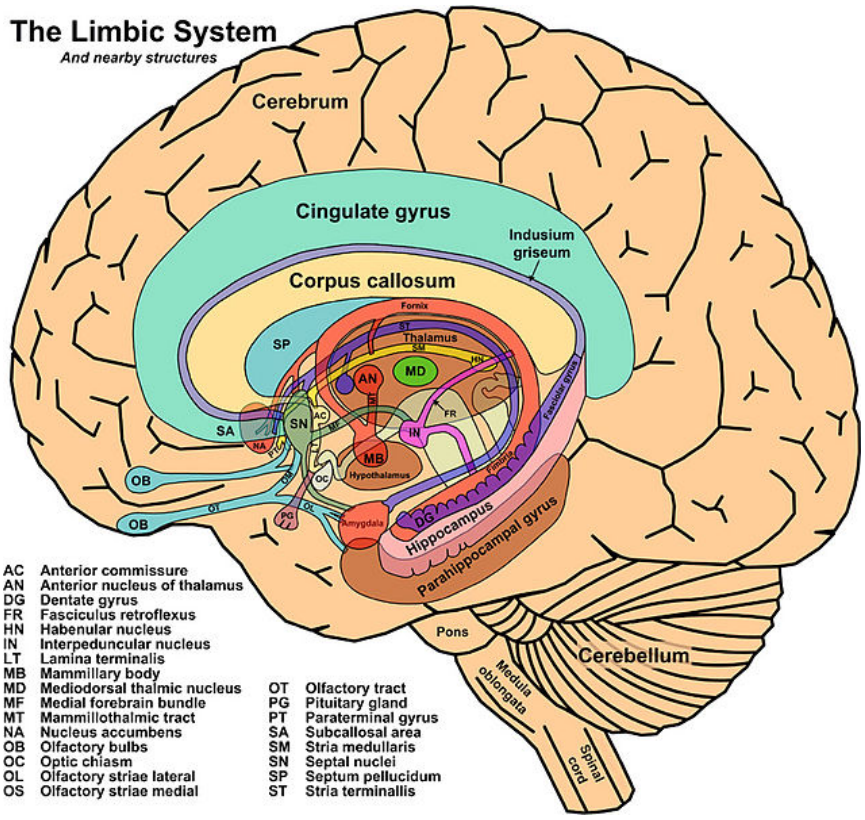


Figure 9.6.5: Limbic system and surrounding structures (Image from Wikimedia; Structures of the Limbic System; https://commons.wikimedia.org/wiki/F...ohn_Taylor.jpg; This work has been released into the **public domain** by its author, John Taylor).

9.6.2.5 Hippocampus

The **hippocampus facilitates associations among various parts of the cortex**, for example, between a tune that you heard at a dinner party represented in auditory cortex in the temporal lobe and the faces of the other guests who were at the table, represented in the visual areas and frontal areas of cortex. However, all other things being equal, such associations would naturally fade over time, so that your mind did not become cluttered with useless memories. What might cause such associations to be strengthened and eventually etched into long-term memory very often depends on "limbic" factors, such as how interested you were in the occasion, or what emotional charge it may have had for you, or how gratifying you found its content.

Recall from prior modules of this chapter that the **hippocampus, the cortical structures surrounding it, and the neural pathways that connect them to the cortex** as a whole are all heavily involved in **declarative memory**–the memory of facts and events. Declarative (explicit) memory is composed of **semantic memory** (memory for facts and knowledge) and **episodic memory** (memory for episodes in your life).

Semantic memory is the system that you use to store your knowledge of the world. It is a knowledge base that we all have and much of which we can access quickly and effortlessly. It includes our memory of the meanings of words–the kind of memory that lets us recall not only the names of the world's great capitals, but also social customs, the functions of things, and their color and odor and other sensory properties.

Semantic memory also includes our memory of the rules and concepts that let us construct a **mental representation of the world** without any immediate perceptions. Its content is thus **abstract and relational** and is associated with the meaning of verbal symbols.

The **hippocampus** also plays a fundamental role in **episodic memory** (sometimes called **autobiographical memory**), the kind of memory that lets you remember events that you personally experienced at a specific time and place. For example, episodic memory lets you remember an especially pleasant dinner party years later. In fact, it seems to be the **hippocampus** that **enables** you to

"**play the scene back**", by reactivating this particular activity pattern in the various regions of the cortex. This phenomenon would be very important during dreams, and would explain the incorporation of events from the last few days into them.

The various structures of the limbic system exert their influence on the hippocampus and the temporal lobe via **Papez's circuit**, also known as the **hippocampal/mammillothalamic tract**. This circuit is a sub-set of the numerous connections that the limbic structures have with one another. The route that information travels in this circuit is **from** the **hippocampus to** the **mammillary bodies of** the **hypothalamus,** then on to the **anterior thalamic nucleus,** the **cingulate cortex,** and the **entorhinal cortex,** before finally returning **to** the **hippocampus** (see Figure 10.5.5).

Once the temporary associations of cortical neurons generated by a particular event have made a certain **number of such "passes" through Papez's circuit**, they will have undergone a physical remodeling that **consolidates** them. Eventually, these associations will have been strengthened so much that they will stabilize and become **independent of the hippocampus**. As you have already learned, bilateral lesions of the hippocampus will prevent new long-term memories from forming, but will not erase those that were encoded and consolidated before the injury.

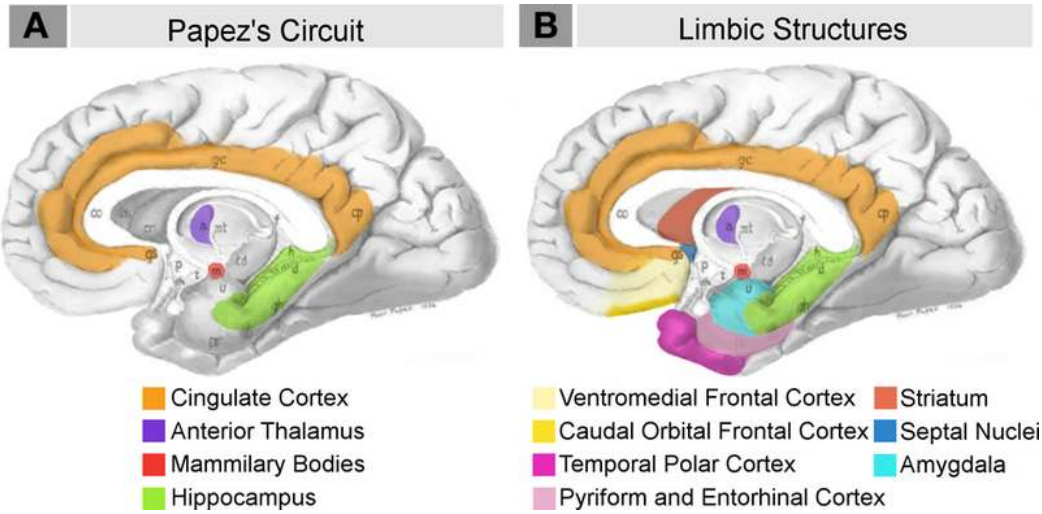


Figure 9.6.6: Papez Circuit and Limbic system structures some of which are involved in memory and emotion. (Images from Wikimedia Commons; File:Neural systems proposed to process emotion.png; https://commons.wikimedia.org/wiki/F...ss_emotion.png; by Barger N, Hanson KL, Teffer K, Schenker-Ahmed NM and Semendeferi K; licensed under the Creative Commons Attribution 3.0 Unported license. Caption by Kenneth A. Koenigshofer, PhD).

With this gradual disengagement of the **limbic system**, the **memories** will **no longer pass through Papez's circuit**, but **instead will be encoded in specific areas** of the **cortex:** the **same ones where the sensory information that created the memories was initially received** (the occipital cortex for visual memories, the temporal cortex for auditory memories, etc.).

Some very intense personal memories that bring what is sometimes called **emotional memory** into play appear to involve another structure of the limbic system besides the hippocampus. This structure is the **amygdala**, located beneath temporal lobe cortex near the hippocampus, and not surprisingly, as discussed in an earlier chapter, the amygdala is already known to manage our reactions to fear. Emotional memories can be very strong and particularly long-lasting. The **release of norepinephrine** during highly emotional events may contribute to the rapid and effective **consolidation** of memory for emotionally-charged events.

9.6.3 Injury to the Limbic System Pathways and Memory

As described above, for a piece of information to be recorded in long-term memory, it must pass through **Papez's circuit**. Injuries to this circuit can result in memory impairments. For example, a **lesion in the mammillary bodies** is responsible for an **amnesic syndrome** whose most classic example is **Korsakoff's** syndrome. In addition to the confabulation, confusion, and disorientation that accompany this syndrome, patients suffer from **anterograde amnesia**: they cannot store new information in their long-term memory. The most typical cause of this syndrome is **vitamin B1 deficiency**, often seen in chronic alcoholics.

9.6.4 Spatial Memory and a Role in Episodic Memory

The **hippocampus** appears to play a fundamental role in **spatial memory** in many animal species, including humans. For example, in a British study, the researchers asked taxi drivers to imagine their travels through the city of London, while their brain activity was monitored by positron emission tomography (PET scan). This task, which was so familiar to these subjects, caused a specific activation of their **right hippocampus**. Unlike our memory of facts and events, **spatial memory** appears to be confined to the hippocampus. And more specifically to the right hippocampus. This structure seems to be able to create a **mental map of space**, thanks to certain cells called **place cells**.

An amazing discovery in the 1970s demonstrated that a rat's **hippocampus** is a veritable **spatial map** of the environment through which it moves. Certain pyramidal neurons in **area CA1** of the **rat hippocampus** become active only when the rat is located in a specific part of its environment. There are 1 million of these "**place cells**" in area CA1 of the rat hippocampus, so that if each one is assigned a specific point in space, together they can form a very precise **cognitive map** that tells the animal where it is at any given time. Moreover, when a rat explores a new environment, it forms a new cognitive map that can be very stable, lasting weeks or months.

According to O'Keefe and Nadel (1978), the researchers who discovered the existence of these **cognitive maps**, one of their functions might be to provide a **context** to which **episodic memories** can be **attached**, in particular, their **location in space and time**. An event recorded in memory could **thus** be made **autobiographical** (situated in personal time and space). This would explain the fundamental **role** that the **hippocampus** plays in **episodic memory** in humans.

The **hippocampus** proper is **composed of** regions with tightly packed pyramidal neurons, mainly areas **CA1, CA2, and CA3.** ("CA" stands for Cornu Ammonis, or Horn of Ammon. The reference is to the ram's horns of the Egyptian god Ammon, whose shape these three areas together roughly resemble.) This is what is called the **trisynaptic circuit** or trisynaptic loop **of** the **hippocampus. Information enters this one-way loop via** the **axons of the entorhinal cortex** (part of the medial temporal cortex), known as **perforant fibers** (or the **perforant path,** because it penetrates through the subiculum and the space that separates it from the dentate gyrus, which is also in the temporal lobe, adjacent to the hippocampus; some anatomists consider it part of the hippocampus). These axons of the **perforant path** make the loop's **first connection**, **with** the **granule cells** of the **dentate gyrus**, the **first region where all sensory modalities merge together** to form representations and **memories that bind stimuli together** (Science Direct; https://www.sciencedirect.com/topics...0and%20memory.), a critical step in learning and memory.

From granule cells of the dentate, the **mossy fibres** in turn project to make the loop's **second connection**, **with** the dendrites of the **pyramidal cells** in area **CA3** of the hippocampus.

The **axons of these CA3 cells divide** into **two branches**. **One** branch forms the commissural **fibers** that project **to** the **contralateral hippocampus via** the **corpus callosum**. The **other branch** forms the Schaffer collateral pathways that make the **third connection** in the loop, **with** the cells in area **CA1** of hippocampus. It is in these synapses that the **spatial memory,** associated with the hippocampus, seems to be encoded.

This region also displays a **high propensity for long-term potentiation (LTP)**, though this same phenomenon is **also** observed **in many other parts of the hippocampus** as well as in the **cortex**.

Lastly, the **axons of** the **cells in CA1** project **to** the neurons of the **subiculum** and of the **entorhinal cortex**. The **receiving portion of** the **hippocampal formation** thus consists of the **dentate gyrus**, while the **sending portion** consists of the **subiculum**. The axons of the **large pyramidal neurons of** the **subiculum** then **project to** the **subcortical nuclei via** the **fimbria**, a thin tract of white matter at the inner edge of the hippocampus (see Figure 10.4.8). **Lastly**, the information **returns to** the **sensory cortical areas from which it came** before it was processed by the hippocampus.

Thus, **entorhinal cortex projects strongly to dentate gyrus and hippocampus** and then **from hippocampus back to cortex** (Van Hoesen and Pandya, 1975b). Being **situated between cortex and the hippocampus, entorhinal cortex plays a critical role in memory** (Zola-Morgan et al., 1989). Even though the neurons of the hippocampus may seem like just a transit point in the establishment of long-term memory, they actually display a great deal of plasticity. This plasticity, as you have learned in previous sections, is manifested chiefly through **long-term potentiation (LTP)**, which was first discovered in the **hippocampus** but has subsequently been demonstrated in **many regions of** the **cortex**.

9.6.5 Summary

Memory can be understood in terms of types and stages. Different brain structures and circuits are involved in these different types and stages of memory. Dorsolateral prefrontal cortex appears to hold information required for reasoning and decision making processes. The prefrontal cortex is important for retention of information during working memory. Working memory has several components which interact and which have links to long-term memory. Consolidation of new declarative memories depends upon feedback loops between the cortex, the hippocampus, and other limbic structures in the medial temporal lobes. A group of these structures involved in memory, called Papez's circuit or the hippocampal/mammillothalamic tract, includes the hippocampus, cingulate cortex, mammillary bodies, and anterior thalamus. Damage to the mammillary bodies, commonly due to B1 vitamin deficiency associated with alcoholism, causes Korsakoff's amnesia. The hippocampus in rats forms spatial cognitive maps involving the use of hippocampal pyramidal neurons that function as place cells which code particular locations in the environment that the rat moves through.

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9.6.7 Attributions

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CHAPTER OVERVIEW

10: Wakefulness and Sleep

10.1: Consciousness
10.2: What is Sleep?
10.3: Stages of Sleep
10.4: More Neuroanatomy of Sleep
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10.1: Consciousness

Learning Objectives

- Differentiate the main theories of consciousness.
- Describe the Default Mode Network including its associated brain structures and its role in varying levels of consciousness

10.1.1 Overview

What does it mean to be conscious? Clearly when someone has fainted, they are unconscious, and when they are sitting up and solving a math problem alongside you they are conscious. But consider the case of a child sleepwalking through their home in the middle of the night and not answering when asked if everything was alright. Would you say she was conscious? Alternately, is there a difference between the kind of consciousness someone experiences while taking an exam, versus when they have eaten some THC edibles or are meditating? This chapter will examine theories about whether consciousness varies on levels or types. We will also explore research looking at the brain underpinnings of these different states including the role of the Default Mode Network (brain areas involved in resting and wakefulness).

10.1.2 Theories of Consciousness

Conscious states can be thought of as global dimensions of consciousness that can modulate how we think, feel and behave (Bayne and Hohwy 2016; Bayne et al. 2016). For example, in the state of ordinary waking awareness, a wide variety of inputs can enter consciousness, and a wide variety of cognitive and behavioral capacities can be exercised. In other conscious states, however, both the range of conscious content and the range of cognitive and behavioral capacities may be curtailed. Conditions that are often associated with changes in conscious state include post-comatose disorders of consciousness (Bruno et al. 2011; Casarotto et al. 2016), sleep and drug-induced sedation (Sarasso et al. 2015), and certain pathologies of consciousness, such as epileptic absence seizures (Gloor 1986; Blumenfeld 2005; Bayne 2011). For example, Minimally Conscious State patients can track certain features of their environment (such as the presence of motion or the semantic content of simple instructions), but they lack the capacity to engage in complex forms of cognition or behavior, and they seem unable to entertain complex thoughts or ideas (Giacino et al. 2002).

The **Integrated Information Theory of Consciousness (IITC)** is one theory suggesting that consciousness can be explained in terms of levels (Tononi & Koch, 2015). However, this assumes that conscious states can be ordered along a single continuum. Indeed, using transcranial magnetic stimulation and computerized compression of the wave patterns that result, Casali et al (2013) figured out a way to objectively measure different states of consciousness including healthy subjects who are awake, dreaming, in NREM sleep, and those who are sedated, as well as in patients who had emerged from coma. But these are still not quite levels, and might indeed be thought of as qualitatively separate states of consciousness.

On the other hand, Bayne and Carter (2018) claim that consciousness ought to be construed in multidimensional terms, and that conscious states can differ from each other along multiple dimensions. For example, one of their central claims is that although the psychedelic state is distinct from the state of ordinary waking awareness, it is neither ‘higher’ nor ‘lower’ than the state of ordinary waking awareness.

The **Global Workspace Theory of Consciousness** (Dahaene et al., 2017) holds that changes in consciousness only involve ‘vigilance’ and ‘wakefulness’ where there is global availability of content. But this theory does not consider the multidimensional nature of consciousness.

Consider the state of consciousness elicited by psychedelic drugs. The psychedelic state involves a state that certainly differs from that associated with ordinary waking awareness, but there is no reason to think that individuals in the psychedelic state are more conscious (or, for that matter, less conscious) than individuals who are not in it. Why do psychedelics increase the vividness, complexity and possibly also the bandwidth of sensory experience? What explains the systematic effects that psychedelics have on the experience of unity across a wide range of domains (e.g. time, space and the self)? Addressing these questions have helped researchers to identify the various dimensions that structure consciousness. Additionally, since much is known about the neurochemical effects of psychedelics, using this knowledge in both animal models and human imaging might provide a window into understanding the neural basis of consciousness.

10.1.3 Default Mode Network

Raichle et al coined the term, **Default Mode Network (DMN)** in 2001 to describe how the brain is constantly active even when not doing anything actively (See Figure 10.1.1). The regions in this network exhibit decreased activation when engaging in goal-oriented or attention-demanding tasks, and therefore facilitate a "default" functional state within the brain. (Raichle et al., 2001; Figure 10.1.1).

The brain is constantly active even when it is not engaged in a task. This network is active when one is in a state of wakeful rest, for example when one is daydreaming, relaxing, or meditating. It used to also be called the task negative network – meaning that it was deactivated when we are engaged in a particular task. The main parts in this network include the medial prefrontal cortex, posterior cingulate cortex/precuneus and angular gyrus.

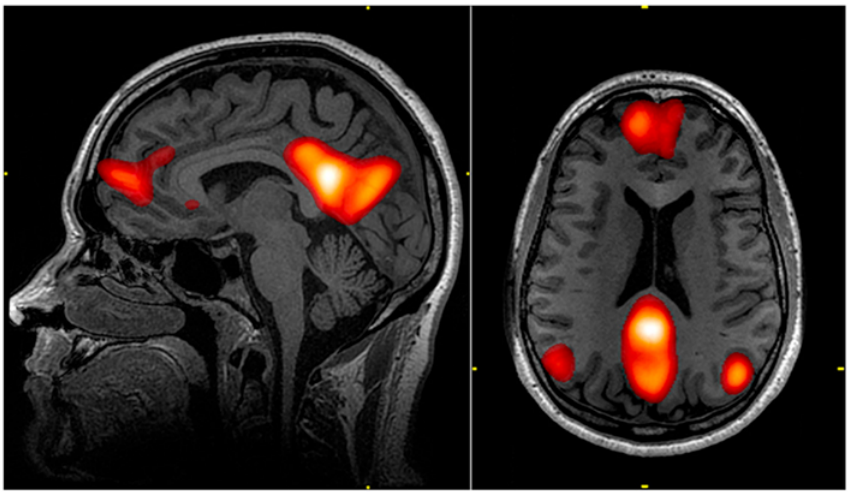


Figure 10.1.1: FMRI of Default Mode Network from Functional MRI in the investigation of blast-related traumatic brain injury by Graner, Oakes, French and Riedy in the Public Domain.

DMN activation is modulated in different types of consciousness changes. Table 10.1.1 summarizes studies showing these connections.

Table 10.1.1: Different studies have shown the ways in which the Default Mode Network (DMN) is affected by psychological events.

Consciousness change	Effect on DMN	Research credit
Acupuncture	DMN connectivity reduced in pain response	Huang et al, 2012
Meditation	Structural changes in areas of precuneus	Fox et al, 2014
Resting wakefulness	Increase in DMN	Picchioni et al, 2013
Sleep deprivation	Decrease in connectivity	McKenna & Eyler, 2012
Use of psychedelics	reduced blood flow to precuneus and medial prefrontal cortex	Carhart-Ellis et al, 2012
Deep brain stimulation	used to rebalance the restful brain structures	Kringelbach et al, 2011
Psychotherapy	helps stabilize the DMN in PTSD sufferers	Sripada et al, 2012
Attention training techniques	help increase connectivity in DMN	Kowalski et al, 2020
Antidepressant use	improves abnormalities in DMN in PTSD sufferers	Akiki et al, 2017
Physical activity and exercise	alters DMN	Shao et al, 2019; Muraskin et al, 2016; Voss et al, 2019

10.1.4 Summary

There has been a lot of research into what consciousness means philosophically and how that ties in with brain activity. Clearly, when one is asleep there is a difference in the awareness of stimuli, thought and function behaviorally. Biological psychologists have attempted to establish whether the differences in consciousness experienced while awake, asleep, under the influence of different drugs, while meditating, and in comatose states are qualitative or quantitative differences. Images of the brain in these different conditions have helped scientists come up with theories - and arguments - for each of these positions

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10.1.6 Attributions

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10.2: What is Sleep?

Learning Objectives

1. Evaluate the complex nature of sleep, rather than simply the absence of wakefulness.
2. Demonstrate a general understanding of the biological nature of sleep.
3. Evaluate the importance of sleep, its functions and the negative ramifications of sleep deprivation.

10.2.1 Overview

When you are asleep are you unconscious? Why do all animals appear to need sleep, some at great expense and danger? Is it true that we "need" sleep every night, or are we just wasting time (about a third of our lives if we follow the 8 hours a day recommendation)? Really all we are doing is laying down and turning off the lights, right? And our brain just shuts off for that time, right?

The nature of sleep as a biological process that is generated by the brain will be discussed in this chapter. In this section, some ideas about how these discoveries came about are contrasted against people's general belief that sleep is just something that happens when one is not doing anything else.

10.2.2 What is Sleep?

Sleep is a complex biological process. While you are sleeping, you may appear unconscious (though there is certainly a difference between being asleep and having fainted), but your brain and body functions are still active. They are doing a number of important jobs that help you stay healthy and function at your best. So when you don't get enough quality sleep, it does more than just make you feel tired. It can affect your physical and mental health, thinking, and daily functioning.

Sleep is an important part of your daily routine—you spend about one-third of your time doing it. Quality sleep – and getting enough of it at the right times -- is as essential to survival as food and water.

Everyone needs sleep, but its full biological purpose remains a mystery. Sleep affects almost every type of tissue and system in the body – from the brain, heart, and lungs to metabolism, immune function, mood, and disease resistance. Research shows that a chronic lack of sleep, or getting poor quality sleep, increases the risk of disorders including high blood pressure, cardiovascular disease, diabetes, depression, and obesity.

Sleep is important to a number of brain functions, including how nerve cells (neurons) communicate with each other. In fact, your brain and body stay remarkably active while you sleep. Recent findings suggest that sleep plays a housekeeping role that removes toxins in your brain that build up while you are awake (Xie et al, 2013).

Without sleep you can’t form or maintain the pathways in your brain that let you learn and create new memories, and it’s harder to concentrate and respond quickly.

Sleep is a complex and dynamic process that affects how you function in ways scientists are now beginning to understand.

10.2.3 Functions of sleep

10.2.3.1 Memory consolidation

One idea about why we sleep is that sleeping **reinforces learning and memory**, while at the same time, helping us to forget or to clear stores of unneeded memories. During the course of a day we are inundated with experiences, some of which should be remembered while others need not be. Perhaps sleep aids in rearranging all of the experiences and thoughts from the day so that those that are important are stored and those that are not are discarded.

There are two main forms of sleep that will be discussed in detail in the next section of this chapter. These are **Rapid Eye Movement** or **REM** sleep and **Non-REM** sleep. REM is usually considered the more active form in terms of brain activity, whereas Non- REM is considered relatively less active and deeper form of sleep. It has been shown that people who get plenty of deep NREM sleep in the first half of the night and REM sleep in the second half improve their ability to perform spatial tasks. This suggests that the full night's sleep plays a role in learning—not just one kind of sleep or the other.

Other research has also shown that activity in the hippocampus during REM sleep supports the idea that **dreams serve a memory consolidation function** since this brain area is intimately involved with learning and memory processes. Further the activity of the

inferior parietal lobule, a part of the cortex that conveys experiences to memory, **decreases during REM** sleep, which probably helps to explain why we have so much trouble in remembering our dreams. There is also a **lot of activity** noted in the **limbic regions** – particularly the amygdala, probably in relation to the emotional quality of dreams that we report. More details on these findings will be described in the next section, as well.

Research with rats, cats, songbirds, and humans have shown that multiple stages in sleep increase memory consolidation. Rasch and Born (2013) reviewed the multiple genetic, neurological, and chemical bases by which memory function is affected during sleep.

Studies show that a good night's sleep improves learning. Whether you're learning math, how to play the piano, how to shoot free throws in basketball, or how to drive a car, sleep helps enhance your learning and problem-solving skills. Sleep also helps you pay attention, make decisions, and be creative.

10.2.3.2 Energy Conservation

This theory states that we sleep to conserve energy and is based on the fact that the metabolic rate is lower during sleep. The theory predicts that total sleep time and NREM sleep time will be proportional to the amount of energy expended during wakefulness. Support for this theory is derived from several lines of evidence. For example, NREM and REM sleep states are found only in **endothermic** animals (that is, those that expend energy to maintain body temperature). Species with greater total sleep times generally have higher core body temperatures and higher metabolic rates. Consider also that NREM sleep time and total sleep time decrease in humans, with age, as do body and brain metabolism. In addition, infectious diseases tend to make us feel sleepy. This may be because molecules called **cytokines**, which regulate the function of the immune system, are powerful sleep inducers. It may be that sleep allows the body to conserve energy and other resources, which the immune system may then use to fight the infection.

10.2.3.3 Brain Development

This proposed function of sleep is related to REM sleep, which occurs for prolonged periods during fetal and infant development. This sleep state may be involved in the formation of brain synapses.

Children and teens who are sleep deficient may have problems getting along with others. They may feel angry and impulsive, have mood swings, feel sad or depressed, or lack motivation. They also may have problems paying attention, and they may get lower grades and feel stressed.

10.2.3.4 Discharge of emotions

Perhaps dreaming during REM sleep provides a safe discharge of emotions. As protection to ourselves and to a bed partner, the muscular paralysis that occurs during REM sleep does not allow us to act out what we are dreaming. Additionally, activity in brain regions that control emotions, decision making, and social interactions is reduced during sleep. Perhaps this provides relief from the stresses that occur during wakefulness and helps maintain optimal performance when awake.

10.2.4 Sleep Deprivation and Deficiency

10.2.4.1 Why Is Sleep Important?

Whichever theory is most effective, it is clear that sleep plays a vital role in good health and well-being throughout your life. Getting enough quality sleep at the right times can help protect your mental health, physical health, quality of life, and safety.

The way you feel while you're awake depends in part on what happens while you're sleeping. During sleep, your body is working to support healthy brain function and maintain your physical health. In children and teens, sleep also helps support growth and development.

The damage from sleep deficiency can occur in an instant (such as a car crash), or it can harm you over time. For example, ongoing sleep deficiency can raise your risk for some chronic health problems. It also can affect how well you think, react, work, learn, and get along with others.

10.2.4.2 Healthy Brain Function and Emotional Well-Being

As seen above, sleep helps your brain work properly. While you're sleeping, your brain is preparing for the next day. It's forming new pathways to help you learn and remember information.

Studies also show that sleep deficiency alters activity in some parts of the brain. If you're sleep deficient, you may have trouble making decisions, solving problems, controlling your emotions and behavior, and coping with change. Sleep deficiency also has

been linked to depression, suicide, and risk-taking behavior.

10.2.4.3 Physical Health

Sleep plays an important role in your physical health. For example, sleep is involved in healing and repair of your heart and blood vessels. Ongoing sleep deficiency is linked to an increased risk of heart disease, kidney disease, high blood pressure, diabetes, and stroke.

- Sleep deficiency also increases the risk of obesity in many age groups. For example, one study of teenagers showed that with each hour of sleep lost, the odds of becoming obese went up.
- Sleep helps maintain a healthy balance of the hormones that make you feel hungry (ghrelin) or full (leptin). When you don't get enough sleep, your level of ghrelin goes up and your level of leptin goes down. This makes you feel hungrier than when you're well-rested.
- Sleep also affects how your body reacts to insulin, the hormone that controls your blood glucose (sugar) level. Sleep deficiency results in a higher than normal blood sugar level, which may increase your risk for diabetes.
- Sleep also supports healthy growth and development. Deep sleep triggers the body to release the hormone that promotes normal growth in children and teens. This hormone also boosts muscle mass and helps repair cells and tissues in children, teens, and adults. Sleep also plays a role in puberty and fertility.
- Your immune system relies on sleep to stay healthy. This system defends your body against foreign or harmful substances. Ongoing sleep deficiency can change the way in which your immune system responds. For example, if you're sleep deficient, you may have trouble fighting common infections.

10.2.4.4 Daytime Performance and Safety

Getting enough quality sleep at the right times helps you function well throughout the day. People who are sleep deficient are less productive at work and school. They take longer to finish tasks, have a slower reaction time, and make more mistakes. After several nights of losing sleep—even a loss of just 1–2 hours per night—your ability to function suffers as if you haven't slept at all for a day or two.

Lack of sleep also may lead to **microsleep**. Microsleep refers to **brief moments of sleep** that occur when you're normally awake. You can't control microsleep, and you might not be aware of it. For example, have you ever driven somewhere and then not remembered part of the trip? If so, you may have experienced microsleep. Even if you're not driving, microsleep can affect how you function. If you're listening to a lecture, for example, you might miss some of the information or feel like you don't understand the point. In reality, though, you may have slept through part of the lecture and not been aware of it.

10.2.4.5 Who Is at Risk for Sleep Deprivation and Deficiency?

Sleep deficiency, which includes sleep deprivation, affects people of all ages, races, and ethnicities.

Sleep deficiency can cause problems with learning, focusing, and reacting. You may have trouble making decisions, solving problems, remembering things, controlling your emotions and behavior, and coping with change. You may take longer to finish tasks, have a slower reaction time, and make more mistakes.

The signs and symptoms of sleep deficiency may differ between children and adults. Children who are sleep deficient might be overly active and have problems paying attention. They also might misbehave, and their school performance can suffer.

Sleep-deficient children may feel angry and impulsive, have mood swings, feel sad or depressed, or lack motivation.

You may not notice how sleep deficiency affects your daily routine. A common myth is that people can learn to get by on little sleep with no negative effects. However, research shows that getting enough quality sleep at the right times is vital for mental health, physical health, quality of life, and safety.

10.2.5 Summary

It is clear that sleep is a complex biological process that all humans, indeed all animals, engage in. Several brain regions are involved in sleep and wakefulness processes, and sleep serves complex functions that continue to be researched. The seemingly simple idea that we put on our pajamas, close our eyes and nod off to sleep involves far more complexity than appears on the surface.

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10.3: Stages of Sleep

Learning Objectives

1. Explain the different stages of sleep.
2. Describe the nature of REM sleep, its biological underpinnings and possible functions.
3. Differentiate the function and neural mechanisms that underlie REM and NonREM sleep
4. Compare and contrast the measurement techniques used to assess variations in the rest/wakefulness cycle and during various sleep stages

10.3.1 Overview

While watching someone sleep might appear as if they are seemingly unconscious with eyes closed for an extended period of time, in fact brain wave recordings show that the brain is cycling through several different stages as an individual sleeps. These stages each have distinct characteristics of brain activity and conscious experience and are divided into two main types known as **Rapid Eye Movement (REM) and Non-REM (NREM)**. This section will explore these characteristics and some of the peculiar and unexpected features of REM sleep, in particular.

10.3.2 The different stages of sleep

From a behavioral standpoint, sleep is defined by four criteria:

1. Reduced motor activity
2. Diminished responses to external stimuli
3. Stereotyped posture (in humans, lying down with eyes closed)
4. Relatively ready reversibility

These criteria distinguish sleep from hibernation and unconscious states, such as coma.

Sleep is a highly organized sequence of events that follows a regular, cyclic program each night. Polysomnograms - literally "many sleep measures" - are used to measure different body functions in a sleep lab (See Figure 10.3.1 to see where electrodes are placed for each of the measurements). Thus, the **EEG (electroencephalogram)** is the technique used to measure sleep most readily and often. For the EEG, electrodes are placed on the head and the brain's electrical activity is amplified and recorded). **EMG** (**electromyograph** that measures muscle tension), and **EOG** (**electrooculogram** that measures eye movement) patterns also change in predictable ways several times during a single sleep period.

NREM sleep is divided into four stages according to the **amplitude** and **frequency** of brain wave activity. In general, the **EEG pattern** of NREM sleep is **slower,** often more **regular**, and usually of **higher voltage** than that of wakefulness. As sleep gets deeper, the brain waves get slower and have greater amplitude. NREM Stage 1 is very light sleep; NREM Stage 2 has special brain waves called **sleep spindles** and **K complexes**; NREM Stages 3 and 4 show increasingly more high-voltage slow waves. In NREM Stage 4, it is extremely hard to be awakened by external stimuli. The muscle activity of NREM sleep is low, but the muscles retain their ability to function. Eye movements normally do not occur during NREM sleep, except for very slow eye movements, usually at the beginning. With the exception of brain activity, the body's general physiology during these stages is fairly similar to the wake state.

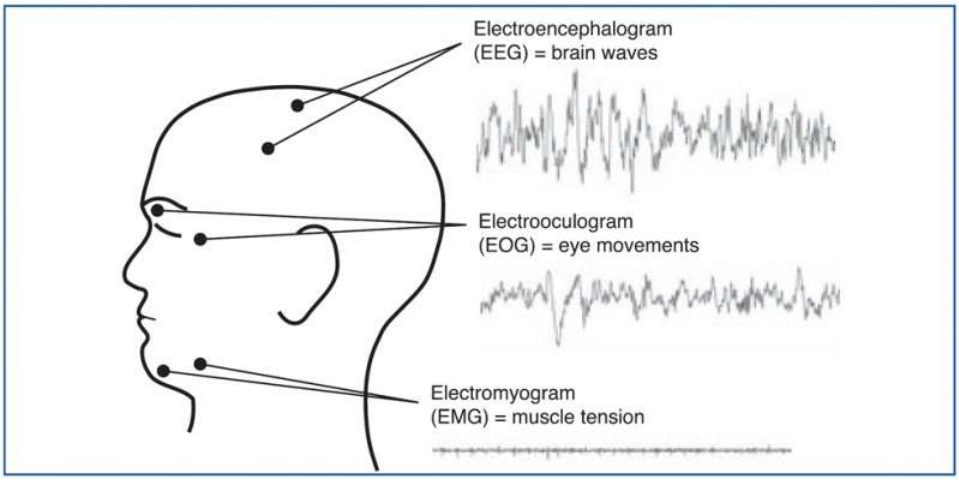


Figure 10.3.1: Placement of electrodes to determine EEG, EOG, and EMG. (NIH in the public domain)

From the time you fall asleep to the time you reach the deepest non-REM sleep, about 90 minutes later, the amplitude of these waves increases continuously, while their frequency diminishes correspondingly. Compared with wakefulness and with REM (rapid eye movement) sleep, non-REM sleep is characterized by an electroencephalogram (EEG) in which the waves have a greater amplitude and a lower frequency.

Hypnograms were developed to summarize the voluminous chart recordings of electrical activities (**EEG, EOG, and EMG**) collected during a night's sleep. Hypnograms provide a simple way to display information originally collected on many feet of chart paper or stored as a large file on a computer. Figure 10.3.2 illustrates a hypnogram. (Of course, it is important to keep in mind that individuals' hypnograms might be much less uniform than this relative "ideal" presented here.)

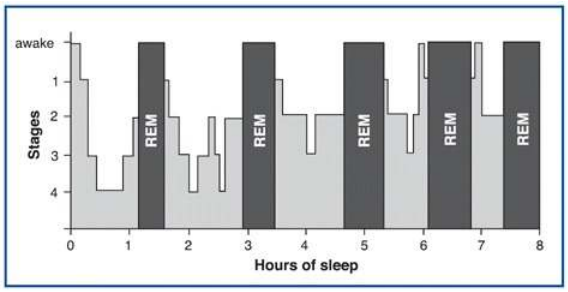


Figure 10.3.2: A typical hypnogram from a young, healthy adult. Light-gray areas represent non–rapid eye movement (NREM) sleep (NIH in the public domain)

We can make several observations about the hypnogram in this figure. First, the periods of NREM and REM sleep alternate during the night. Second, the deepest stages of NREM sleep occur in the first part of the night. Third, the episodes of REM sleep are longer as the night progresses. This hypnogram also indicates two periods during the night when the individual awakened (at about six and seven hours into the night).

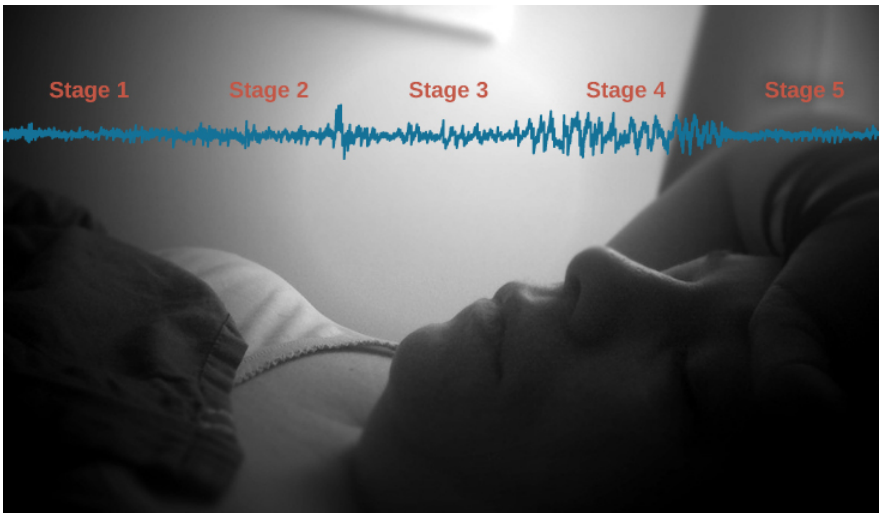
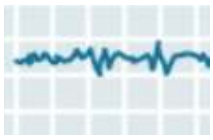
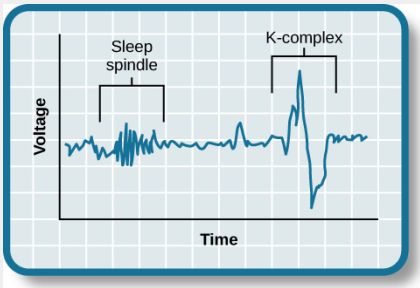


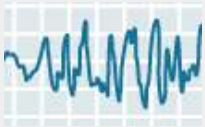
Figure 10.3.3: Note the amplitude and frequency of the wave patterns during different stages of sleep (Stage 5 indicates REM sleep). (CC BY 4.0; Lumen Learning)

The four types of brain waves (shown in Figure 10.3.3, and others discussed below, are important criteria that have been used to define four distinct stages of non-REM (NREM) sleep. Obviously, falling into a deeper and deeper sleep as the night progresses is actually a gradual, continuous process, but these four stages still provide a convenient means of describing the relative depth of NREM sleep.

Table 11.3.1 Stages of sleep

Stage	EEG	Description
Stage 1		Stage 1 non-REM sleep begins when you first lie down and close your eyes. After a few sudden, sharp muscle contractions in the legs, the muscles relax. Then, as you continue falling asleep, the rapid beta waves of wakefulness are replaced by the slower alpha waves of someone who is relaxed with their eyes closed. Soon, the even slower theta waves begin to emerge. Though your reactions to stimuli from the outside world diminish, Stage 1 is still the phase of sleep from which it is easiest to wake someone up. In experiments where people are awakened from Stage 1 sleep and asked about their state of consciousness, they usually report that they had just fallen asleep or had been in the process of doing so. They also often report having had stray thoughts and short dreams. Each period of Stage 1 sleep generally lasts 3 to 12 minutes,

Stage	EEG	Description
Stage 2		Stage 2 non-REM sleep is a stage of light sleep in which the frequency of the EEG trace decreases further while its amplitude increases. The theta waves characteristic of Stage 2 sleep are interrupted by occasional series of high-frequency waves known as sleep spindles. These bursts of activity have a frequency of 8 to 14 Hz and an amplitude of 50 to 150 µV. Sleep spindles generally last 1 to 2 seconds. They are generated by interactions between thalamic and cortical neurons. During Stage 2 sleep, the EEG trace may also show a fast, high-amplitude wave form called a K-complex. The K-complex seems to be associated with brief awakenings, often in response to external stimuli. People in Stage 2 sleep are unlikely to react to a light or a noise, unless it is extremely bright or loud. It is still possible to awaken them, even if they then report that they were really sleeping during the 10 to 20 minutes that this stage lasts during the earliest of the night's sleep cycles. But because people go through Stage 2 sleep several times during the cycles in a night, this is the stage in which adults spend the greatest proportion of their sleep–nearly 50% of the total time that they sleep each night.

Stage	EEG	Description
Stage 3		Stage 3 non-REM sleep marks the passage from moderately to truly deep sleep. Delta waves appear and soon account for nearly half of the waves in the EEG trace. Sleep spindles and K-complexes still occur, but less often than in Stage 2. The greater activity observed in the electro-oculogram (EOG) trace during stages 3 and 4 reflects the greater amplitude of EEG activity in the prefrontal areas, rather than movements of the eyes. Stage 3 lasts about 10 minutes during the first sleep cycle of the night but accounts for only about 7% of a total night's sleep. During Stage 3, the muscles still have some tonus, and sleepers show very little response to external stimuli unless they are very strong or have a special personal meaning (for example, when someone calls your name, or when a baby cries within earshot of its mother).
Stage 4		Stage 4 non-REM sleep is the deepest, the one in which we sleep the most soundly. The EEG trace is dominated by delta waves, and overall neuronal activity is at its lowest. The brain's temperature is also at its lowest, and breathing, heart rate, and blood pressure are all reduced under the influence of the parasympathetic nervous system. In adults, Stage 4 lasts about 35 to 40 minutes during the first sleep cycle of the night; it accounts for 15 to 20% of total sleep time in young adults. The muscles still have their tonus, and some movements of the arms, legs, and trunk are possible. This is the stage of sleep that accomplishes most of the body's repair work and from which it is most difficult to wake someone up. This is also the stage of sleep in which children may have episodes of somnambulism (sleepwalking) and night terrors.

10.3.3 REM Sleep

REM sleep is a distinct, homeostatically controlled brain state characterized by an activated electroencephalogram (EEG) in combination with paralysis of skeletal muscles and is associated with vivid dreaming.

In 1953, Aserinsky and Kleitman first reported the existence of rapid eye movement (REM) sleep in humans as a periodically recurring brain state marked by a **low amplitude** electroencephalogram (EEG) and **rapid eye movements** (Aserinsky and Kleitman, 1953). Soon afterward, Kleitman and Dement found that the EEG during REM sleep **resembles** that during **alert**

waking and showed that REM sleep coincides with **periods of vivid dreaming** (Dement and Kleitman, 1957). Two years later, Jouvet discovered in cats that the activated EEG during REM sleep is associated with a **complete paralysis of skeletal muscles**, reflected in a flat electromyogram (EMG), and therefore coined the term **paradoxical sleep** (Jouvet and Michel, 1959).

10.3.3.1 REM and Dreams

It was shown by the 1950s that the cortex is as active in REM as when someone is awake – which is one reason why REM is also called paradoxical sleep.

In humans, sleep is punctuated by REM (rapid eye movement) sleep about every 90 min (Ohayon et al., 2004). This is when most dreaming occurs (Hobson, 2009). Although some forms of dreaming can occur during non-REM sleep, such dreams are quite different from REM dreams; non-REM dreams usually are related to plans or thoughts, and they lack the visual vividness and hallucinatory and delusory components of REM dreams (Roffwarg et al., 1962; Nielsen, 2000). Rapid eye movement during sleep is thought to be associated with visual experience of dreaming (Andrillon et al., 2015).

REM sleep is characterized by striking neurophysiological and behavioral features, including high-amplitude theta oscillations in the hippocampus, muscle twitches, autonomic and respiratory activation, an elevated arousal threshold and bursts of large waves in the local field potential (LFP), called **PGO-waves** (P= pons, G= (lateral) geniculate nucleus, O= occipital cortex). The PGO waves originate in the pons and travel to the lateral geniculate nucleus, occipital cortex, and other brain areas (Datta, 1997; Karashima et al., 2010).

10.3.3.2 Theories of Dreams

The **threat simulation theory** of dreams suggests that dreaming should be seen as an ancient biological defense mechanism. Dreams are thought to provide an evolutionary advantage because of their capacity to repeatedly simulate potential threatening events. This process enhances the neurocognitive mechanisms required for efficient threat perception and avoidance.

The **expectation-fulfillment theory** posits that dreaming serves to discharge emotional arousals (however minor) that haven't been expressed during the day. This practice frees up space in the brain to deal with the emotional arousals of the next day and allows instinctive urges to stay intact. In effect, the expectation is fulfilled (the action is "completed") in a metaphorical form so that a false memory is not created. This theory explains why dreams are usually forgotten immediately afterwards.

One prominent neurobiological theory of dreaming is the **activation-synthesis theory** of dreams which states that dreams don't actually mean anything. They are merely electrical brain impulses that pull random thoughts and imagery from our memories. The theory posits that humans construct dream stories after they wake up, in a natural attempt to make sense of the nonsensical. However, given the vast documentation of the realistic aspects of human dreaming, as well as indirect experimental evidence that other mammals such as cats also dream, evolutionary psychologists have theorized that dreaming does indeed serve a purpose.

The **continual-activation theory** proposes that dreaming is a result of brain activation and synthesis. Dreaming and REM sleep are simultaneously controlled by different brain mechanisms. The hypothesis states that the function of sleep is to process, encode, and transfer data from short-term memory to long-term memory through a process called consolidation. However, there is not much evidence to back this up. NREM sleep processes the conscious-related memory (declarative memory), and REM sleep processes the unconscious related memory (procedural memory).

The underlying assumption of continual-activation theory is that, during REM sleep, the unconscious part of the brain is busy processing procedural memory. Meanwhile, the level of activation in the conscious part of the brain descends to a very low level as the inputs from the senses are basically disconnected. This triggers the "continual-activation" mechanism to generate a data stream from the memory stores to flow through to the conscious part of the brain.PGO Waves - (Pons - geniculate - occipital cortex)

10.3.3.3 REM and PGO Waves

PGO waves are among the various phasic events that occur during REM sleep, along with the rapid eye movements and changes in breathing and heart rates. PGO waves can be generated in the absence of REM sleep by stimulation of the pons with acetylcholine. As shown in figure10.3.7, the pons send signals to the thalamus which in turn signal the occipital cortex.

REM sleep is triggered by a specialized set of neurons in the pons (Hobson et al., 1975). Increased activity in this neuronal population has two consequences. First, elaborate neural circuitry keeps the body immobile during REM sleep by paralyzing major muscle groups (Chase, 2008). The muscle shut-down allows the brain to simulate a visual experience without moving the body at the same time. Second, we experience vision when waves of activity travel from the pons to the lateral geniculate nucleus and then to the occipital cortex (these are known as ponto-geniculo-occipital waves or PGO waves) (Gott et al., 2017). When the spikes of

activity arrive at the occipital pole, we feel as though we are seeing even though our eyes are closed (Nir and Tononi, 2010). The visual cortical activity is presumably why dreams are pictorial and filmic instead of conceptual or abstract.

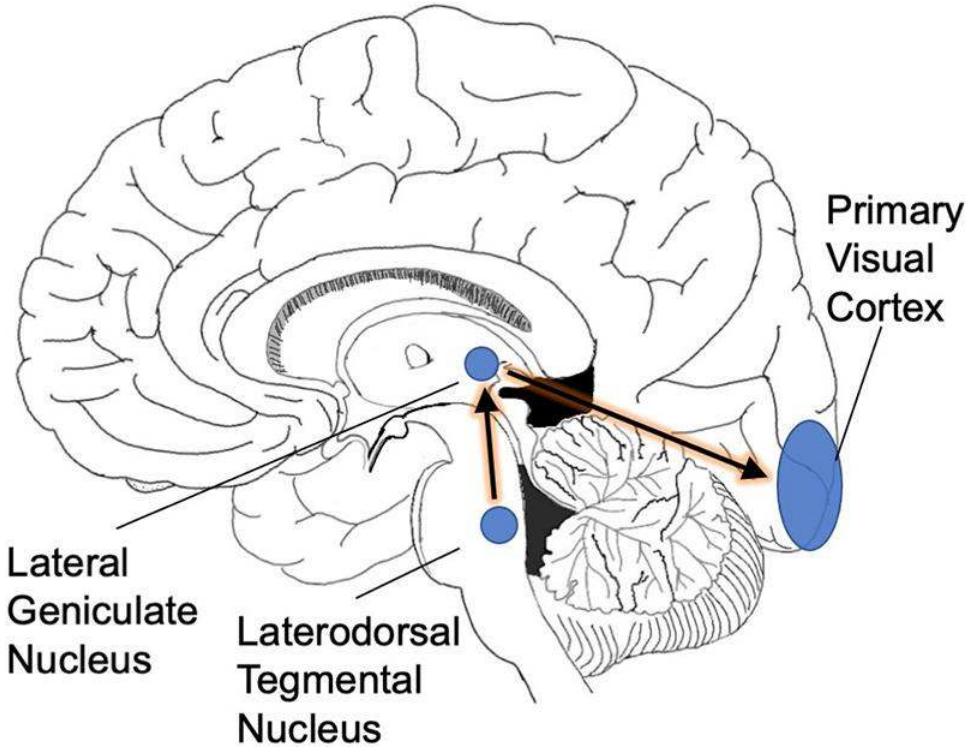


Figure 10.3.7: PGO waves. During REM sleep, waves of activity move from the brainstem into the occipital cortex. (PGO waves in The Defensive Activation Theory: REM Sleep as a Mechanism to Prevent the Takeover of the Visual Cortex by David Eagleman and Don Vaughn licensed CC-BY 4.0)

10.3.3.4 More Neuroanatomy and Neurochemistry of REM

In addition to maintaining wakefulness, several of the nuclei from the brainstem and the pons send excitatory information to the cortex using acetylcholine and glutamate as neurotransmitters. These inputs excite many areas of the cortex during the waking state and are also partly responsible for the cortical activation that occurs during REM sleep.

The midbrain **reticular activating formation** projects massively into the thalamic nuclei, which in turn influence the entire cortex. The role of this formation is to desynchronize the cortex in the broad sense, thus facilitating not only wakefulness but REM sleep as well. Formerly known as the ascending activating reticular system, it is now regarded simply as part of the wakefulness network.

The **prefrontal cortex** is relatively silent in REM falls in line with the fact that our dream content is often bizarre, illogical and socially inappropriate. In other words, the prefrontal cortex is not available to provide the higher cognitive functioning required for a "reality check."

The **amygdala** is one of the parts of the brain that is most active during REM sleep, but this state is actually generated deep in the brainstem. The set of cortical and limbic structures involved in REM sleep do not just passively submit to orders issued by the brainstem. On the contrary, the particular kind of dream images associated with REM sleep are the result of a dynamic interaction between certain key structures in the brainstem and the rest of the brain (See Figure 10.3.4).

It was also found using MRIs that while the **primary visual cortex** was relatively **silent** in REM (clearly their eyes are closed and therefore they aren't seeing anything), the secondary visual areas of the cortex, that interpret and analyze visual information, are relatively active in REM state. This is consistent with the fact that when we are awakened from REM sleep we often report highly elaborate visual dream scenes.

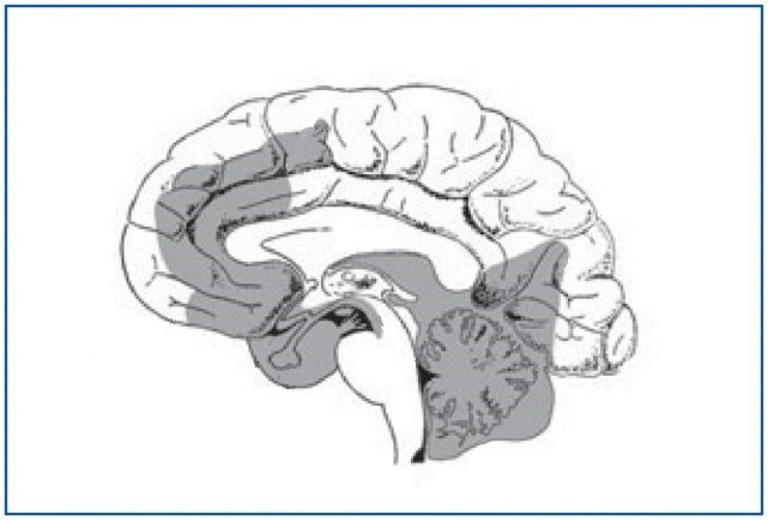


Figure 10.3.4: Areas of brain active during REM sleep and dreaming. (Adapted from NIH in the public domain)

REM is a combination of increase in cholinergic (acetylcholine) activity (in pontine tegmentum/pons and midbrain) and decrease in aminergic (monoamines - serotonin and norepinephrine) activity (in dorsal raphe nucleus and locus coeruleus).

That a sudden elevation in the activity of the cholinergic neurons of the pons is necessary for the onset of REM sleep may seem somewhat strange, because the brain's acetylcholine systems are known for their role in wakefulness. How then can this system associated with wakefulness be activated during one of the phases of sleep? The answer probably lies in the simultaneous reduction in the activity of two other nuclei that produce other wakefulness neurotransmitters, a reduction that is just as necessary for REM sleep as the increase in cholinergic activity. The two nuclei in question are the **dorsal raphe nucleus**, a group of serotonergic neurons, and the **locus coeruleus**, a group of noradrenergic neurons, and both of them are located in the rostral portion of the pons.

REM sleep cannot begin unless all activity in these two main aminergic systems of the brainstem ceases (See Figure 10.3.5 for some of the comparisons of neurochemical activation) . The serotonergic and noradrenergic neurons in these systems are referred to as REM-off neurons because of their inactivity during REM sleep, and they can be said to act as a sort of permissive system for REM sleep, in the sense that REM sleep becomes possible only when their activity has ceased. The shutdown of these neurons might, for example, help to suppress consciousness during REM sleep. Also, the periods of REM sleep end when these aminergic neurons become active again.

The rapid eye movements - that REM gets named for - come from originating signals in the pontine reticular formation sending signals to the midbrain and which coordinate the duration and direction of eye movements.

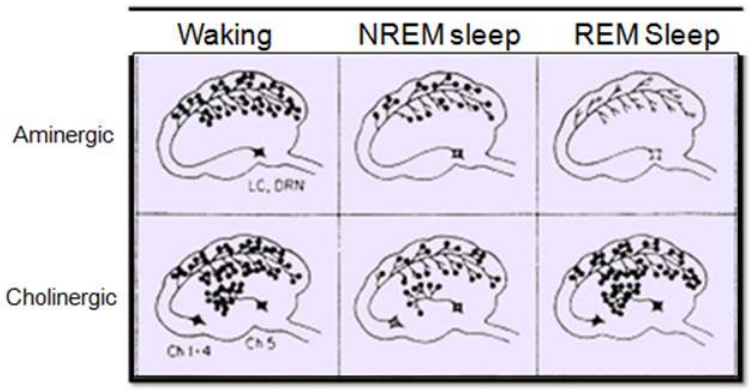


Figure 10.3.5: The numbers of black dots are proportional to the activity of the aminergic and cholinergic systems during the various stages of wakefulness and sleep. REM sleep (paradoxical sleep) characteristics by Dr. Mohammad Torabi Nami and Dr. Khsoro Sadeghniaat. Licensed CC BY 3.0 via Webmed Central

10.3.3.5 Musculature and "Pseudoparalysis" in REM

One of the most singular characteristics of REM sleep—the paralysis of the large muscles of the body that it causes —also is explained by phenomena that occur in certain parts of the brainstem. Intense neural activity of REM sleep excites majority of neurons in the cortex including those in the primary motor cortex. These generate organized sequences of activities that represent commands for bodily movements. But they never reach motor neurons of arms and legs (only the respiratory muscles, those of eye and middle ear actually respond to those commands). See Figure 10.3.6 for the coordination of EEG and EMG in the 24-hour hypnogram of a mouse. Increase of cholinergic activity in the pons will, ultimately, inhibit motor neurons in the spinal cord.

When you are awake, your brain's wakefulness circuits exert controls that prevent you from displaying the forms of brain activity that characterize REM sleep. But in the human fetus, these controls are not yet in place, which may explain why, during the last few months of gestation, the fetus spends such a large proportion of its sleeping time (about 80%) in REM sleep.

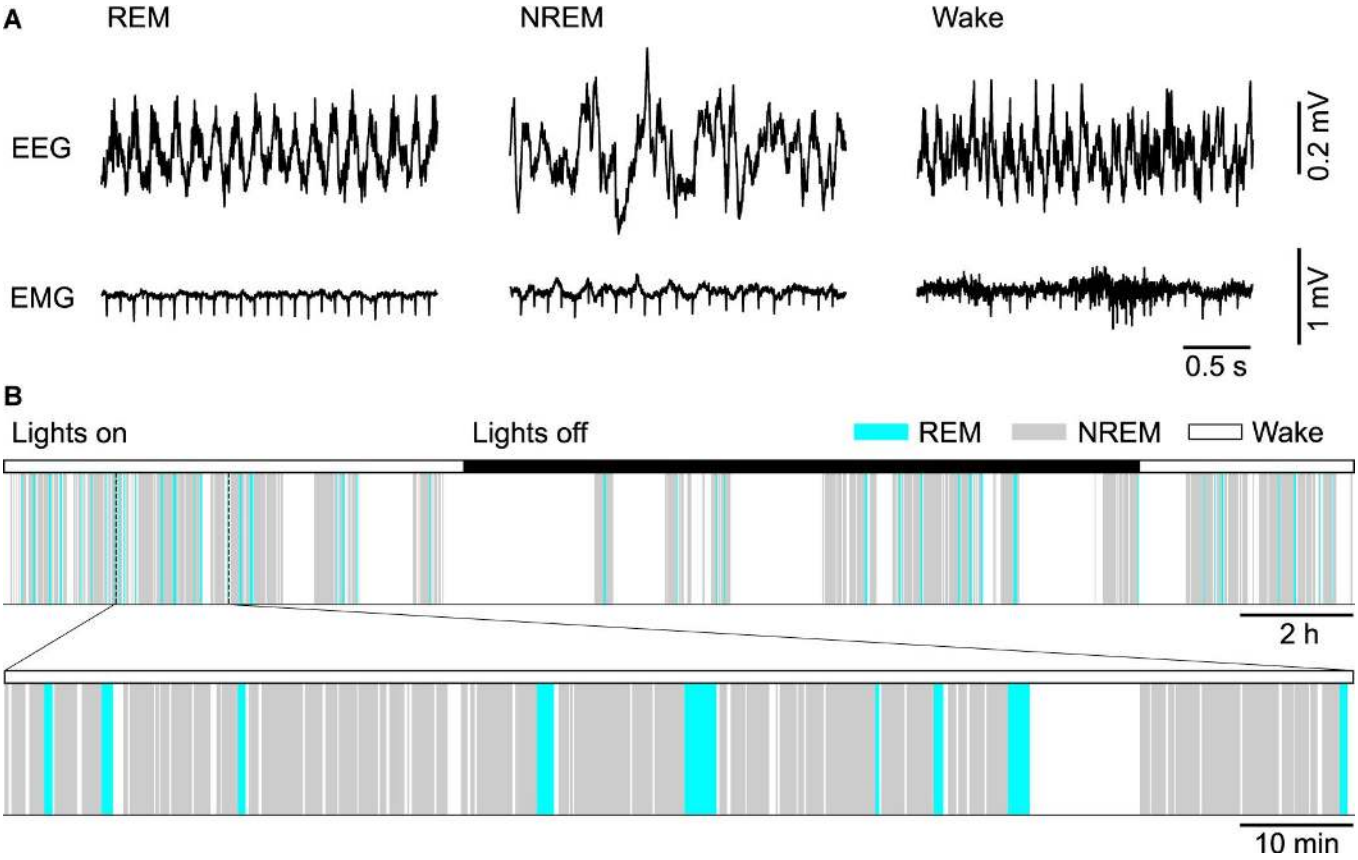


Figure 10.3.6: Sleep in mice. **(A)** Example electroencephalogram (EEG) and electromyogram (EMG) recordings from a mouse during REM sleep, NREM sleep and wakefulness (Wake). **(B)** Top, color-coded brain state (hypnogram) for a continuous 24 h recording from a mouse during dark and light cycles. Bottom, a 2 h segment of the hypnogram shown at an expanded scale. (Neural and Homeostatic Regulation of REM sleep by Park and Weber, CC-BY)

10.3.3.6 Summary

In an 8 hour typical night's sleep we move through distinct stages of sleep, several times through the night. We go from relative wakefulness to the deepest stages of sleep, cycle back out and into REM multiple times. Each of these stages correspond with different EEG wave patterns as well as the involvement of different regions of the brain and neurochemicals. The nature of REM sleep is paradoxical in a number of ways, and it seems to be different from the other stages in terms of quality and quantity.

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10.4: More Neuroanatomy of Sleep

Learning Objectives

1. Describe the role of the pons, medulla, hypothalamus (SCN), thalamus, basal forebrain and pineal gland in the initiation and maintenance of sleep.
2. Analyze the role of different neurochemicals, particularly the inhibitory neurotransmitter GABA and the sleep hormone melatonin in sleep initiation and maintenance.
3. Contrast the role of other neurochemicals like excitatory neurotransmitters glutamate and norepinephrine in wakefulness and sleep.

10.4.1 Overview

During the Spanish flu of 1918 some patients went into a coma and some were sleepless before they died. Autopsies were performed and found different types of lesions in the brain. Researchers concluded that the posterior hypothalamus/upper part of midbrain might be a wakefulness center, and the preoptic area of anterior hypothalamus might be a sleep center. These areas are illustrated in Figure 10.4.1. Later countless autopsies suggested that when one goes into a coma, their brainstem has suffered damage.

In general, there are several regions of the brain that work in concert to increase wakefulness and arousal, or to cause us to fall asleep or stay asleep. This section will review these regions of the Forebrain, Midbrain, and Hindbrain that play key roles in the control of sleep and wakefulness. In addition, the neurochemistry involved with control of the rest/activity cycle will also be explored. The influence of the primary excitatory neurotransmitters like glutamate and acetylcholine and the primary inhibitory neurotransmitter GABA along with other transmitters and hormones will be reviewed.

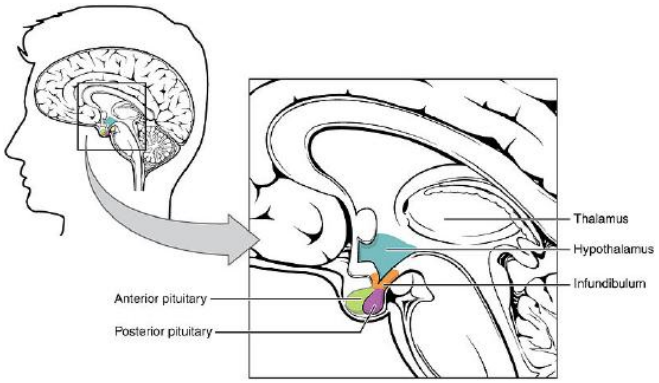


Figure 10.4.1: This sagittal section of the brain shows where the anterior and posterior pituitary, hypothalams and thalamus are located and their relations to each other in the inset - the thalamus is above the hypothalamus and the latter is above the pituitary glands. (CC BY 3.0; OpenStax College via Wikimedia Commons)

10.4.2 Sleep is not a state of neural silence

Work by Moruzzi and Magoun (1949) also suggested that when the **reticular formation** of cats was destroyed, comas were triggered, and stimulating this part led to awakening from normal sleep. Also, since this part receives incoming messages via sensory pathways, they developed the concept of "**ascending activating reticular system**" or the prime contender for "**wakefulness center**."

But these initial experiments had several issues. Since neurotoxic substances that were used to destroy the neurons/cell bodies of the posterior hypothalamus and reticular formation kept the axons that originated elsewhere intact, the wakefulness function that was diminished initially, quickly returned to normal.

Most importantly, these studies also showed that sleep is not a passive process, in which being deprived of sensory input causes sleep. Many people believe that sleep is something that happens in the absence of anything else like when someone is bored. For example, medical students attending a lecture in a subject that does not totally interest them will fall off to sleep. However, it is important to keep in mind that that is **not** actually what is happening. If a group of seven year old children who had had enough sleep the previous nights were sitting in the same lecture, they would not fall asleep but rather be bouncing off the walls!

In subsequent studies, application of electrical stimuli to the thalamus of cats when they were awake caused them to fall asleep. This indicates that sleep involves interactions between the thalamus and cortex. Also, when it was discovered that sleep and wakefulness cycles were not disrupted by sensory activation and that during REM there is intense activity in the cortex, the idea of sleep as passivity was further discredited.

There are two major neural circuits in the brainstem that operate in opposition to and alternation with each other. One of these circuits stimulates wakefulness, the other stimulates sleep, and their interaction is regulated by the body's internal clock (SCN).

Some large areas of the cortex are thus under the control of these networks of small groups of neurons that are located in the **brainstem** and that form complex circuits, not single "sleep centers" or "wakefulness centers." Wakefulness, which is indispensable for survival, is thus ensured by a whole network of redundant structures.

10.4.3 Forebrain regions involved in sleep

In Figure 10.4.2 you can see the hypothalamus where the specific area of the brain, the suprachiasmatic nucleus (SCN) is located. This area is intimately involved in the body's daily/circadian rhythm regulation.

10.4.3.1 Anterior hypothalamus/SCN

10.4.3.1.1 SCN

The SCN is considered "**body's internal clock**." The SCN is a bilateral structure located in the anterior part of the hypothalamus. It is the central pacemaker of the circadian timing system and regulates most circadian rhythms in the body (Hastings et al, 2018). The SCN receives signals from many different places. The major one is the retinohypothalamic tract originating from photosensitive (light-sensitive) ganglion cells of the retina. The SCN sends signals to structures such as the pineal gland, producing melatonin during the night for induction of sleep. Disruptions in the SCN circadian system have been found to correlate with various mood disorders and sleep disorders.

10.4.3.1.2 Preoptic area

The anterior hypothalamus also plays a fundamental role in the process of falling asleep. This structure, and in particular its preoptic area, appears to be sensitive to the serotonin released during waking periods. Apparently, when serotonin stimulates this preoptic area of the anterior hypothalamus, its GABAergic (GABA producing) neurons in turn inhibit the posterior hypothalamus, thus encouraging sleep. Damage to these GABAergic neurons is known to cause insomnia, whereas stimulating them causes experimental subjects to fall asleep rapidly.

10.4.3.1.3 Sleep-wakefulness switch

In vitro experiments have indicated that the wake-promoting neurotransmitters serotonin, norepinephrine, and acetylcholine inhibit identified preoptic GABA neurons (Gallopin et al., 2000); therefore, mutually inhibitory interactions between the sleep-promoting preoptic region and the arousal-related hypothalamic and midbrain structures may provide a substrate for a "sleep–wakefulness switch" (McGinty and Szymusiak, 2000; Saper et al., 2001). Thus, activation of preoptic sleep-promoting cells could lead to sleep onset by inhibiting arousal structures; in turn, activation of arousal hypothalamic and midbrain structures could suppress activity by preoptic NREM sleep-promoting cells as well as REM-promoting neurons (Reinoso-Suárez et al., 2010) and facilitate the switch to wakefulness.

10.4.3.2 Posterior hypothalamus

Stimulating the posterior hypothalamus produces a state of wakefulness comparable to that induced by stimulating the reticular formation in the brainstem. The activity of the posterior hypothalamus diminishes naturally during sleep, when it releases less histamine, a molecule that it uses as a neurotransmitter. The antihistamines that people take for allergy symptoms are known to cause some sleepiness, by reducing the activity of histamine.

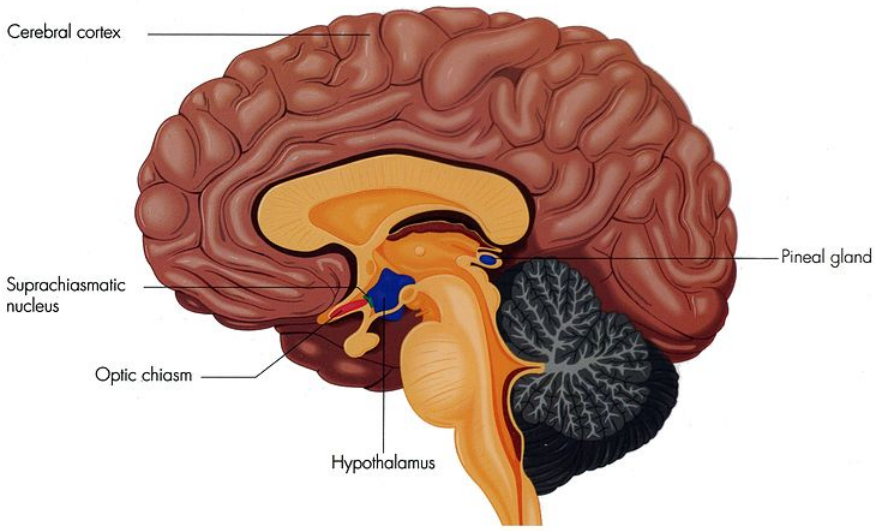


Figure 10.4.2: Sagittal view of the brain - note the hypothalamus shown in blue, located below the thalamus, and just above the pituitary gland (CC BY-SA 3.0; 黃雨伞 via Wikimedia Commons)

10.4.3.3 Thalamus

The thalamus contains neurons that send projections throughout the cortex. The activation of these thalamocortical neurons causes them to release excitatory amino acids such as aspartate and glutamate, thus contributing to excitation of the cortex and to wakefulness. During wakefulness, these neurons generate single action potentials at regular intervals. However, as the individual falls asleep these neurons begin firing in bursts instead, thus causing the cortex to display the synchronized EEG pattern that is typical of sleep (see section * for sleep stages).

10.4.3.4 Basal forebrain

The system of the basal forebrain is composed of neurons that synthesize **acetylcholine and/or GABA**. On their own, these neurons account for 70% of the cholinergic innervation of the cortex (where the cortex is activated by acetylcholine), while also sending projections to the thalamic nuclei. Stimulating these neurons causes wakefulness, but destroying them with neurotoxic substances causes wakefulness to decline for only a very short time.

In the situations just described, the cortical activation that causes wakefulness results from the direct stimulation of the cortical neurons by the various components of the wakefulness network. But these cortical neurons can also be activated in another way: by the inhibition of those neurons that naturally inhibit cortical activity. And that is exactly what the GABAergic neurons located in the posterior hypothalamus and the basal forebrain do: they inhibit other, cortical GABAergic neurons.

This executive network for wakefulness is itself activated by other systems arising in the brainstem.

It is thus all of these wakefulness signals that stop reaching the cortex at the onset of non-REM sleep. They are interrupted at the thalamus, which serves as a true gatekeeper to the cortex and is greatly influenced by the diffuse neuromodulatory systems of the brainstem. The complexity of these interactions in NREM sleep is illustrated in the diagram of the cat brain below (See Figure 10.4.3). This diagram illustrates a complex set of connections between cortical, subcortical, and brainstem structures that mediate various aspects of REM and NREM sleep. The figure is complicated, and the details are not important for our purpose here. It is included to illustrate the complexity of the connections between different brain sub-structures and signals being sent in order to maintain the individual's movement through the different stages of sleep throughout the night.

[A legend indicates that the thalamus–cerebral cortex complex or unit is darker to emphasize that these structures are necessary for the behavioral and bioelectric signs that characterize NREM sleep. AC, anterior commissure; CC, corpus callosum; DCN, deep cerebellar nuclei; Fo, fornix; G7, genu of the facial nerve; IC, inferior colliculus; IO, inferior olive; LV, lateral ventricle; MRF; midbrain reticular formation; MT, medullary tegmentum; OCh, optic chiasm; PGS, periaqueductal gray substance; RPC, caudal pontine reticular nucleus; RPO, oral pontine reticular nucleus; SC, superior colliculus; SC and PN, spinal cord and peripheral nerves; SN, solitary nucleus; TB, trapezoid body.]

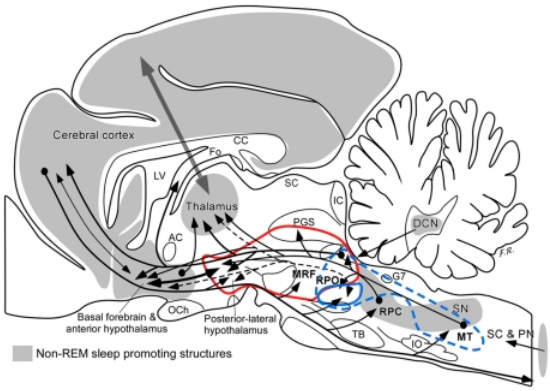


Figure 10.4.3: Schematic representation of the encephalic NREM sleep-promoting structures. Modified from Reinoso-Suárez et al. (2011). (Functional anatomy of non-REM sleep by Isabel De Andres, Miguel Garzón, and FernandoReinoso-Suárez via ResearchGate licensed CC-BY 4.0)

The rhythmic activity pattern established by the thalamocortical neurons that disconnects the cortex from internal and external signals at the onset of non-REM sleep. In contrast, during the REM phases of sleep, the thalamus probably continues to pass at least some of these signals on to the cortex, at least in some fragmentary, filtered, or distorted form.

The regulation of wakefulness is essential for survival and involves several different redundant structures in the brain. None of these structures, taken in isolation, is indispensable for activation of the cortex. But three of these brain structures that send projections to the cortex are sufficient to maintain the desynchronized EEG pattern that is characteristic of wakefulness. These structures are the 1. posterior hypothalamus, 2. the (intralaminar nuclei of the) thalamus and 3. the basal forebrain. Together they are often referred to as the “executive network”.

10.4.3.5 Pineal Gland

Inferior and somewhat posterior to the thalamus is the **pineal gland**, a tiny endocrine gland whose functions are not entirely clear. The **pinealocyte** cells that make up the pineal gland are known to produce and secrete the amine hormone **melatonin**, which is derived from serotonin.

The secretion of melatonin varies according to the level of light received from the environment. When **photons of light** stimulate the retinas of the eyes, a nerve impulse is sent to the SCN. From the SCN, the nerve signal is carried to the spinal cord and eventually to the pineal gland, where the **production of melatonin is inhibited**. As a result, blood levels of melatonin fall, promoting wakefulness. In contrast, as light levels decline—such as during the evening—melatonin production increases, boosting blood levels and causing drowsiness.

The secretion of melatonin may influence the body’s circadian rhythms, the dark-light fluctuations that affect not only sleepiness and wakefulness, but also appetite and body temperature. Interestingly, children have higher melatonin levels than adults, which may prevent the release of gonadotropins from the anterior pituitary, thereby inhibiting the onset of puberty. Finally, an antioxidant role of melatonin is the subject of current research.

Jet lag occurs when a person travels across several time zones and feels sleepy during the day or wakeful at night. Traveling across multiple time zones significantly disturbs the light-dark cycle regulated by melatonin. It can take up to several days for melatonin synthesis to adjust to the light-dark patterns in the new environment, resulting in jet lag. Some air travelers take melatonin supplements to induce sleep.

10.4.4 Hindbrain regions involved in sleep

There are several "lower regions" of the brainstem that seem to be involved in sleep regulation according to early and current research.

10.4.4.1 Pons

The brainstem region known as the pons is critical for initiating REM sleep. During REM sleep, the pons sends signals to the visual nuclei of the thalamus and to the cerebral cortex (this region is responsible for most of our thought processes). The pons also sends signals to the spinal cord, causing the temporary paralysis that is characteristic of REM sleep. This is what happens in the

experience of temporary sleep paralysis that many people might have experienced. Since the pons is effectively still "asleep" while the cortex is "awake," people experience the terrifying inability to move their body while they are completely conscious!

Also, the structures like the anterior hypothalamus play an important role in the onset of sleep.

10.4.4.2 Medulla and RAS

The reticular activating system (RAS) plays an important role in conscious awareness. According to Iwanczuk and Guzniczak (2015), "The ascending reticular activating system (ARAS) is responsible for a sustained wakefulness state. It receives information from sensory receptors of various modalities, ... [and those pathways] reach the thalamus directly or indirectly... The reticular activating system begins in the dorsal part of the posterior midbrain and anterior pons, continues into the diencephalon, and then divides into two parts reaching the thalamus and hypothalamus, which then project into the cerebral cortex."

The solitary tract nucleus region in the dorsal medulla is thought to provide a link between visceral activities such as respiratory, cardiovascular and gastrointestinal functions, and the sleep–wakefulness states. The solitary tract nucleus does not directly project to the cerebral cortex (Saper, 1995), although it does project to several brainstem, thalamic, and hypothalamic areas that innervate the cortex and can mediate EEG and sleep responses, such as the lateral hypothalamus, and nuclei of the midline thalamus.

10.4.5 Summary

The main brain regions working together to produce sleep and wakefulness have been discussed here. The neurons of the RAS play a role in arousal and sleep to some degree. The "executive network" seems to play an important role in regulating the responsiveness of the cortex to outside stimulation. The anterior hypothalamus and pineal regulate and fine tune many of these functions as well.

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10.5: Daily Rest/Activity Cycle- The Circadian Rhythm

Learning Objectives

- Evaluate the functions of sleep in relation to the biological mechanisms underlying it and affected by it.
- Describe the circadian nature of sleep.
- Describe the homeostatic or recuperative theory of sleep, and other theories of why we sleep.

10.5.1 Overview

When you ask most people why they think they sleep – the answer is “so I can rest” or “because I am tired from the activities of the day.” However, the animals that work the hardest do not sleep the longest and even after pulling an all-nighter we don’t sleep for the entire following day to make up for the lack of sleep. There are two theories of sleep that work in conjunction to explain why we sleep – recuperative and circadian.

Research indicates that for someone to be able to fall asleep, two bodily processes must be properly synchronized. The first is the **circadian rhythm**, which has a 24-hour period and is governed by your body’s biological clock. The circadian rhythm controls the cyclical secretion of several hormones, including melatonin, that are involved in sleep. The second process is the **recuperative function** illustrated by the accumulation of hypnogenic substances in your body for 16 hours every day. These substances induce a desire to sleep that does not go away until you in fact get some sleep.

Thus you can fall asleep only when two conditions have been met: your body’s biological clock must have brought it into a hormonal balance conducive to sleep, and it must have been a good while since you last slept, so that your levels of hypnogenic (sleep-producing) substances have built up sufficiently. The following section describes these two theories in greater detail, as well as other functions of sleep.

10.5.1.1 Sleep Regulation and Circadian Rhythms: A Two-Process Model

Sleep is a dynamic process that adjusts to the body’s needs every day. What time you fall asleep, how long you sleep, and how well you sleep all result from the combined effects of two forces: the homeostatic debt and the phase of your circadian rhythm. Individuals of course differ as to what time they go to bed and how much sleep they need to function well, but on the whole, the characteristics of sleep can be regarded as the result of complex interactions between two processes.

The first of these processes is called homeostatic debt (see below) or recuperative theory, which increases as a function of how long you have been awake and decreases as you sleep. The process is somewhat like the sand accumulating in one end of an hourglass and having to be emptied into the other after a certain time. See Figure 10.5.1 for a graph of how the pressure to sleep increases as a function of time spent awake, and then decreases as we sleep.

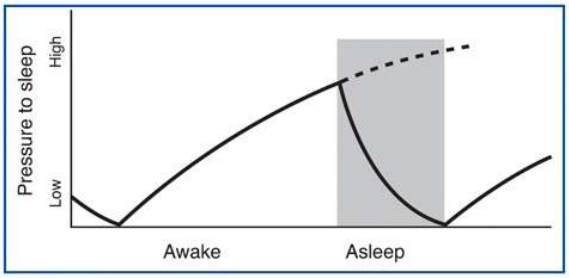


Figure 10.5.1: Homeostatic regulation of sleep: the pressure to sleep grows stronger across the day as one stays awake and then dissipates when one sleeps at night (shaded area). Sleep pressure increases (dashed line) as one stays awake longer into the normal sleeping hours. (NIH in the public domain)

The second process that greatly influences the onset, duration, and quality of your sleep is the phase of your circadian rhythm. This phase is governed by your biological clock, whose rhythm is endogenous but is reset regularly by daylight. This clock therefore produces a cycle lasting about 24 hours during which the optimal times for falling asleep, dreaming, waking up, and doing work occur over the course of each day. The external cues or zeitgebers (German for "time-givers") - of which sunlight is the most important - entrain your endogenous (internal) body clock to fall in line with the earth's day.

Endogenous sleep rhythms can be depicted graphically. Figure 10.5.2 shows a day-by-day representation of one individual's sleep/wake cycle. The black lines indicate periods of sleep, and the gray lines indicate periods of wakefulness. The upper portion of

the figure (days 1 through 9) represents this individual's normal sleep/wake cycle. Under these conditions, the individual is exposed to regularly timed exposure to alternating daylight and darkness, which has entrained this person's sleep/wake cycling to a period of 24 hours.

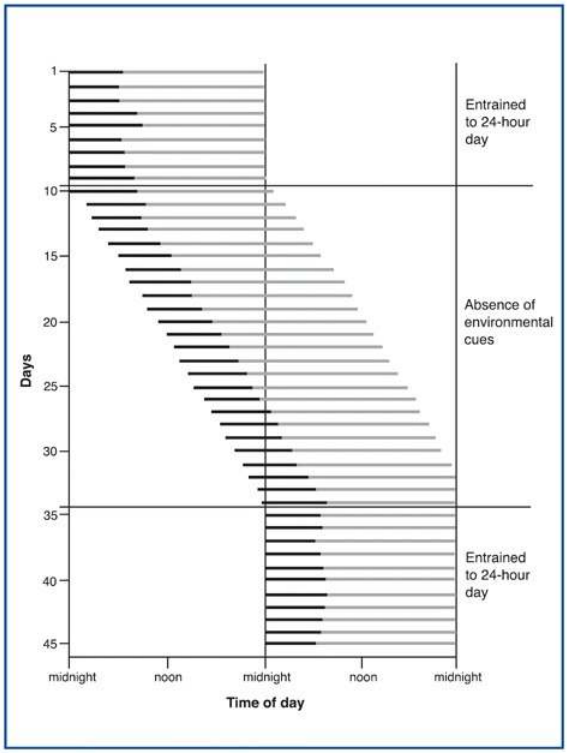


Figure 10.5.2: Entrainment of the biological clock. Black bars=sleep, gray bars=awake. (NIH in the public domain)

Thus your entire sleep-wake cycle operates as if your circadian oscillator made falling asleep easier at certain times of day, making you appreciably sleepier from 1:00 PM to 4:00 PM, and even sleepier from 2:00 AM to 5:00 AM. These patterns are confirmed by the statistics on workplace and highway accidents.

This two-process model - homeostatic and circadian - for regulating sleep can be diagrammed as a double pendulum.

Under normal circumstances, your periods of activity and rest are in phase with the alternation of day and night—your “circadian” pendulum and your “homeostatic” pendulum are in synch, you sleep well when you fall asleep, and you function well when you wake up.

But when this relationship is disturbed and the two pendulums are no longer in phase, then the quality both of your sleep and of your performance when awake deteriorate significantly. The peaks of activity for several circadian markers occur at inconvenient times in the sleep-wake cycle, which is the source of the problems caused by jet lag and by working night shifts.

In other words, the longer you stay awake, the greater the pressure you will feel to go to sleep. This process of homeostatic debt, or sleep debt, also explains why, if you stay up all night, then the next night, not only will you sleep longer, but your percentage of deep sleep will be higher.

10.5.2 Molecules that build up and make you sleep – Adenosine and Melatonin

As each day draws to a close, you feel the need to lie down and go to sleep. The onset of sleep, which seems like such a simple phenomenon from a behavioral perspective, is actually quite complex from a molecular one.

10.5.2.1 Adenosine and homeostasis/recuperation

It was in the early 1980s that scientists first discovered the chemical mechanism by which drinking coffee helps people to stay awake: **caffeine**, the psychoactive substance in coffee, **prevents adenosine from binding** to certain neurons in the brain. Both the caffeine in coffee and the theophylline in tea are examples of such **adenosine antagonists** and are well known for their stimulant effects.

Once this discovery was made, adenosine became a subject of interest for more and more neurobiologists who were doing sleep research. Numerous animal experiments eventually confirmed that adenosine definitely plays a role in the sleep/wake cycle. Some of the experimental findings that led to this conclusion: a) blocking the effects of adenosine made animals more alert; b) injecting animals with an adenosine agonist (enhancer) caused them to fall asleep; c) in certain parts of the brain, the concentration of adenosine normally increases naturally during the day and decreases at night, but if animals are forced to stay awake at night, this concentration keeps increasing.

These experiments thus showed that **adenosine**, along with other chemicals such as **serotonin and melatonin**, is one of the molecules whose concentration in the brain **influences the onset of sleep**.

Adenosine is produced by the degradation of adenosine triphosphate (ATP), the molecule that serves as the "energy currency" for the body's various cellular functions. The amount of adenosine produced in the brain thus reflects the activity level of its neurons and glial cells. The brain's intense activity during periods of wakefulness consumes large amounts of ATP and hence causes adenosine to accumulate.

Glycogen=ATP reserves or energy currency of the brain

Brain uses energy --> ATP degrades into adenosine

More brain energy used = more adenosine accumulates

More adenosine levels --> non-REM sleep triggered

Non-REM sleep = less active brain --> recovery/rebuild glycogen stores

The accumulation of adenosine during waking periods is thus associated with the depletion of the ATP reserves stored as glycogen in the brain. The increased adenosine levels trigger non-REM sleep, during which the brain is less active, thus placing it in a recovery phase that is absolutely essential—among other things, to let it rebuild its stores of glycogen.

But how exactly does adenosine exert this influence? During periods of wakefulness, neuronal activity increases the concentration of adenosine, which has an inhibitory effect on a great many neurons. Among these are the neurons of the hormonal systems that are the most active when we are awake: the norepinephrine, acetylcholine, and serotonin systems. Experiments have shown, for example, that when the levels of adenosine in the basal forebrain are raised artificially, the neurons in this structure that project axons throughout the cortex produce less acetylcholine. As a result, cortical activity slows, and the individual falls asleep.

The synchronized brain activity characteristic of non-REM sleep can then become established. But once non-REM sleep has continued for a while, the adenosine levels begin to decline. The systems responsible for wakefulness can then start becoming more active, causing the individual to awaken and the cycle to begin all over again. Thus we see that the sleep/wake cycle involves a highly efficient negative feedback loop.

10.5.3 Circadian Rhythms - Review and More

There are two important structures for the circadian cycle that could be considered our biological clocks.

10.5.3.1 The Suprachiasmatic Nucleus, the Pineal Gland and Melatonin

Most human bodily functions and behaviors are not "steady-state". Instead, they fluctuate in 24-hour cycles, such as the sleeping and waking cycle and the cycles for body temperature, hunger, and the secretion of various hormones. The central clock that regulates all of these circadian cycles is located in two tiny structures in the brain, at the base of the left and right hypothalamus. Each of these structures is no larger than a pencil tip and contains several tens of thousands of neurons. These structures are called the **suprachiasmatic nuclei (SCN)** because they are located just above the optic chiasma, where the left and right optic nerves cross paths.

This strategic position enables the suprachiasmatic nuclei to receive projections from the optic nerve from special retinal ganglion cells that tell them about the intensity of the ambient light entering the eyes. The neurons of these nuclei use this information to resynchronize themselves with daylight every day, because like any clock, the human biological clock is not perfect and does need to be reset periodically. One interesting thing about the retinohypothalamic path is that it is separate from those for vision such that even blind people (and blind mole rats, a species that is otherwise blind) receive information from light to reset their biological clocks.

Despite this need to resynchronize with an external cue, it has been shown that the suprachiasmatic nuclei do in fact constitute a biological clock with its own independent rhythm. First, many experiments have shown that the fluctuations of the human circadian

cycle persist even when individuals are cut off from the light of day. Second, in experiments where the suprachiasmatic nuclei were destroyed in animals such as hamsters, their cyclical behaviors, such as their sleep/wake cycles, become completely disorganized. And when suprachiasmatic nuclei were then transplanted from hamster fetuses into these animals, their biological rhythms returned, but with the properties of the donors.

These findings indicate that the mammalian biological clock mechanism is in fact not only endogenous, but also of genetic origin. Scientists have now even determined that these rhythms are the result of the cyclical activity of certain genes.

The circuit of light entering the eye, the signal going to the SCN and to the pineal gland is shown in the figure 10.5.3. Melanopsin in retinal ganglion cells in the eye respond to light (natural or artificially) and transmit signals to the SCN. Then light-induced activation of the SCN prevents the pineal gland from producing melatonin and; conversely, melatonin production and secretion is increased during the dark period.

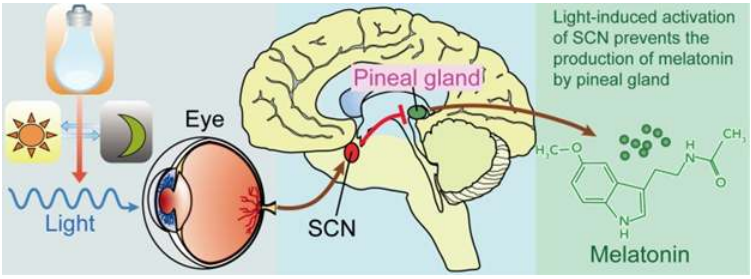


Figure 10.5.3: Light, suprachiasmatic nuclei (SCN), and the pineal/melatonin circuit. (Zhiqiang Ma, Yang Yang, Chongxi Fan, Jing Han, Dongjin Wang, Shouyin Di, Wei Hu, Dong Liu, Xiaofei Li, Russel J. Reiter, and Xiaolong Yan, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons)

10.5.3.2 Pineal gland

Using these cyclical rhythms, the suprachiasmatic nuclei send signals along their output pathways–for example, to the pineal gland–to regulate the cycles of a number of physiological and behavioral functions. In birds, reptiles, and fish, this small gland located at the top of the brain is sensitive to light and co-ordinates some cyclical phenomena on its own. In mammals, however, though the pineal gland does retain its ability to produce secretions cyclically (specifically, the hormone melatonin, at night), it does not constitute a clock on its own; instead, its cyclical synthesis of melatonin is controlled by timing signals that it receives from the SCN.

Each day, the pineal gland begins to produce melatonin (sometimes called the “sleep hormone”) as night falls. As the level of melatonin in the blood rises, body temperature falls slightly, and the individual feels sleepier and sleepier. The melatonin level remains high for just about 12 hours, then starts falling again in the early morning, as daylight (via the SCN) inhibits this gland’s activity.

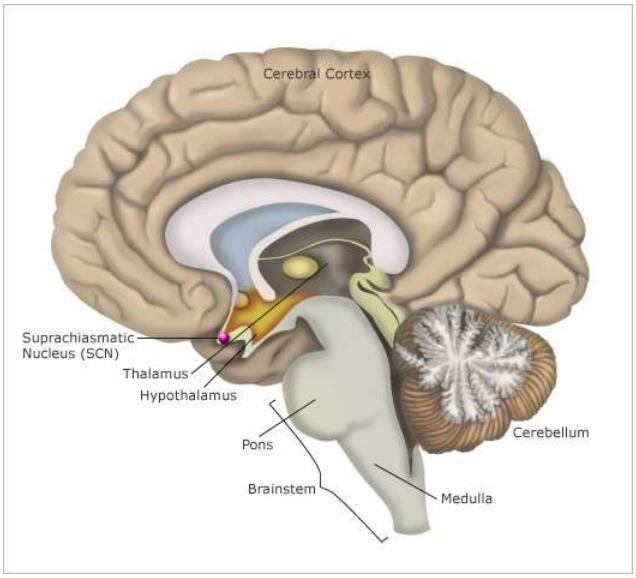


Figure \(\PageIndex{4\): The SCN in the anterior part of the hypothalamus is indicated along with the brainstem - pons and medulla - below (Sagittal image of brain licensed CC BY-SA)

The main neurotransmitter regulating the activity of the pineal gland is norepinephrine. When norepinephrine binds to its receptors, it triggers a cascade of second messengers, including cyclic AMP. This cyclic AMP contributes to the synthesis of melatonin. This melatonin is released into the bloodstream, through which it reaches every organ in the body. That is how it participates in the modulation of the circuits of the brainstem that ultimately control the sleep-wake cycle.

10.5.3.3 Output of SCN

The output pathways from each SCN (see Figure 10.5.4 for another picture of its location) consist of axons that innervate mainly the hypothalamus and nearby structures. Some of these axons also project to other parts of the forebrain, while others project to the midbrain.

Scientists do not yet know the details of how the central biological clock in the SCN regulates so many different human cyclical behaviors. But they do know that it uses the pineal gland to do so, and they have shown that destroying the SCN's output pathways also destroys the body's circadian rhythms. Because GABA is the essential neurotransmitter for almost all of the SCN's neurons, one would expect an inhibitory effect on the neurons that they innervate. In addition to sending out messages along these axonal pathways, the SCN's neurons seem to secrete a neuropeptide called vasopressin in a cyclical pattern.

Figure 10.5.5 shows the relative location of the different structures involved in the regulation of the circadian rhythms.

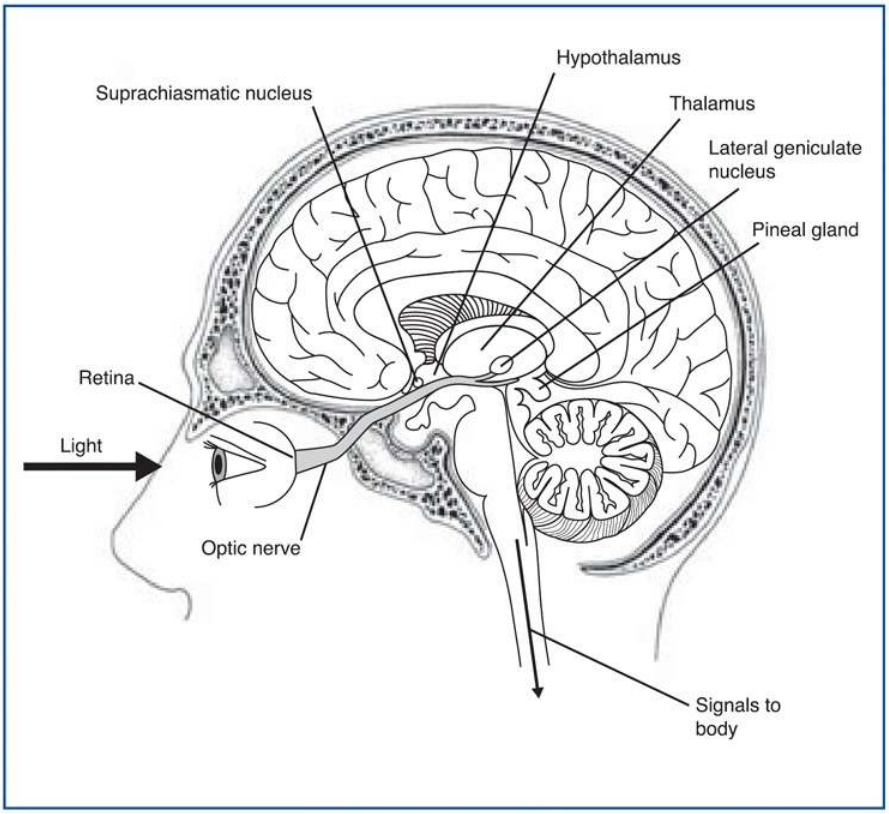


Figure 10.5.5: The biological clock is located in the SCN of the brain (NIH in the public domain)

Scientists have now discovered that the neurotransmitter GABA excites the cells of the dorsal SCN but inhibits those of the ventral SCN. These opposing effects might influence the differing reaction times of these two sub-regions when someone travels across several time zones. This discovery thus opens new insights into the mechanisms behind the disturbing symptoms of jet lag.

Scientists removed neurons from the suprachiasmatic nuclei of rats and isolating these cells in a culture medium in vitro and found that feedback loops inside each of the cells discharge at frequencies varying in cycles lasting about 24 hours. But unlike suprachiasmatic nucleus cells in the brain, which synchronize their activity with the day/night cycle, suprachiasmatic nucleus cells in vitro do not. Like any other clock, the human body's biological clock needs to be reset periodically. For that to happen, every cell in this clock must resynchronize itself daily with external cues that tell it when the day begins and ends. These external cues, also known as Zeitgebers (German for "time givers"), include the ambient temperature, the consumption of meals, ambient noise, and the body's activity level. But the strongest of these cues is undoubtedly the overall intensity of the ambient light.

10.5.4 Resetting the body's internal clocks - Zeitgebers

10.5.4.1 Light-sensitive ganglion cells

Thanks to various tagging methods, scientists now know that a certain sub-population of the ganglion cells in the human retina contain a photosensitive pigment and project their axons directly into the suprachiasmatic nuclei as well as into other brain structures that are concerned with the intensity of ambient light.

These light-sensitive ganglion cells have large receptive fields, because of their long, widely dispersed dendrites. In these cells, accurate reception of information on shape, orientation, and movement is sacrificed to general sensitivity. These cells clearly constitute another light-sensitive system that runs parallel to the visual system but is dedicated to detecting light intensity rather than to forming images.

10.5.4.2 Molecular clockwork

Many human functions, such as alertness, body temperature, and the secretion of certain hormones, work better if they are adjusted according to whether it is day or night. As you might therefore expect, a mechanism has evolved within the human body to co-ordinate its major functions with the time of day.

The human biological clock is extremely regular, though not exactly 24 hours: it is accurate to within 1%. But just like a watch that is never absolutely accurate on its own and needs to be reset occasionally, this biological clock needs a mechanism to prevent tiny errors from accumulating in each cell. Also, it needs to synchronize itself with external signs that tell it when each new day begins. The growing intensity of the natural light is the first sign of daybreak, and special photopigments in the retina detect this change in light intensity and transmit this information to the human biological clock.

In Figure 10.5.6, the levels of organization of information and operation of the circadian systems are shown. Circadian systems need to be considered in relation to three differing levels of organization of information and operation. First is the way in which the physical environment communicates (or ‘Inputs’) key information, particularly related to differentiation of night from day, to the internal ‘master’ clock (located in the brain’s suprachiasmatic nucleus (SCN)). Second are the ‘Intrinsic’ brain factors, consisting of the master clock and its linked regulatory systems (notably secretion of melatonin from the pineal gland). These contribute to sleep onset, sleep architecture, sleep-wake cycles and other central nervous system (CNS)-dependent behavioral changes. Third is the way in which the circadian system coordinates all other hormonal, metabolic, immune, thermoregulatory, autonomic nervous and other physiological processes to optimize the relationships between behavior and body functions (that is, the ‘Outputs’).

At the cellular level, almost all individual cells and, hence, organ systems have their own intrinsic clocks. As these cellular (for example, fibroblasts, fat cells, muscles) and organ-based (for example, liver, pancreas, gut) clocks run to intrinsically different period lengths, the differing physiological systems need to be aligned in coherent patterns. Fundamentally, the master circadian clock permits the organism to align key behavioral and intrinsic physiological rhythms optimally to the external 24-hour light–dark cycle.

In the figure, the black arrows from eye (and sunlight), genes, and environment/daily patterns (eating/sleeping/exercising) to the SCN indicate input received by the master clock. The red arrows from the raphe nuclei and pineal gland (via melatonin) to the SCN, and from the SCN to the pituitary indicate intra-CNS modulation of the signals. The blue arrows from melatonin to sleep regulation signals, from the SCN to ANS activity and temperature regulation, and pituitary to hormone regulation (ACTH and TSH) indicate output from the brain controlling other organ systems in the body.

The table at the end illustrates how muscle, liver, fat and pancreas function changes depending on time of day or night. During the day, muscle uptake fatty acid, and increase glycolitic metabolism. For fats, there is lipogenesis and adiponectin production. In the liver, there is glycogen, cholesterol and bile acid synthesis. In the pancreas there is insulin secretion. At night, muscles engage in oxidative metabolism. Fats have lipid catabolism and leptin secretion. The liver engages in gluconeogenesis, glycogenolysis, and mitochondrial biogenesis. The pancreas secrete glucagon.

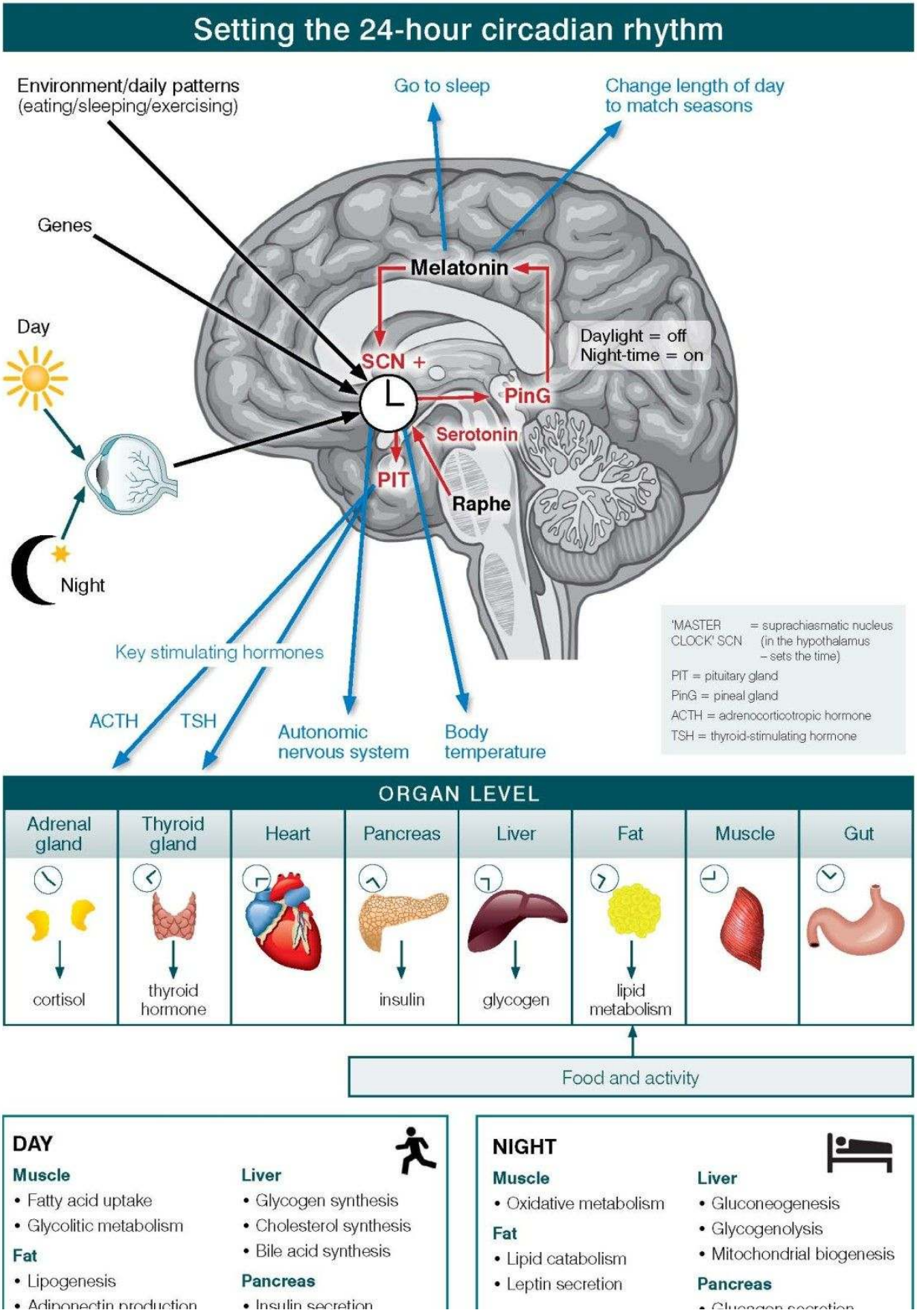

Setting the 24-hour circadian rhythm
Environment/daily patterns
(eating/sleeping/exercising)
Go to sleep
Change length of day
to match seasons
Genes
Melatonin
Day
Daylight = off
Night-time = on
SCN +
PinG
Serotonin
PIT
Raphe
Night
Key stimulating hormones
ACTH
TSH
Autonomic
nervous system
Body
temperature
'MASTER CLOCK' SCN = suprachiasmatic nucleus (in the hypothalamus – sets the time)
PIT = pituitary gland
PinG = pineal gland
ACTH = adrenocorticotropic hormone
TSH = thyroid-stimulating hormone
ORGAN LEVEL
Adrenal gland
Thyroid gland
Heart
Pancreas
Liver
Fat
Muscle
Gut
cortisol
thyroid hormone
insulin
glycogen
lipid metabolism
Food and activity
DAY
Muscle
• Fatty acid uptake
• Glycolitic metabolism
Fat
• Lipogenesis
• Adiponectin production
Liver
• Glycogen synthesis
• Cholesterol synthesis
• Bile acid synthesis
Pancreas
• Insulin secretion
NIGHT
Muscle
• Oxidative metabolism
Fat
• Lipid catabolism
• Leptin secretion
Liver
• Gluconeogenesis
• Glycogenolysis
• Mitochondrial biogenesis
Pancreas
• Glucagon secretion



Figure 10.5.6: The master clock (SCN) receives input from external stimuli, connects with other brain regions (primarily the pineal gland), and regulates/moderates several organ systems and functions in the body. (The master circadian clock in the human brain.jpg by Ian B Hickie, Sharon L Naismith, Rébecca Robillard, Elizabeth M Scott, and Daniel F Hermens, licensed CC BY 3.0, via Wikimedia Commons)

10.5.5 Summary

Under normal circumstances, there are two main mechanisms by which our sleep is regulated - homeostatic or recuperative and circadian or rhythmic. Adenosine appears to be the main chemical underlying the homeostatic/recuperative functions of sleep. Indeed most of us are aware of how we feel tired after long periods of wakefulness. Melatonin and the free running rhythms of the SCN seem to underlie the circadian/rhythmic aspects of sleep. Jet lag, shift work, and the overall disruption of people's body clocks during the COVID pandemic provide testimony to how this theory is also an important basis of sleep. Certainly it is clear that humans need sleep for a variety of reasons and that when we are sleep deprived, there are many mental and physical health consequences.

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10.6: Sleep Disorders

Learning Objectives

1. Describe the different kinds of sleep disorders.
2. Describe the causes of different sleep disorders.
3. Analyze different treatment options for sleep disorders.
4. Describe current research on the connection between sleep disorders and other physical health conditions.

10.6.1 Overview

Research has demonstrated that good sleep habits result in improved health and psychological functioning (Hyyppa & Kronholm, 1989). In fact poor sleep quality can result in severe psychiatric symptoms. Worldwide, approximately 30 percent of adults report difficulty initiating or maintaining sleep or experiencing poor sleep quality.

About 50 to 70 million Americans have sleep or wakefulness disorders. Sleep deficiency and untreated sleep disorders are associated with a growing number of health problems, including heart disease, high blood pressure, stroke, diabetes, obesity, and certain cancers. Sleep disorders can also be costly. Each year sleep disorders, sleep deprivation, and sleepiness add to the national health care bill. Undiagnosed sleep apnea alone is estimated to cost the US $150 billion annually. Additional costs to society for related health problems, lost worker productivity, and accidents make sleep disorders a serious public health concern.

In this section insomnia, circadian rhythm disorders, sleep apnea and narcolepsy are discussed.

10.6.2 Insomnia

Insomnia is a common sleep disorder. With insomnia, you may have trouble falling asleep, staying asleep, or getting good quality sleep. Chronic (long-term) insomnia occurs three or more nights a week, lasts more than three months, and cannot be fully explained by another health problem or a medicine.

Insomnia can affect your memory and concentration. Chronic insomnia raises your risk of high blood pressure, coronary heart disease, diabetes, and cancer.

In addition to finding out your medical history and having you keep a sleep diary, your doctor may have you take the following tests.

- **A sleep study** to look for other sleep problems, such as circadian rhythm disorders, sleep apnea, and narcolepsy.
- **Actigraphy** to measure how well you sleep. This requires you wear a small motion sensor three to 14 days.
- **Blood tests** to check for thyroid problems or other medical conditions that can affect sleep.

In the short term, insomnia can make it hard to concentrate or think clearly. You may feel irritable, sad, and unrested or have headaches. Insomnia raises your risk of falling, having a road accident, or missing work.

In addition, chronic insomnia can affect how well your brain, heart, and other parts of your body work. It can raise your risk of certain health problems or make existing problems worse. These conditions include:

- **Breathing problems** such as asthma
- **Heart problems** such as arrhythmia, heart failure, coronary heart disease, and high blood pressure
- **Mental health conditions** such as anxiety, depression, and thoughts of suicide. Insomnia can also make it difficult for you to stick to treatment for a substance use disorder.
- **Pain.** People who have chronic pain and insomnia may become more aware of and distressed by their pain.
- **Pregnancy complications** such as having more pain during labor, giving birth preterm, needing a cesarean section (C-section), and having a baby with low birth weight.
- **Problems with your immune system,** your body's natural defense against germs and sickness. These problems can lead to inflammation in your body or make it harder to fight infections.
- **Problems with your metabolism.** Not getting enough sleep can change the levels of hormones that control hunger and how you break down food. This can raise the risk of overweight and obesity, metabolic syndrome, and diabetes.

10.6.2.1 Treatment

Doctors may recommend healthy lifestyle habits such as a regular sleep schedule, cognitive behavioral therapy for insomnia, and medicines to help manage the insomnia.

10.6.2.2 **Medicines**

10.6.2.2.1 Prescription medicines

Many prescription medicines are used to treat insomnia. Some are meant for short-term use while others are meant for longer-term use. Some insomnia medicines can be habit-forming and all of these medicines may cause dizziness, drowsiness, or worsening of depression or suicidal thoughts. All of the medicines listed below may also cause insomnia.

- **Benzodiazepines,** like Valium, and **Benzodiazepine receptors agonists,** such as zolpidem**,** zaleplon, and eszopiclone can be habit-forming and should be taken for only a few weeks. Benzodiazepines are GABA agonists. Remember, from chapter *, that GABA is one of the most common inhibitory neurotransmitters in the central nervous system. Hence Benzodiazepines (and Benzodiazepine receptor agonists) make it even less likely that neurons will fire. Additional side effects of Benzodiazepine receptor agonists may include anxiety. Rare side effects may include a severe allergic reaction or unintentionally doing activities while asleep such as walking, eating, or driving.
- **Melatonin receptor agonists,** such as ramelteon. Rare side effects may include doing activities while asleep such as walking, eating or driving or a severe allergic reaction.
- **Orexin receptor antagonists,** such as suvorexant. This medicine is not recommended for people who have narcolepsy. Rare side effects may include doing activities while asleep such as walking, eating, or driving or not being able to move or speak for several minutes while going to sleep or waking up.

10.6.2.2.2 Off-label medicines

In some special cases healthcare providers may prescribe medicines that are commonly used for other health conditions but are not yet approved by the FDA to treat insomnia. Some of these medicines may include antidepressants, antipsychotics, and anticonvulsants.

10.6.2.2.3

Some over-the-counter (OTC) products that contain antihistamines are sold as sleep aids. Although these products might make you sleepy, talk to your doctor before taking them. Antihistamines can be unsafe for some people. Also, these products may not be the best treatment for your insomnia. Your doctor can advise you whether these products will help you.

Melatonin supplements are lab-made versions of the sleep hormone melatonin. Many people take melatonin supplements to improve their sleep. However, research has not proven that melatonin is an effective treatment for insomnia. Talk to your doctor before using these supplements. Dietary supplements can be beneficial to your health, but they can also have health risks.

The U.S. Food and Drug Administration regulates dietary supplements under a different set of regulations than those covering "conventional" foods and medicines. It does not have the authority to review dietary supplement products for safety and effectiveness before they are marketed.

Side effects of melatonin may include daytime sleepiness, headaches, upset stomach, and worsening depression. It can also affect your body's control of blood pressure, causing high or low blood pressure.

10.6.2.2.4 **Other treatments**

Your doctor may recommend that you use light therapy to set and maintain your sleep-wake cycle. With this treatment, you plan time each day to sit in front of a light box, which produces bright light similar to sunlight.

10.6.3 Sleep apnea

Sleep apnea is a common condition in the United States. It can occur when the upper airway becomes blocked repeatedly during sleep, reducing or completely stopping airflow. This is known as obstructive sleep apnea. If the brain does not send the signals needed to breathe, the condition may be called central sleep apnea.

Healthcare providers use sleep studies to diagnose sleep apnea. They record the number of episodes of slow or stopped breathing and the number of central sleep apnea events detected in an hour. They also determine whether oxygen levels in the blood are lower during these events.

Sleep studies can be done in a special center or at home. Studies at a sleep center can detect apnea events, detect low or high levels of activity in muscles that control breathing, monitor blood oxygen levels, brain and heart activity during sleep.

Other medical conditions that can cause sleep apnea are diagnosed in the following manner:

- Blood tests to check the levels of certain hormones and to rule out endocrine disorders that could be contributing to sleep apnea. Thyroid hormone can rule out hypothyroidism. Growth hormone tests can rule out acromegaly. Total testosterone and dehydroepiandrosterone sulphate (DHEAS) tests can help rule out polycystic ovary syndrome (PCOS).
- Pelvic ultrasound to examine the ovaries and detect cysts. This can rule out PCOS.

Doctors may want to know whether there is use of medicines, such as opioids, that could be affecting sleep or causing breathing symptoms of sleep apnea. Doctors may also want to know whether the patient has traveled recently to altitudes greater than 6,000 feet, because these low-oxygen environments can cause symptoms of sleep apnea for a few weeks after traveling.

Undiagnosed or untreated sleep apnea can lead to serious complications such as heart attack, glaucoma, diabetes, cancer, and cognitive and behavioral disorders.

Breathing devices such as continuous positive air pressure (CPAP) machines and lifestyle changes are common sleep apnea treatments.

10.6.4 Narcolepsy

Narcolepsy is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles. People with narcolepsy may feel rested after waking, but then feel very sleepy throughout much of the day. Many individuals with narcolepsy also experience uneven and interrupted sleep that can involve waking up frequently during the night.

10.6.4.1 Symptoms

Narcolepsy is a lifelong problem, but it does not usually worsen as the person ages. Symptoms can partially improve over time, but they will never disappear completely. The most typical symptoms are excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. Though all have excessive daytime sleepiness, only 10 to 25 percent of affected individuals will experience all of the other symptoms during the course of their illness.

- **Excessive daytime sleepiness (EDS).** All individuals with narcolepsy have EDS, and it is often the most obvious symptom. EDS is characterized by persistent sleepiness, regardless of how much sleep an individual gets at night. However, sleepiness in narcolepsy is more like a "sleep attack", where an overwhelming sense of sleepiness comes on quickly.
- **Cataplexy**. This sudden loss of muscle tone while a person is awake leads to weakness and a loss of voluntary muscle control. It is often triggered by sudden, strong emotions such as laughter, fear, anger, stress, or excitement. Some people may only have one or two attacks in a lifetime, while others may experience many attacks a day. Attacks may be mild and involve only a momentary sense of minor weakness in a limited number of muscles, such as a slight drooping of the eyelids. The most severe attacks result in a total body collapse during which individuals are unable to move, speak, or keep their eyes open. But even during the most severe episodes, people remain fully conscious, a characteristic that distinguishes cataplexy from fainting or seizure disorders. The loss of muscle tone during cataplexy resembles paralysis of muscle activity that naturally occurs during REM sleep.
- **Sleep paralysis**. The temporary inability to move or speak while falling asleep or waking up usually lasts only a few seconds or minutes and is similar to REM-induced inhibitions of voluntary muscle activity. Sleep paralysis resembles cataplexy except it occurs at the edges of sleep.
- **Hallucinations**. Very vivid and sometimes frightening images can accompany sleep paralysis and usually occur when people are falling asleep or waking up. Most often the content is primarily visual, but any of the other senses can be involved.

Additional symptoms of narcolepsy include:

- **Fragmented sleep and insomnia**. While individuals with narcolepsy are very sleepy during the day, they usually also experience difficulties staying asleep at night. Sleep may be disrupted by insomnia, vivid dreaming, sleep apnea, acting out while dreaming, and periodic leg movements.
- **Automatic behaviors**. Individuals with narcolepsy may experience temporary sleep episodes that can be very brief, lasting no more than seconds at a time. A person falls asleep during an activity (e.g., eating, talking) and automatically continues the activity for a few seconds or minutes without conscious awareness of what they are doing. This happens most often while

people are engaged in habitual activities such as typing or driving. They cannot recall their actions, and their performance is almost always impaired.

In a normal sleep cycle, a person enters rapid eye movement (REM) sleep after about 60 to 90 minutes. Dreams occur during REM sleep, and the brain keeps muscles limp during this sleep stage, which prevents people from acting out their dreams. People with narcolepsy frequently enter REM sleep rapidly, within 15 minutes of falling asleep. Also, the muscle weakness or dream activity of REM sleep can occur during wakefulness or be absent during sleep. This helps explain some symptoms of narcolepsy. Narcolepsy affects both males and females equally. Symptoms often start in childhood, adolescence, or young adulthood (ages 7 to 25), but can occur at any time in life. It is estimated that anywhere from 135,000 to 200,000 people in the United States have narcolepsy. However, since this condition often goes undiagnosed, the number may be higher. Since people with narcolepsy are often misdiagnosed with other conditions, such as psychiatric disorders or emotional problems, it can take years for someone to get the proper diagnosis.

Individuals may be asked by their doctor to keep a sleep journal noting the times of sleep and symptoms over a one- to two-week period. Although none of the major symptoms are exclusive to narcolepsy, cataplexy is the most specific symptom and occurs in almost no other diseases.

A physical exam can rule out or identify other neurological conditions that may be causing the symptoms. Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy:

- **Polysomnogram (PSG or sleep study)**. The PSG is an overnight recording of brain and muscle activity, breathing, and eye movements. A PSG can help reveal whether REM sleep occurs early in the sleep cycle and if an individual's symptoms result from another condition such as sleep apnea.
- **Multiple sleep latency test (MSLT).** The MSLT assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter REM sleep. On the day after the PSG, an individual is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in less than 8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, individuals with narcolepsy also have REM sleep start abnormally quickly. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy.

  Occasionally, it may be helpful to measure the level of hypocretin in the fluid that surrounds the brain and spinal cord. To perform this test, a doctor will withdraw a sample of the cerebrospinal fluid using a lumbar puncture (also called a spinal tap) and measure the level of hypocretin-1. In the absence of other serious medical conditions, low hypocretin-1 levels almost certainly indicate type 1 narcolepsy.

10.6.4.2 Causes

Narcolepsy may have several causes. Nearly all people with narcolepsy who have cataplexy have extremely low levels of the naturally occurring chemical hypocretin, which promotes wakefulness and regulates REM sleep. Hypocretin levels are usually normal in people who have narcolepsy without cataplexy.

Although the cause of narcolepsy is not completely understood, current research suggests that narcolepsy may be the result of a combination of factors working together to cause a lack of hypocretin. These factors include:

- **Autoimmune disorders**. When cataplexy is present, the cause is most often the loss of brain cells that produce hypocretin. Although the reason for this cell loss is unknown, it appears to be linked to abnormalities in the immune system.
- **Family history**. Up to 10 percent of individuals diagnosed with narcolepsy with cataplexy report having a close relative with similar symptoms.
- **Brain injuries**. Rarely, narcolepsy results from traumatic injury to parts of the brain that regulate wakefulness and REM sleep or from tumors and other diseases in the same regions.

10.6.4.3 Treatment

Early recognition and diagnosis of narcolepsy could be significant for certain treatment possibilities. Although under debate, autoimmunity is believed to be responsible for the hypocretin neuron loss. Some case reports and uncontrolled small studies suggest that immunomodulatory treatment, such as intravenous immunoglobulin, is able to ameliorate narcolepsy symptoms and influence hypocretin status (see Giannoccaro, 2020 for an overview). Based on the assumption that immunomodulatory treatment could prevent neuronal death, it should be administered as close to disease onset as possible. However, the presence of cataplexy already indicates the loss of the majority of hypocretinergic cells. Recognition of narcolepsy even before cataplexy onset is

therefore crucial in order to modify the course of the pathological process. The emerging evidence of T-cell activation in the blood and CSF of narcolepsy type 1 patients in a very early stage of the disease might become useful in early recognition as well as timing of immunomodulatory treatment.

Although there is no cure for narcolepsy, some of the symptoms can be treated with medicines and lifestyle changes. When cataplexy is present, the loss of hypocretin is believed to be irreversible and lifelong. Excessive daytime sleepiness and cataplexy can be controlled in most individuals with medications.

10.6.4.3.1 Medications

- **Modafinil**. The initial line of treatment is usually a central nervous system stimulant such as modafinil, which is less addictive and has fewer side effects than older stimulants.
- **Amphetamine-like stimulants**. In cases where modafinil is not effective, doctors may prescribe amphetamine-like stimulants such as methylphenidate to alleviate EDS. The potential for side effects and abuse is higher so monitoring is necessary.
- **Antidepressants**. Two classes of antidepressant drugs have proven effective in controlling cataplexy in many individuals: tricyclics (including imipramine, desipramine, clomipramine, and protriptyline) and selective serotonin and noradrenergic reuptake inhibitors (including venlafaxine, fluoxetine, and atomoxetine).
- **Sodium oxybate**. Sodium oxybate (also known as gamma hydroxybutyrate or GHB) has been approved by the U.S. Food and Drug Administration to treat cataplexy and excessive daytime sleepiness in individuals with narcolepsy.

10.6.4.3.2 Lifestyle changes

Not everyone with narcolepsy can consistently maintain a fully normal state of alertness using currently available medications. Drug therapy should accompany various lifestyle changes such as taking short naps, maintaining a regular sleep schedule, avoiding caffeine, large meals and alcohol before bed, avoiding smoking, relaxing before bedtime, and exercising daily. Safety precautions while driving, operating heavy machinery and even walking down long flights of stairs are important.

10.6.5 Circadian Rhythm Disorders (Also known as Sleep-Wake Cycle Disorders)

Circadian rhythm disorders are problems that occur when your sleep-wake cycle is not properly aligned with your environment and interferes with your daily activities.

Your body tries to align your suprachiasmatic nuclei and endogenous sleep-wake cycle to cues from the environment, for example, when it gets light or dark outside, when you eat, and when you are physically active. When your sleep-wake cycle is out of sync with your environment, you may have difficulty sleeping, and the quality of your sleep may be poor. Disruptions of your sleep-wake cycle that interfere with daily activities may mean that you have a circadian rhythm disorder.

Disruptions in your sleep patterns can be temporary and caused by external factors such as your sleep habits, job, or travel. Jet lag and shift work are two major contemporary conditions that are a result of technology and our present social and economic realities. Or a circadian rhythm disorder can be long-term and caused by internal factors such as your age, your genes, or a medical condition. Symptoms may include extreme daytime sleepiness, insomnia, tiredness, decreased alertness, and problems with memory and decision-making.

To diagnose a circadian rhythm disorder, your doctor may ask about your sleep habits, suggest sleep tests, a diary to track when and how long you sleep, and test the levels of certain hormones in your blood or saliva. Your treatment plan will depend on the type and cause of your circadian rhythm disorder. Treatment may include light therapy, medicines to help you fall asleep or stay awake, or healthy lifestyle changes including steps to improve your sleep habits. If left untreated, circadian rhythm disorders may increase the risk of certain health problems or lead to workplace and road accidents.

There are many sleep-wake phase disorders which include Advanced sleep-wake phase disorder, Delayed sleep-wake phase disorder, Irregular sleep-wake rhythm disorder, and Non–24-hour sleep-wake rhythm disorder.

Circadian rhythm disorders cause problems with metabolism in shift workers. When shift work triggers a circadian rhythm disorder, it can disrupt your metabolism in a few ways. Normally, your biological clock helps control your hunger hormones. However, when you do not get enough good-quality sleep, your body makes less leptin, the hormone that tells your body when you are full, and more ghrelin, the hormone that tells your body you are hungry. You may respond by eating larger amounts of food than normal, as well as more fatty, sweet, and salty foods.

Improving health with current research

Learn about the following ways the NHLBI continues to translate current research into improved health for people who have circadian rhythm disorders. Research on this topic is part of the NHLBI's broader commitment to advancing sleep science and sleep disorders scientific discovery.

- NHLBI's National Center on Sleep Disorders Research (NCSDR). For 25 years, the NCSDR has led foundational research on sleep and circadian biology across the NIH and has worked with federal and private organizations to disseminate sleep health information. The NCSDR administers sleep and circadian research projects, training, and educational awareness programs, and serves as an NIH point of contact for federal agencies and public interest organizations. The Center also participates in research translation and dissemination of scientific sleep and circadian advances to healthcare professionals, public health officials, and the public.
- Advancing Circadian Rhythm Research. We have organized workshops to help direct future research into circadian rhythms and circadian rhythm disorders. These workshops have brought together experts in the fields of sleep and circadian rhythm research to identify pertinent areas of research into the role of circadian rhythms in the development and progression of several health conditions. Learn more about Developing Biomarker Arrays Predicting Sleep and Circadian-Coupled Risks to Health and Circadian-Coupled Cellular Function and Disease in Heart, Lung, and Blood.
- Investigating the Link between Circadian Rhythms and Lung Diseases. We have hosted workshops to address current gaps in our understanding of acute and chronic lung diseases. Our workshops have helped direct research to build upon preliminary discoveries showing that lung diseases such as asthma may be influenced by circadian rhythms. Learn more about The Circadian Clock's Influence on Lung Health.
- Research Conference on Sleep and the Health of Women. This 2018 conference focused on the importance of sleep for women's health. It showcased a decade of federally funded research advances in understanding the health risks, societal burden, and treatment options associated with sleep deficiency and sleep disorders in women. Topics discussed at this conference included the influence of sleep and circadian rhythms on alcohol consumption and cancer in women, and the social, environmental, and biological factors that affect sleep in women, including during pregnancy, postpartum, and menopause. Learn more from the Research Conference on Sleep and the Health of Women.
- Improving the Quality of Medical School Education on Sleep Disorders. As part of its efforts to ensure that research advances are utilized by healthcare providers, the NCSDR has supported the development of medical school curricula and durable educational materials on sleep disorders, including circadian rhythm disorders.
- Sleep Disorders Research Advisory Board (SDRAB). The NHLBI has administered this specialty program advisory panel since 1993. Board members, including medical professionals, federal partners, and members of the public, meet regularly to provide feedback to the NIH on sleep-related research needs and to discuss how to move sleep research forward. The SDRAB has supported advances to improve our understanding of circadian rhythms and circadian rhythm disorders. Visit the Sleep Disorders Research Advisory Board for more information.
- National Sleep Research Resource (NSRR). This resource was established by the NHLBI to provide biomedical researchers a large, well-characterized data collection from NIH-funded sleep research studies. These data can be used in new research studies to advance sleep research, including research into circadian rhythm disorders. Visit the National Sleep Research Resource external link for more information.

Learn more about how the NHLBI is contributing to knowledge about circadian rhythm disorders.

- Helping to improve the health and well-being of shift workers. Shift work is known to increase the risk of several medical conditions, including cardiovascular disease, diabetes, metabolic syndrome, and obesity. We have funded research to help understand how disruptions in the sleep-wake cycle can cause these conditions. We have also supported research that uses computer analysis to help understand shift work disorder.
- Identifying the genes that control circadian rhythms. We have supported research into discovering the genes that control our circadian clocks and how these genes help us align our circadian rhythms with the environment. In 2017, researchers supported by several NIH Institutes, including the NHLBI, won the Nobel Prize in physiology or medicine for discovering several genes that control circadian rhythms. View Wake-up call: 2017 Nobel Prize in Medicine awarded for studies of the body's internal clock for more information.

10.6.6 Summary of Disorders

Disorder	Causes	Symptoms	Treatments
Insomnia	Risk factors can include age, family history, environmental factors, stress and physical conditions.	Lying awake for a long time, sleeping for only short periods, waking up too early in the morning and/or having poor quality sleep.	Lifestyle changes can include - making bedroom sleep-friendly, going to sleep and waking up at same time everyday, avoiding caffeine, nicotine and alcohol, getting regular physical activity, avoiding daytime naps, eating meals on a regular schedule, limiting fluid intake close to bedtime, learning new ways to manage stress, and avoiding certain over-the-counter meds. Psycholotherapeutic treatments can include – cognitive therapy, relaxation or meditation therapy, sleep education, sleep restriction therapy, stimulus control therapy. Medical treatments can include – Benzodiazepines, Benzodiazepine receptor agonists, Melatonin receptor agonists, Orexin receptor agonists, sometimes antidepressants, antipsychotics and anticonvulsants are used, and Melatonin supplements
Sleep apnea	Obesity, large tonsils, endocrine disorders, neuromuscular conditions, heart or kidney failure, genetic syndromes, and premature birth	Reduced or absent breathing, known as apnea events, frequent loud snoring, gasping for air during sleep, excessive daytime sleepiness and fatigue, decreases in attention, vigilance, concentration, motor skills, and verbal and visuospatial memory, dry mouth or headaches when waking, sexual dysfunction or decreased libido, waking up often during the night to urinate	Healthy lifestyle changes include - Heart healthy eating, regular physical activity, aiming for healthy weight, healthy sleeping habits, and quitting smoking. Breathing devices such as continuous positive airway pressure (CPAP) machine. Oral devices including - Mandibular repositioning mouthpieces, tongue retaining devices Implants including those that detect breathing and nerve stimulator. Therapy for mouth and facial muscles called orofacial therapy. Surgical procedures including – Tonsillectomy, Maxillary/jaw advancement and tracheostomy
Narcolepsy		Unwillingly fall asleep in middle of driving, eating or talking, sudden muscle weakness (cataplexy), vivid dream-like images or hallucinations, total paralysis just before falling asleep or just after waking (sleep paralysis), excessive daytime sleepiness, fragmented sleep and insomnia, automatic behaviors	Medications including Modafinil, Amphetamine-like stimulants, Antidepressants and Sodium oxybate (also called GHB) Lifestyle changes including - taking short scheduled naps, maintaining regular sleep schedules, avoiding caffeine or alcohol before bed, avoiding smoking, exercising daily, avoiding large heavy meals right before bedtime, relaxing before bed and safety precautions particularly while driving.

Circadian rhythm or sleep wake cycle disorders	Genetic conditions, lifestyle issues like jet lag, environment or occupational factors, age, sex and other medical conditions like ASD and blindness	Consistent difficulty falling asleep, staying asleep, or both, excessive daytime sleepiness or sleepiness during shift work, fatigue and exhaustion, lethargy, decreased alertness and difficulty concentrating, impaired judgment and trouble controlling mood and emotions, aches and pains, including headaches, stomach problems, in people who have jet lag disorder	Healthy lifestyle changes, bright light therapy and melatonin

10.6.7 Summary

Since sleep is such a complex biological and psychological process, it should come as no surprise that there are many different kinds of disorders of sleep. These disorders have different symptoms, can be caused by a variety of different situational and biological issues, and can be treated in a variety of ways.

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CHAPTER OVERVIEW

11: Motivation - General Theories and Ingestive Behavior Models

11.1: Motivation - Foundation Theories
11.2: Hunger - Theories, Detectors, and the Hypothalamus
11.3: Digestion and the Hormonal Control of Metabolism
11.4: Ingestive Behavior in Context- Diabetes and Obesity
11.5: Maintaining Water Balance
11.6: Triggering Drinking Behavior - Osmometric and Volumetric Thirst

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11.1: Motivation - Foundation Theories

Learning Objectives

1. Explain what a drive state is and the properties of a drive state.
2. Discuss drive-reduction theories and their limitations.
3. Define homeostasis and identify its elements.
4. Discuss body temperature as an example of a homeostatic system.
5. Compare and contrast homeotherms and poikilotherms.

11.1.0.1 Overview

Motivation can be studied and understood from a variety of perspectives. Within the field of Biological Psychology these range from broad evolutionary theories to more reductionistic explanations at the anatomical, cellular, and molecular level. In addition, there are a number of different types of motivations, some which can be quite difficult to narrow down to specific causal factors. When this is the case, often Biological Psychologists will focus on a "model" system that is at least somewhat less varied in its scope and easier to study. The two main motivational systems that will be covered in this chapter will be hunger and thirst. Prior to delving into the details of these systems, several general theories of motivation and foundational neural systems will be discussed.

11.1.0.1 Motivation and the Reward Circuitry

Motivated behaviors are voluntary behaviors that individuals find rewarding or pleasurable. Certain behaviors or stimuli, like food or sex, are naturally rewarding because they are necessary for the survival of a species; they are adaptive, and the nervous system has evolved to make these behaviors pleasurable. Rewarding stimuli increases brain activation in brain regions that comprise the **reward circuit**.

The reward circuit depends on the action of **dopamine and endorphins** along with several other key transmitters. Dopamine is synthesized and released by neurons located in the **ventral tegmental area** (VTA), a midbrain region adjacent to the substantia nigra (remember the substantia nigra from the basal ganglia chapter).

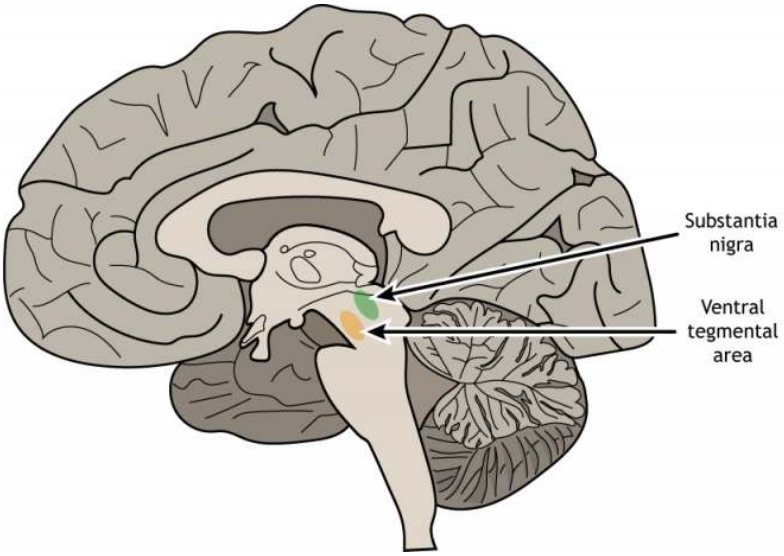


Figure 11.1.1: *The ventral tegmental area (orange region) is located in the midbrain region near the substantia nigra (green region). Both regions release dopamine onto downstream targets. 'Ventral Tegmental Area' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.*

There are two primary pathways from the VTA that are important for reward. The **mesolimbic pathway** connects the VTA to the **nucleus accumbens**, a region located in the ventral striatum (again, remember the basal ganglia chapter). The **mesocortical** pathway connects the VTA with the **prefrontal cortex**.

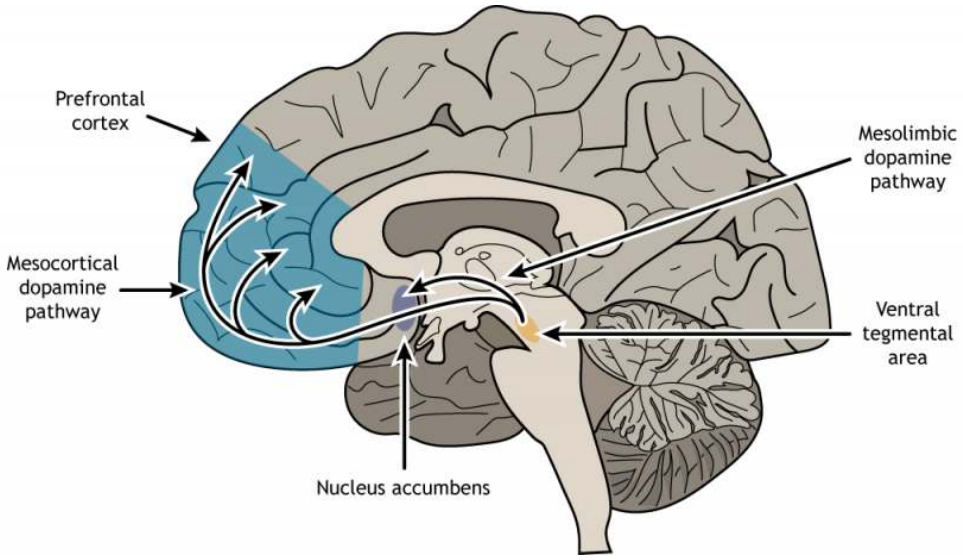


Figure 11.1.2: *The ventral tegmental area (orange region) releases dopamine into the nucleus accumbens (purple region) via the mesolimbic pathway and releases dopamine into the prefrontal cortex (blue region via the mesocortical pathway. 'Mesolimbic and Mesocortical Pathways' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.*

Early experimental studies showed that rodents with an electrode placed along these dopaminergic pathways will complete tasks, like a bar press, to self-stimulate the regions. Often the animals would forgo other behaviors, like eating, to continue pressing the bar. Treatment with drugs that block the receptors for dopamine reduce the self-stimulating behavior, indicating that dopamine is the critical neurotransmitter involved in making the stimulation of these brain regions rewarding.

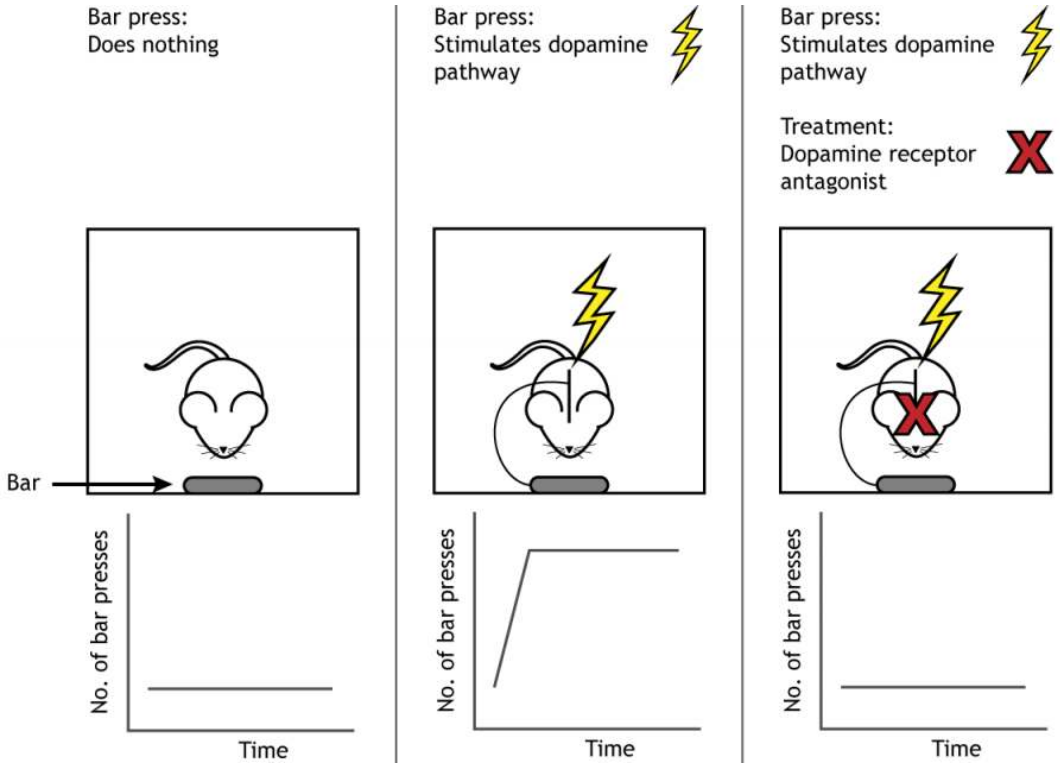


Figure 11.1.3: *When an activity like bar pressing is paired with stimulation of the reward system circuitry, rats will show a marked increased in the behavior (center panel) compared to controls (left panel). If a dopamine receptor antagonist is given in addition to the bar press stimulation, the behavior decreases, presumably because dopamine cannot have its reward effect (right panel). 'Dopamine Pathway Stimulation' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.*

However, continued research suggests the connection between dopamine release and reward may not be as simple as the self-stimulation studies imply. It appears that it is not the reward itself that increases dopamine, but the predicted expectation of the reward . Dopamine signaling increases during anticipation of a predicted reward. If the level of reward is more than predicted, reward learning occurs, and dopamine signaling and motivation to repeat that behavior increases. If the level of reward is less than predicted, then dopamine signaling decreases as does motivation to repeat the behavior.

11.1.1 Rewarding stimuli

Natural rewards that increase survival and fitness of a species activate the reward circuit. These behaviors and stimuli include certain food (like those containing high sugar or fat levels), social bonding, parental bonding, and sex. Most drugs of abuse also activate the reward circuit and dopamine signaling, which plays a critical role in the formation of addiction. For example, cocaine blocks dopamine reuptake into presynaptic VTA terminals; heroin and nicotine increase dopamine release from the VTA. These alterations increase dopamine effect on neurons in the nucleus accumbens.

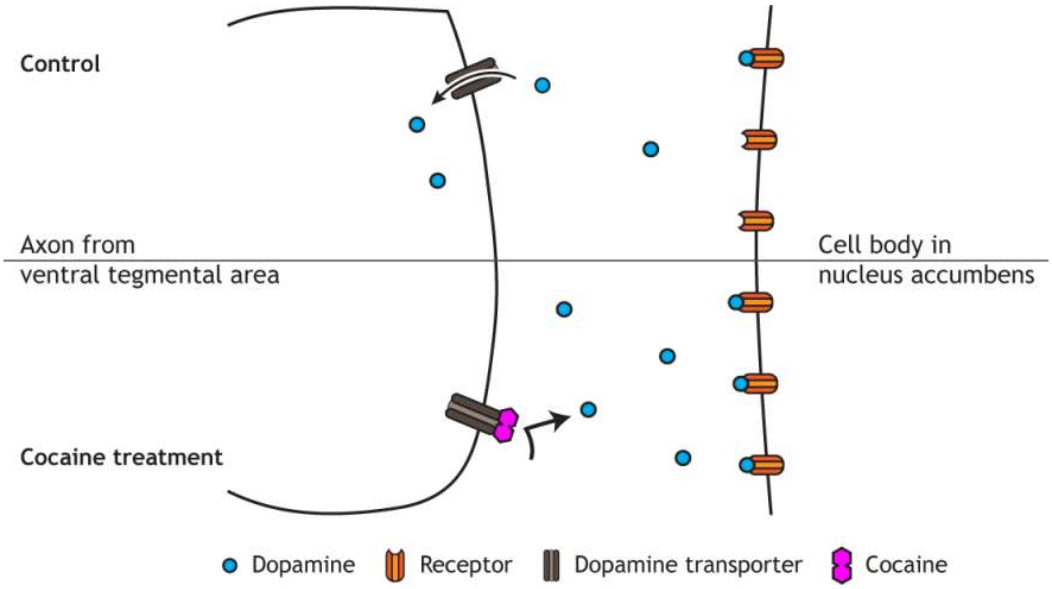


Figure 11.1.4: *Control (top) panel: Dopamine effects are typically terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Cocaine treatment (bottom) panel: Cocaine blocks DAT, preventing reuptake of dopamine. The increased action of dopamine on the nucleus accumbens leads to increased activation of the reward circuit, a mechanism underlying addiction to the drug. 'Cocaine Effects' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License.*

11.1.1.1 Drive-Reduction Theories

Drive-reduction theories focus on how motivation originates from biological needs or drives. In these theories, it is proposed that behavior is an external display of the desire to satisfy physiological needs. In other words, a biological need creates a drive and reducing that drive motivates an organism to engage in behaviors to reduce the drive, presumably by meeting the biological need. As this theory focuses on biological needs, it is connected to the principle of homeostasis and the use of behaviors to maintain or restore homeostasis. Homeostasis refers to the stable state across all physiological systems that organisms strive to maintain and will be discussed shortly.

A "**drive**" is a **state of arousal** or tension triggered by a physiological or biological need. These needs include those that we are all aware of and that are the focus of this chapter, hunger and thirst. **Drive-reduction theory** proposes that **drives give rise to motivation**. When a drive emerges, it creates an **unpleasant state of tension** that leads to **behaviors** intended to **reduce this tension**. To reduce the tension, the organism will begin seeking out ways to satisfy the biological need. For instance, you will look for water to drink if you are thirsty. You will seek food if you are hungry.

According to the theory, any behavior that reduces the drives will be repeated by humans and animals. This is because the reduction of the drive serves as a positive reinforcement for the behavior that caused such drive reduction.

While drive-reduction theory explains how primary reinforcers (those things that are naturally reinforcing because they meet biological needs) are effective in reducing drives, many psychologists argue that the theory is not applicable in the concept of secondary reinforcers. For example, money is a powerful secondary reinforcer, as it can be used to purchase primary reinforcers like food and water. However, money in itself cannot reduce an individual's drives. Another problem with the theory is that it does not provide an explanation about the reason behind people engaging in behaviors that are not meant to reduce drives, such as a person eating even if they are not hungry.

11.1.1.2 Key Properties of Drive States

Drive states differ from other affective or emotional states in terms of the biological functions they accomplish. Whereas all affective states are either desirable or undesirable and serve to motivate approach or avoidance behaviors (Zajonc, 1998), drive states are unique in that they generate behaviors that result in specific benefits for the body. For example, hunger directs individuals

to eat foods that increase blood sugar levels in the body, while thirst causes individuals to drink fluids that increase water levels in the body.

Different drive states have different triggers. Most drive states respond to both internal and external cues, but the combinations of internal and external cues, and the specific types of cues, differ between drives. Hunger, for example, depends on internal, visceral signals as well as sensory signals, such as the sight or smell of tasty food. Different drive states also result in different cognitive and emotional states, and are associated with different behaviors. Yet despite these differences, there are a number of properties common to all drive states. Most notably, the link between drives and motivation (as already discussed) and the common features of homeostatic mechanisms.

11.1.1.3 Homeostasis

Humans, like all organisms, need to maintain a stable state in their various physiological systems. For example, the excessive loss of body water results in dehydration, a dangerous and potentially fatal state. However, too much water can be damaging as well. Thus, a moderate and stable level of body fluid is ideal. The tendency of an organism to maintain this stability across all the different physiological systems in the body is called **homeostasis**.

Homeostasis is maintained by two mechanisms. First, the state of the system being regulated must be monitored and compared to an ideal or optimal level, a **set point**. Second, there need to be mechanisms for moving the system back to this set point - that is, to restore homeostasis when deviations from it are detected. While our focus here is on homeostatic mechanisms that connect to behavior, there is a wide-range of such systems throughout the body. To better understand the functioning of a homeostatic system, think of the thermostat in your own home. It detects when the current temperature in the house is different from the temperature you have it set at (i.e., the set point). Once the thermostat recognizes the difference, the heating or air conditioning turns on (or off) to bring the overall temperature back to the designated level. This process is often referred to as **negative feedback** (see section below).

Many homeostatic mechanisms, such as blood circulation and immune responses, are automatic and strictly physiological. Others, however, involve behavioral responses and deliberate action. Most drive states motivate action to restore homeostasis using both “punishments” and “rewards” to modify behavioral responses. Imagine that these homeostatic mechanisms are like molecular parents. When you behave poorly by departing from the set point (such as not eating or being somewhere too cold), they raise their voice at you. You experience this as the bad feelings, or “punishments,” of hunger, thirst, or feeling too cold or too hot. However, when you behave well (such as eating nutritious foods when hungry), these homeostatic parents reward you with the pleasure that comes from any activity that moves the system back toward the set point. For example, when body temperature declines below the set point, any activity that helps to restore homeostasis (such as putting one’s hand in warm water) feels pleasurable; and likewise, when body temperature rises above the set point, anything that cools it feels pleasurable.

While homeostatic mechanisms are often likened to a thermostat that determines what the desired value is and then systems are turned on and off in order to establish the optimal value, both hunger and thirst are not only triggered by need. Both systems anticipate need - they are both proactive and reactive. Before exploring these ingestive behaviors further, we'll consider temperature regulation in more detail as an introduction to how homeostatic mechanisms operate.

11.1.1.3.1 Elements of a Homeostatic System

Regardless of the homeostatic system we are discussing, it must have specific features.

- System variable - what's being regulated.
- Set point - optimal value.
- Detector - a mechanism must exist for monitoring the levels of the variable of interest.
- Correctional mechanisms - there must be a way for deviations to be altered.

When it comes to body temperature, there is an ideal temperature that an organism strives to maintain. Temperature would be the system variable and that ideal temperature would be the set point. The detector or detectors would be temperature sensors in the skin and brain. What are the correctional mechanisms? Temperature is interesting in that these mechanisms can be behavioral and physiological for some species, while for others they are only behavioral. If a human is cold, they can put on a coat (behavioral) and they may shiver, a physiological response that generates heat. In contrast, some animals do not have the benefit of those physiological mechanisms for adjusting temperature and must rely exclusively on behavioral responses. Mammals and birds are **homeotherms**, they possess both physiological and behavioral means of altering body temperature. Homeotherms are able to

maintain the same body temperature, our temperatures don't fluctuate with changes in environmental temperature. **Poikilotherms** regulate their body temperature entirely with behavioral means. Reptiles, amphibians, and many fish are poikilotherms.

Regardless of the homeostatic system in question, all have a system variable, a set point, a detector, and at least one correctional mechanism. When we need food or water, physiological and behavioral mechanisms assist us in meeting the need.

11.1.1.3.2 Negative Feedback

As mentioned earlier, **negative feedback** is an important feature of homeostatic systems. A good example of this is demonstrated with the stress response the effect of the "stress" hormone, cortisol.

Once a stress response has been initiated, cortisol enters the circulation and activates the body and brain in order to deal with the stressor. Interestingly, cortisol itself is able to act on the hypothalamus and pituitary and inhibit production of the cortisol releasing factors, CRH and ACTH. This is called a **negative feedback loop**; the active hormone (cortisol) can shut off its own production. Negative feedback is possible because neurons in the hypothalamus and pituitary express glucocorticoid receptors that are activated by cortisol.

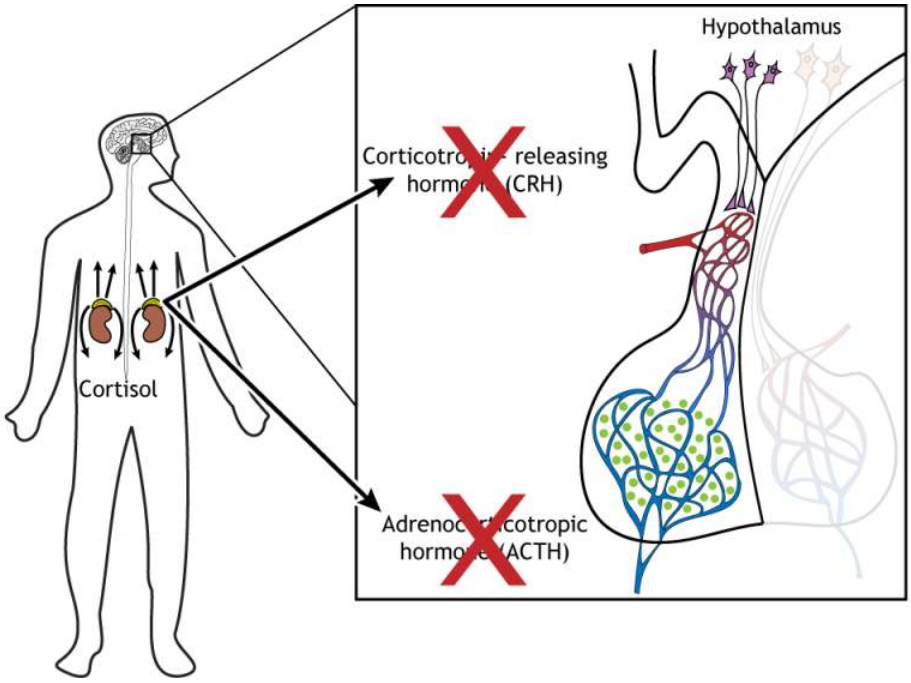


Figure 11.1.5: *Cortisol released by the adrenal cortex inhibits the synthesis and release of CRH and ACTH from the hypothalamus and pituitary, respectively. via a negative feedback loop. 'Cortisol Feedback' by Casey Henley is licensed under a CC BY-NC-SA 4.0 International License..*

As mentioned previous, all regulatory mechanisms employ negative feedback - if the optimal value is exceeded, responses will be turned off. But are corrective mechanisms only "turned off" when the desired value is obtained? The answer is no - we stop eating prior to the restoration of blood glucose levels and we start to drink before we actually have a fluid need. So, the systems can also *predict* needs and predict when needs have been satisfied.

11.1.1.4 Drive States and Ingestive Behavior

"**Ingestive Behavior**" (i.e. eating and drinking), is a fascinating topic when considered from the perspective of a biological psychologist. Why? The connection between the biological need for food (energy, nutrients) and water (hydration) lead to drive states (hunger and thirst) that motivate us to engage in behaviors to meet those needs. In other words, the connection between the body's need for food and water, the **drive states** of **hunger** and **thirst**, and seeking food and drink (the behaviors designed to meet the body's needs) is something that we are all familiar with. At the same time, the impact of learning on what we eat, when we eat, and even how we feel about food is also something that we're aware of. And there even is a link to mental illness - instances where the mind leads to ingestive behaviors (such as overeating or under-eating) that are harmful to the body. While it would be easy to

create an entire book (or course) that focuses on ingestive behavior, we are going to explore the topic by focusing on the biological bases for eating and drinking - with an emphasis on how we know what we know about these surprisingly complex behaviors.

What are the biological mechanisms that determine when we need to eat or drink - and how does the detection of a need trigger behaviors intended to meet that need? And how are those hunger and thirst signals turned off? Consider what causes you to "feel" hungry - where would you look for detectors of hunger or satiety (being "full")?

Hunger is a drive state, an affective experience (a mood or a feeling) that motivates organisms to fulfill goals that are generally beneficial to their survival and reproduction. Like other drive states, such as thirst or sexual arousal, hunger has a profound impact on the functioning of the mind. It affects psychological processes, such as perception, attention, emotion, and motivation, and influences the behaviors that these processes generate. Drive states serve to motivate a variety of behaviors.

11.1.1.5 Attributions

Adapted from Bhatia, S. & Loewenstein, G. (2022). Drive states. In R. Biswas-Diener & E. Diener (Eds), *Noba textbook series: Psychology.* Champaign, IL: DEF publishers. Retrieved from http://noba.to/pjwkbt5h (CC BY-NC-SA)

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11.2: Hunger - Theories, Detectors, and the Hypothalamus

Learning Objectives

1. Explain the concept of a set-point theory and how the detection of blood glucose levels and body fat explains some elements of feeding behavior.
2. Discuss the evidence for and against the existence of hypothalamic hunger and satiety centers.
3. Explain the effects of glucose, insulin, CCK, NPY, leptin, Ghrelin, and serotonin on eating behavior.

11.2.1 Overview

What determines when we are hungry - how is the need for food detected? How does the detection of a need lead to eating? And what determines when we stop eating? In this section we will explore potential hunger signals and various theories that explain some elements of eating behavior. As previously noted, human eating behavior is complicated by a wide array of environmental factors. As a consequence, much of our understanding of the biological factors involved in eating comes from animal studies.

Eating behavior is controlled by two separate, yet related, systems - one that signals a need to eat (i.e. hunger) and another that signals when that need has been met (i.e. fullness or satiety). In homeostatic terms, hunger is a complex "drive state" that involves multiple system variables and detector mechanisms. The key to the function of these systems may be located in specific hypothalamic nuclei. In addition, various chemical factors, including **glucose, ghrelin, cholecystokinin (CCK), Neuropeptide Y (NPY),** and **leptin** can act as systems variables which play key roles in eating behavior.

11.2.2 Hunger - The Drives Motivating Eating

Hunger is a classic example of a **drive state**, one that results in thoughts and behaviors related to the consumption of food. As we will see, hunger is often triggered by **low glucose levels** in the blood (Rolls, 2000), and behaviors resulting from hunger aim to restore homeostasis regarding those glucose levels. But various other **internal and external cues** can also cause hunger (Figure 11.2.1). For example, when fats are broken down in the body for energy, this initiates a chemical cue that the body should search for food (Greenberg, Smith, & Gibbs, 1990). External cues include the time of day, estimated time until the next feeding (hunger increases immediately prior to food consumption), and the sight, smell, taste, and even touch of food and food-related stimuli. Note that while hunger is a generic feeling, it can also lead to the eating of specific foods that correct for nutritional imbalances we may not even be conscious of. For example, a couple who was lost adrift at sea found that they began to crave the eyes of fish. Only later, after they had been rescued, did they learn that fish eyes are rich in vitamin C - a very important nutrient that they had been depleted of while lost on the ocean (Walker, 2014).

We'll begin our exploration of ingestive behaviors with eating, the behavior motivated by hunger. While you might think the control of eating is quite simple, the regulated variables involved in eating are not so well described.



Figure 11.2.1: External cues, like the sight and smell of food, can ignite feelings of hunger. [Image: Marco Verch, https://goo.gl/c4TC5A, CC BY 2.0, https://goo.gl/BRvSA7]

11.2.3 Homeostatic Set-Point Theories

Before we look at the mechanisms that produce hunger, we'll first consider some of the major theories that strive to explain hunger and eating. There are many theories that we could consider and, perhaps, someday a single theory will emerge that is superior to all others, but at the present time we don't have a single theory that accounts for how all the different factors that impact feeding

determine what we do. Most significantly, while human eating behavior tends to align with biological expectations over the long-term, the theories that focus on this fail to explain the increase in obesity that we see today (Speakman et al., 2011). In other words, there is a correlation between how much we eat (the calories we ingest) and how much we use (the calories we burn) when we consider our behavior over an extended period of time - but not when we look at individual meal-taking and daily eating behavior. *(This example should remind you of the discussion of **Homeostasis** from the previous section of this chapter. If not, you should take a step back before continuing.)*

You've probably been exposed to the notion of a body weight "**set-point**", the idea that you have an "ideal" weight and it takes a lot of work to move away from that set-point, that optimal value that our body strives to achieve. Perhaps we have some ideal level of energy that is necessary and that we eat to restore this value. In other words, perhaps we have a set-point for available energy. Is hunger an attempt to restore energy reserves and is hunger merely signaled when energy reserves are depleted? This would predict a consistency in energy use and food intake that we simply do not see (Hall et al., 2021).

11.2.3.1 Hunger & Glucostatic (Glucose Utilization) and Lipostatic (Fat Levels) Theories

What makes you feel hungry or full? Do you feel hungry when your stomach is empty? Do you feel satisfied when your belly actually feels full? How does the stomach tell the brain that nutrients are there? Interestingly, a stomach full of food will still put a stop to feeding, even if there are no nerves connecting it to the brain. And a full stomach - with no nutrients present - can also end feeding. These are just some of the interesting questions and phenomena that suggest the complexity of the signaling involved in hunger and satiety (fullness).

It turns out that the brain responds to two types of hunger signals:

- Short-term. Receptors in the liver and the brain are involved in responding to short-term signals. For example, they respond to levels of available fuel (i.e. the sugar, glucose) among other messages in the blood.
- Long-term. Long-term hunger signals are a consequence of the monitoring of fat stores. When fat cells are full, they produce a hormone called **leptin**. Leptin then inhibits the brain mechanisms that control eating - leptin makes the brain less responsive to short-term signals. Leptin effectively turns hunger signals off (negative feedback).

Perhaps the maintenance of blood **glucose** (readily available fuel in the blood) could be what controls feeding for the short-term and the maintenance of body fat (stored energy) could provide a long-term explanation of eating behavior. These are both variations on the set-point theory. While each of these theories has its problems, they are consistent with some findings.

Glucostatic theories propose that we work to maintain some ideal level of blood glucose. In contrast, **lipostatic** theories propose that we monitor the level of **body fat** that we have stored and then alter our eating to compensate when fat levels are not at the desired level. Having identified what is being regulated (our system variable, blood glucose or body fat) and presuming some set point, are there detectors to monitor our regulated variables?

Consistent with **glucostatic theory**, the usual trigger for hunger is a **drop in blood glucose** (hypoglycemia). We can artificially trigger short-term hunger, by one of two mechanisms:

- Decrease blood glucose with the administration of **insulin**. This causes available glucose to be stored and used by body cells. Recall from the previous section on digestion that the increase in insulin during the cephalic phase of digestion can increase your pre-meal hunger.
- Inject 2-deoyglucose (2-DG). 2-DG is structurally similar to glucose, but cells are unable to metabolize it. This produces glucoprivation - although glucose is available, cells are unable to use it. Both body and brain cells are deprived of glucose.

Both manipulations above deprive body cells of glucose and both will produce eating, consistent with a glucostatic hypothesis (Thompson & Campbell, 1977). Please see the next section of this chapter on digestion mechanisms for more details on the interaction between glucose and insulin and their role in hunger..

Lipostatic theory proposes that when stored fat drops below an optimal value, hormones are secreted that increase food intake and promote weight gain (Gale et al., 2004). It also proposes that when energy stores exceed that optimal value, adipose (fat) cells release leptin to reduce eating.

In addition to the relatively straightforward mechanisms of glucose and fat signals, there are a multitude of other neural and digestive inputs that can modulate our eating behavior.

11.2.4 Hunger, Satiety, and the Role of Gut Peptides

The stomach and other parts of the gastrointestinal tract produce peptides that can function as hormones, traveling in the blood stream to their site of action. One peptide that has been studied quite extensively is **cholecystokinin (CCK)**. In the absence of a neural connection, a chemical in the blood would be an ideal mechanism for the stomach to use to communicate with the brain. It turns out that CCK does cause food-deprived rats to eat smaller meals - but is that because they are feeling satiety? It turns out that CCK can make one feel ill - which would be likely to decrease eating.

While a whole host of peptides are thought to be involved in satiety, two have been found to play a role in hunger. **Neuropeptide Y (NPY)** and galanin both cause eating when injected into the paraventricular nucleus of the hypothalamus. NPY creates a hunger for carbohydrates and galanin for fats. Both decrease metabolism and increase fat production, suggesting they play a role in combating starvation. How does this work to regulate eating outside of a lab? Food deprivation results in an increase in NPY levels and eating decreases NPY levels. If NPY receptors in the hypothalamus are blocked, eating caused by NPY or deprivation is not seen.

What role do neurotransmitters play with respect to eating? It turns out that serotonin inhibits food intake, especially carbohydrate ingestion. Why is this so? One possibility is that serotonin inhibits NPY. There are numerous theories for how serotonin produces this effect on food intake. To make this situation more murky, there is counterintuitive findings that many SSRI, antidepressants that increase serotonin function also *increase* hunger and subsequent weight gain.

11.2.4.1 Ghrelin Effects on Hunger and More

Much of the research and findings regarding the role of the chemical **ghrelin** has focused on its ability to stimulate hunger. In fact, it is a significant signal for hunger that is based on both digestive properties in the gut and the preparation for incoming food.

Colldén, Tschöp, & Müller (2017) conducted a comprehensive review of the role of the chemical ghrelin on eating and a variety of other effects. As they point out, ghrelin is unique in terms of gut hormones in that it is the only one which can directly stimulate eating behavior and weight gain by acting on CNS mechanisms. They also describe a variety of additional effects that ghrelin is capable of influencing, some related to hunger and satiety and others not. Among these are ghrelin's ability to affect "enhanced gastric acid secretion and gastric motility, taste sensation, stress and anxiety, the sleep/wake cycle, glucose metabolism, and brown fat thermogenesis."

Colldén et al. (2017) go on to point out that, "Due to these and numerous other beneficial effects on systems metabolism... the endogenous ghrelin system is widely considered a promising approach to treat a variety of metabolic complications, most prominently ... pathological underweight associated with anorexia nervosa or cancer cachexia."

11.2.4.2 From Set-Point to Settling Point

If you accept that a set-point theory does not explain our day-to-day eating behavior, what about the notion of a set-point as an explanation for why we can't seem to lose those last 5 pounds? We certainly tend to maintain a relatively constant body weight - why is that? And should we listen to our bodies? Should you eat whenever your body tells you to?

While these observations may suggest that we ultimately seek to defend a particular level of body fat, another notion is that we maintain a weight at which all the factors that influence body weight reach an equilibrium - a so-called "settling point".

11.2.5 Determining What to Eat

Let's look more closely at what determines the specifics of eating behavior. What we find is that, despite the findings with non-human subjects, human eating behavior has little to do with energy stores. What we do see is natural preferences for food that would facilitate survival in times of energy need - what types of food taste good? Sweet and fatty foods are energy dense and our cravings for them make sense from an evolutionary perspective - there was a time when we had to literally work for our food (hunting and gathering) as opposed to opening the refrigerator or placing an order for delivery. At the same time, bitter and sour tastes are typically associated with toxins. So, we have species-typical taste preferences and aversions (dislikes).

In addition to our inherited preferences, we also have those that are learned. We learn to eat what those around us eat - that which is familiar to us is going to be more appealing. Even if you like to try new things, I'm sure that there are limits to what you will eat.

How does an animal in the wild know what to eat in order to get the nutrients it needs? Researchers have looked at what happens when a diet lacks a nutrient and found that animals will respond - they will seek out variety when not getting all the needed nutrients and develop aversions to (dislike of) foods lacking in some nutrient. Most nutrients can't be tasted - especially with our diet today. But we do see cravings and desires at certain times - perhaps because those foods meet a need. Perhaps pickles have

some benefit during pregnancy. And maybe ice cream fills a need created by a broken heart. Theoretically, we should have some ability to select the right foods, as we see in animals. But perhaps the learned elements of our eating (eating at meal times, clean your plate) have disrupted the body's ability to direct our eating choices. Further complicating ensuring we consume a balanced diet are personal decisions to restrict the types of foods eaten.Detecting Satiety

What determines how much we eat? How do we get satiety, what makes us feel "full"? Food in the body can induce satiety, but so can simply causing the stomach to distend - as was initially demonstrated in the early 1900's by researchers who observed the impact of inflating and deflating a swallowed ballon on hunger pangs (Cannon and Washburn, 1912). The fact is that the size of the stomach impacts how much one eats. Satiety created by food ingestion does seem to be dependent on nutritive density - to some degree food ingestion will be altered when the caloric content is changed. If you increase or decrease the calories per unit volume of food, animals will adjust their diet accordingly. Yet other studies have demonstrated with the use of sham feeding (where an animal feeds, but the food is ultimately not digested or absorbed) that the changes in food ingestion are not merely due to changes in the immediate caloric impact of the food.

We all know that we do respond to how food tastes - and we get tired of eating even those things that we do like - as studies of sensory-specific satiety have demonstrated. Rats (and humans) will eat more when presented with a varied diet of tasty food - a cafeteria diet. Here you see the incentive value of food overriding the normal mechanisms that control food intake.

11.2.6 Physiological Mechanisms of Hunger and Eating

There are a number of physiological mechanisms that serve as the basis for hunger. When our stomachs are empty, they contract. Typically, a person then experiences hunger pangs. Chemical messages travel to the brain, and serve as a signal to initiate feeding behaviour. When our blood glucose levels drop, the pancreas and liver generate a number of chemical signals that induce hunger (Konturek et al., 2003; Novin, Robinson, Culbreth, & Tordoff, 1985) and thus initiate feeding behaviour.

For most people, once they have eaten, they feel **satiation**, or **fullness** and satisfaction, and their eating behavior stops. Like the initiation of eating, satiation is also regulated by several physiological mechanisms. As blood glucose levels increase, the pancreas and liver send signals to shut off hunger and eating (Drazen & Woods, 2003; Druce, Small, & Bloom, 2004; Greary, 1990). The food’s passage through the gastrointestinal tract also provides important satiety signals to the brain (Woods, 2004), and fat cells release **leptin**, a satiety hormone.

Controlling the size of the stomach or the fullness of it can be used to help regulate eating. Bariatric surgery involves modifying the digestive system to achieve weight-loss. Approaches to such surgeries are varied, but decreasing the amount of food the stomach can hold is one such approach. Although recognized as an effective long-term approach for many, surgery may not be an option for many with a need for weight loss. Today, intragastric balloons are an alternative to surgical interventions.

The various hunger and satiety signals that are involved in the regulation of eating are integrated in the brain. Research suggests that several areas of the hypothalamus and hindbrain are especially important sites where this integration occurs (Ahima & Antwi, 2008; Woods & D’Alessio, 2008). Ultimately, activity in the brain determines whether or not we engage in feeding behavior.

11.2.7 The Role of the Hypothalamus

The hypothalamus plays a very important role in eating behavior. It is responsible for synthesizing and secreting various hormones. The **lateral hypothalamus (LH)** is concerned largely with hunger and, in fact, lesions (i.e., damage) of the LH can eliminate the desire for eating entirely - to the point that animals starve themselves to death unless kept alive by force feeding (Anand & Brobeck, 1951). Additionally, artificially stimulating the LH, using electrical currents, can generate eating behavior if food is available (Andersson, 1951).

Activation of the LH can not only increase the desirability of food but can also reduce the desirability of nonfood-related items. For example, Brendl, Markman, and Messner (2003) found that participants who were given a handful of popcorn to trigger hunger not only had higher ratings of food products, but also had lower ratings of nonfood products—compared with participants whose appetites were not similarly primed. That is, because eating had become more important, other non-food products lost some of their value.

While the feeling of hunger gets you to start eating, the feeling of satiation gets you to stop. Hunger and satiation are two distinct processes, controlled by different circuits in the brain and triggered by different cues. Distinct from the LH, which plays an important role in hunger, the **ventromedial hypothalamus (VMH)** plays an important role in satiety. Though lesions of the VMH

can cause an animal to overeat to the point of obesity, the relationship between the LH and the VMH is quite complicated. Rats with VMH lesions can also be quite finicky about their food (Teitelbaum, 1955).

Is it that simple? Is the LH the key to hunger and the VMH the source of satiation (satiety)?

Evidence supporting the LH as a hunger center and the VMH as a satiety center:

- Lesioning (destroying) the lateral hypothalamus leads to anorexia (loss of appetite) and aphagia (absence of eating). At the same time, stimulating this region produces both eating and drinking. If you need a way to remember which is which - if you lesion the LH you get a lean hamster. If you lesion the VMH you get a very meaty hamster.
- Lesioning the ventromedial hypothalamus leads to hyperphagia (excessive eating) and weight gain. And stimulation of the VMH suppresses eating.

Evidence against the LH as a hunger center and the VMH as a satiety center:

- Lesions of the LH interfere with all motivated behaviors, not just feeding. In other words, perhaps the LH is a motivation center as opposed to a hunger center.
- Lesions of the VMH suppress the activity of sympathetic nervous system and increase the activity of the parasympathetic nervous system. In other words, the body is in rest and restore mode. Rats with VMH lesions become picky eaters, preferring carbohydrates. Due to the increased PNS activity, there is no fasting phase of metabolism; they are never living off of their reserves - rats continue to eat as they are not using their energy stores.

Other brain areas, besides the LH and VMH, also play important roles in eating behavior. The sensory cortices (visual, olfactory, and taste), for example, are important in identifying food items. These areas provide informational value, however, not hedonic evaluations. That is, these areas help tell an organism what is good or safe to eat, but they don't provide the pleasure (or hedonic) sensations that *actually* eating the food produces. While many sensory functions are roughly stable across different psychological states, other functions, such as the detection of food-related stimuli, are enhanced when the organism is in a hungry drive state.

After identifying a food item, the brain also needs to determine its reward value, which affects the organism's motivation to consume the food. The reward value ascribed to a particular item is, not surprisingly, sensitive to the level of hunger experienced by the organism. The hungrier you are, the greater the reward value of the food. Neurons in the areas where reward values are processed, such as the orbitofrontal cortex, fire more rapidly at the sight or taste of food when the organism is hungry relative to if it is satiated.

11.2.8 Summary

Eating behavior is complicated, controlled by two systems, one that controls hunger and one that signals satiety. In other words, we have a system that turns hunger on and another that determines that the need has been met. The lateral hypothalamus plays a role in hunger and the ventromedial hypothalamus appears to play a central role in satiation. Further complicating the control of hunger is the presence of two ways of signaling an energy need, a system that responds to the available levels of fuel and responding to short-term need and one that monitors energy stores. In the short-term, levels of available glucose are monitored, while stored fats are the focus for the long-term system.

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11.2.10 Attributions

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11.3: Digestion and the Hormonal Control of Metabolism

Learning Objectives

- Distinguish between digestion and metabolism.
- Described the process of digestion, noting the roles of the mouth, stomach, intestines (small and large), and accessory organs.
- Describe how hormones regulate metabolism.
- Describe the three phases of digestion.

11.3.1 Overview

While we know that eating is motivated by the drive state of hunger, what is being regulated? What is the system variable - or variables - that are monitored? Glucose (i.e. sugar) is one such variable that is critical to our survival since it is a major source of energy for all systems of the body. In addition, other substances provide the building blocks that we use to construct and maintain our bodies. Thus, we need to monitor not only the quantity (how much) of food we eat, but the quality (what we eat). In other words, an ideal system for the control of our eating would be one that triggers a hunger that is specific - ensuring that we both get the quantity we need to meet our energy needs, but also the right types of foods to meet our nutritional needs.

In this section, we will explore the key role of the variables of glucose and insulin in the control of hunger. In addition, the anatomy and role of the digestive system in the consumption and processing of food and its constituents will be examined.

11.3.2 **The Human Digestive System**

The process by which we obtain the substances that the body needs begins with the consumption of food and is achieved when the nutrients provided by food are absorbed. This is the process of digestion, the process of ingesting, breaking down food, and absorbing the nutrients. Ultimately, food is delivered to the body in three forms: Lipids (fats), amino acids (proteins), and glucose (carbohydrates).

These fuels enter the body by way of the digestive tract, but the digestive tract is often empty. Because of this, and the importance of having fuel available, we have mechanisms that allow us to store energy to support us. This stored energy is primarily fats, but also glycogen and proteins. Before discussing how we store energy (and access stored energy), we need to understand the process of digestion.

The process of digestion begins in the mouth with the intake of food (Figure 11.3.1). The teeth play an important role in masticating (chewing) or physically breaking food into smaller particles. The enzymes present in saliva also begin to chemically break down food. The food is then swallowed and enters the esophagus - a long tube that connects the mouth to the stomach. Using peristalsis, or wave-like smooth-muscle contractions, the muscles of the esophagus push the food toward the stomach. The stomach contents are extremely acidic. This acidity kills microorganisms, breaks down food tissues, and activates digestive enzymes. Further breakdown of food takes place in the small intestine where bile produced by the liver, and enzymes produced by the small intestine and the pancreas, continue the process of digestion. The smaller molecules are absorbed into the blood stream through the epithelial cells lining the walls of the small intestine. The waste material travels on to the large intestine where water is absorbed and the drier waste material is compacted into feces; it is stored until it is excreted through the anus.

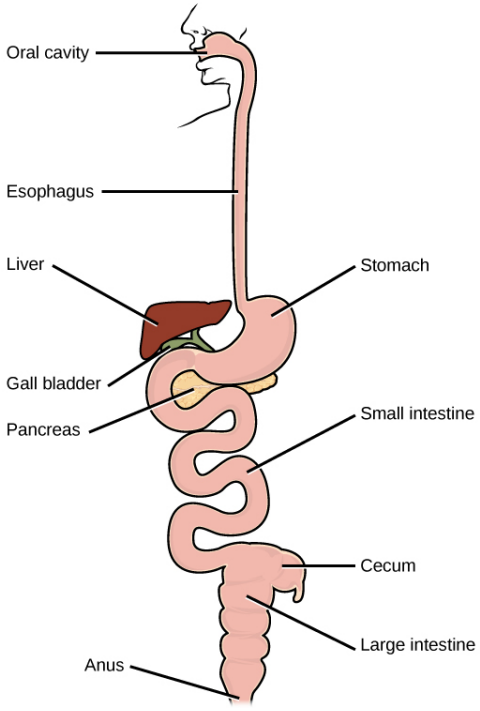


Figure 11.3.1: The components of the human digestive system are shown.

11.3.2.1 Oral Cavity

Both physical and chemical digestion begin in the mouth or oral cavity, which is the point of entry of food into the digestive system. The food is broken into smaller particles by mastication, the chewing action of the teeth. Almost all mammals have teeth and can chew their food to begin the process of physically breaking it down into smaller particles. (Mammals without teeth have very limited diets - ants or plankton - and include pangolins, anteaters and some species of whales.)

The chemical process of digestion begins during chewing as food mixes with saliva, produced by the salivary glands. Saliva contains mucus that moistens food and buffers the pH of the food. Saliva also contains enzymes that begin the process of breaking down some foods. The chewing and wetting action provided by the teeth and saliva prepare the food into a mass called the bolus for swallowing. The tongue helps in swallowing - moving the bolus from the mouth into the pharynx. The pharynx opens to two passageways: the esophagus and the trachea. The esophagus leads to the stomach and the trachea leads to the lungs. The epiglottis is a flap of tissue that covers the tracheal opening during swallowing to prevent food from entering the lungs.

11.3.2.2 Esophagus

The esophagus is a tubular organ that connects the mouth to the stomach. The chewed and softened food passes through the esophagus after being swallowed. The smooth muscles of the esophagus undergo peristalsis that pushes the food toward the stomach. The peristaltic wave moves food from the mouth to the stomach, and reverse movement is not possible, except in the case of vomiting (initiated by the gag reflex). The peristaltic movement of the esophagus is an involuntary reflex; it takes place in response to the act of swallowing.

Ring-like muscles called sphincters form valves in the digestive system. The gastro-esophageal sphincter (or cardiac sphincter) is located at the stomach end of the esophagus. In response to swallowing and the pressure exerted by the bolus of food, this sphincter opens, and the bolus enters the stomach. When there is no swallowing action, this sphincter is shut and prevents the contents of the stomach from traveling up the esophagus. Acid reflux or “heartburn” occurs when the acidic digestive juices escape into the esophagus.

11.3.2.3 Stomach

A large part of protein digestion occurs in the stomach. The stomach is a saclike organ that secretes gastric digestive juices.

Protein digestion is carried out by an enzyme called pepsin in the stomach chamber. The highly acidic environment kills many microorganisms in the food and, combined with the action of the enzyme pepsin, results in the catabolism (break down) of protein

in the food. Chemical digestion is facilitated by the churning action of the stomach caused by contraction and relaxation of smooth muscles. The partially digested food and gastric juice mixture is called **chyme**. Gastric emptying occurs within two to six hours after a meal. Only a small amount of chyme is released into the small intestine at a time. The movement of chyme from the stomach into the small intestine is regulated by hormones, stomach distension, and muscular reflexes that influence the pyloric sphincter.

The stomach lining is unaffected by pepsin and the acidity because pepsin is released in an inactive form and the stomach has a thick mucus lining that protects the underlying tissue.

11.3.2.4 Small Intestine

Chyme moves from the stomach to the small intestine. The small intestine is the organ where the digestion of protein, fats, and carbohydrates is completed. The small intestine is a long tube-like organ with a highly folded surface containing finger-like projections called the villi. The top surface of each villus has many microscopic projections called microvilli. The epithelial cells of these structures absorb nutrients from the digested food and release them to the bloodstream on the other side. The villi and microvilli, with their many folds, increase the surface area of the small intestine and increase absorption efficiency of the nutrients.

The human small intestine is divided into three parts: the **duodenum**, the jejunum, and the ileum. The duodenum is separated from the stomach by the pyloric sphincter. The chyme is mixed with pancreatic juices, an alkaline solution rich in bicarbonate that neutralizes the acidity of chyme from the stomach. Pancreatic juices contain several digestive enzymes that break down starches, disaccharides, proteins, and fats. Bile is produced in the liver and stored and concentrated in the gallbladder; it enters the duodenum through the bile duct. Bile contains bile salts, which make lipids accessible to the water-soluble enzymes. The monosaccharides, amino acids, bile salts, vitamins, and other nutrients are absorbed by the cells of the intestinal lining.

The undigested components of the food are sent to the colon from the ileum via peristaltic movements. The ileum ends and the large intestine begins at the ileocecal valve. The vermiform, “worm-like,” appendix is located at the ileocecal valve.

11.3.2.5 Large Intestine

The large intestine reabsorbs the water from indigestible food material and processes the waste material (Figure 11.3.2). Compared to the small intestine, the human large intestine is much smaller in length but larger in diameter. It has three parts: the cecum, the colon, and the rectum. The cecum joins the ileum to the colon and is the receiving pouch for the waste matter. The colon is home to many bacteria or “intestinal flora” that aid in the digestive processes. The colon has four regions, the ascending colon, the transverse colon, the descending colon and the sigmoid colon. The main functions of the colon are to extract the water and mineral salts from undigested food components, and to store waste material.

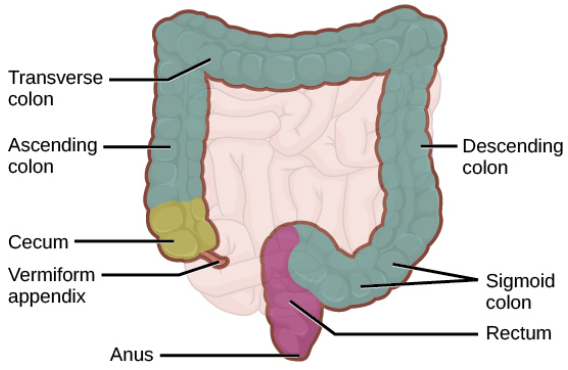


Figure 11.3.2: The large intestine reabsorbs water from undigested food and stores waste until it is eliminated. (credit: modification of work by Mariana Ruiz Villareal)

The rectum (Figure 11.3.2) stores feces until defecation. The feces are propelled using peristaltic movements during elimination. The anus is an opening at the far-end of the digestive tract and is the exit point for the waste material. Two sphincters regulate the exit of feces, the inner sphincter is involuntary and the outer sphincter is voluntary.

11.3.2.6 Accessory Organs

The organs discussed above are the organs of the digestive tract through which food passes. Accessory organs add secretions and enzymes that break down food into nutrients. Accessory organs include the salivary glands, the liver, the pancreas, and the gall

bladder (Figure 11.3.3). The secretions of the liver, pancreas, and gallbladder are regulated by hormones in response to food consumption.

The liver is the largest internal organ in humans and it plays an important role in digestion of fats and detoxifying blood. The liver produces bile, a digestive juice that is required for the breakdown of fats in the duodenum. The liver also processes the absorbed vitamins and fatty acids and synthesizes many plasma proteins. The gallbladder is a small organ that aids the liver by storing bile and concentrating bile salts.

The pancreas secretes bicarbonate that neutralizes the acidic chyme and a variety of enzymes for the digestion of protein and carbohydrates.

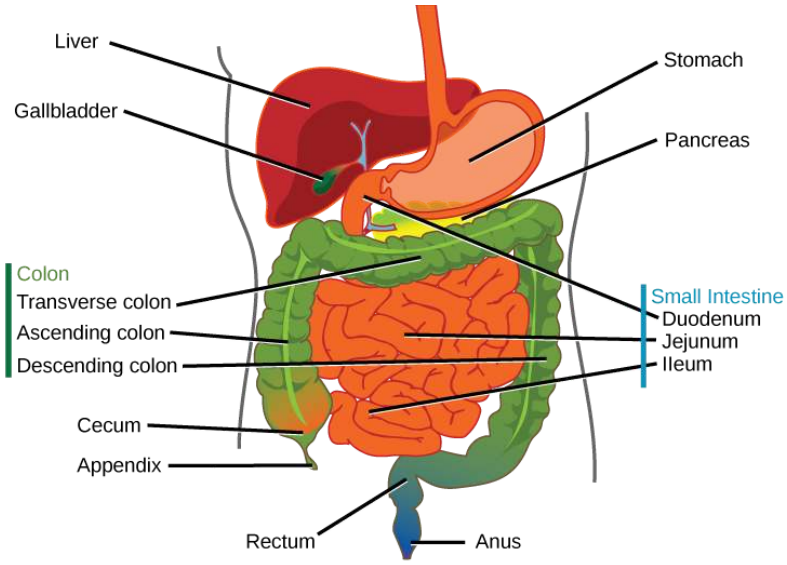


Figure 11.3.3: The stomach has an extremely acidic environment where most of the protein gets digested. (credit: modification of work by Mariana Ruiz Villareal)

11.3.3 Nutrition

The human diet should be well-balanced to provide nutrients required for bodily function and the minerals and vitamins required for maintaining structure and regulation necessary for good health and reproductive capability. The organic molecules required for building cellular material and tissues must come from food.

During digestion, digestible carbohydrates are ultimately broken down into glucose and used to provide energy to the cells of the body and the brain. Complex carbohydrates can be broken down into glucose through biochemical modification; however, humans do not produce the enzyme necessary to digest fiber. The intestinal bacteria in the human gut are able to extract some nutrition from these plant fibers. These plant fibers are known as dietary fiber and are an important component of the diet. The excess sugars in the body are converted into glycogen and stored for later use in the liver and muscle tissue. Glycogen stores are used to fuel prolonged exertions, such as long-distance running, and to provide energy during food shortage. Fats are stored under the skin of mammals for insulation and energy reserves and provide cushioning and protection for many organs.

Proteins in food are broken down during digestion and the resulting amino acids are absorbed. All of the proteins in the body must be formed from these amino acid constituents; no proteins are obtained directly from food.

Fats add flavor to food and promote a sense of satiety or fullness. Fatty foods are also significant sources of energy, and fatty acids are required for the construction of lipid membranes. Fats are also required in the diet to aid the absorption of fat-soluble vitamins and the production of fat-soluble hormones.

While the human body can synthesize many of the molecules required for function from precursors, there are some nutrients that must be obtained from food. These nutrients are termed essential nutrients, meaning they must be eaten, because the body cannot produce them.

11.3.4 Metabolism - An Overview

Metabolism is the process of making energy available for use. If your metabolism is high, you are breaking stored fuel down at a high rate - you are burning more calories. Note that the different forms of stored energy are found in different places in the body and the flow of energy into and out of storage is under the control of hormones. What hormones are involved directly in this process? Glycogen is the form in which carbohydrate is stored in cells of the liver and muscles. Ingested carbohydrates, in the form of glucose, are converted into glycogen by insulin and then stored. Insulin both promotes the storage of glucose as glycogen and allows body cells to use glucose. In other words, the cells of the body do not have access to glucose if insulin is not present. While insulin promotes the storage and use of glucose, glucagon (a hormone created in the pancreas) promotes the conversion of stored fuels to a form that can be readily used. In other words, if glucose is gone, glucagon makes more fuel available.

11.3.4.1 Regulation of Blood Glucose Levels by Insulin and Glucagon

Blood glucose levels vary widely over the course of a day as periods of food consumption alternate with periods of fasting. Insulin and glucagon are the two hormones primarily responsible for maintaining homeostasis of blood glucose levels. Additional regulation is mediated by the thyroid hormones.

Cells of the body require nutrients in order to function, and these nutrients are obtained through feeding. Excess intake is converted to stores and removed when needed. Hormones moderate our energy stores. Insulin is produced by the beta cells of the pancreas, which are stimulated to release insulin as blood glucose levels rise (for example, after a meal is consumed). Insulin lowers blood glucose levels by enhancing the rate of glucose uptake and use by cells. Insulin also stimulates the liver to convert glucose to glycogen, which is then stored by cells for later use. Some cells, including those in the kidneys and brain, can access glucose without the use of insulin. Insulin also stimulates the conversion of glucose to fat in adipocytes and the synthesis of proteins. These actions mediated by insulin cause blood glucose concentrations to fall, called a hypoglycemic “low sugar” effect, which inhibits further insulin release from beta cells through a negative feedback loop.

Impaired insulin function can lead to a condition called diabetes mellitus, the main symptoms of which are illustrated in Figure 11.3.4. This can be caused by low levels of insulin production by the beta cells of the pancreas, or by reduced sensitivity of tissue cells to insulin. This prevents glucose from being absorbed by cells, causing high levels of blood glucose, or hyperglycemia (high sugar). High blood glucose levels make it difficult for the kidneys to recover all the glucose from the urine, resulting in glucose being lost in urine. High glucose levels also result in less water being reabsorbed by the kidneys, causing high amounts of urine to be produced; this may result in dehydration. Over time, high blood glucose levels can cause nerve damage to the eyes and peripheral body tissues, as well as damage to the kidneys and cardiovascular system. Oversecretion of insulin can cause hypoglycemia, low blood glucose levels. This causes insufficient glucose availability to cells, often leading to muscle weakness, and can sometimes cause unconsciousness or death if left untreated.

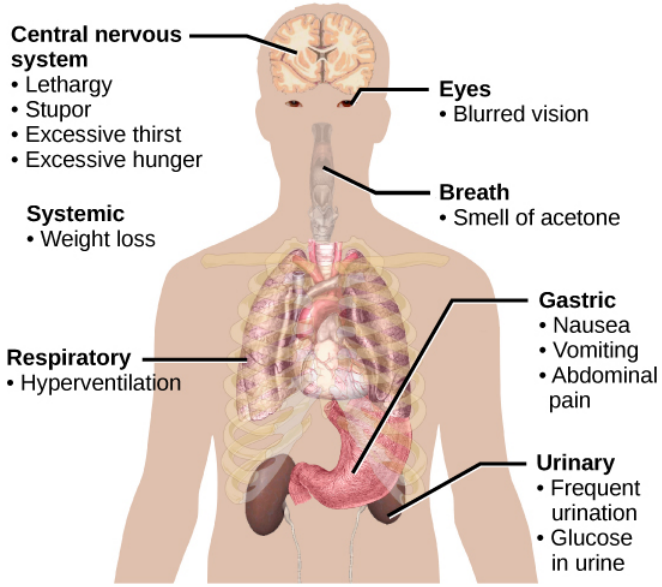


Figure 11.3.4: The main symptoms of diabetes are shown. (credit: modification of work by Mikael Häggström)

When blood glucose levels decline below normal levels, for example between meals or when glucose is utilized rapidly during exercise, the hormone glucagon is released from the alpha cells of the pancreas. Glucagon raises blood glucose levels, causing what is called a hyperglycemic effect, by stimulating the breakdown of glycogen to glucose in skeletal muscle cells and liver cells in a process called glycogenolysis. Glucose can then be utilized as energy by muscle cells and released into circulation by the liver cells. Glucagon also stimulates absorption of amino acids from the blood by the liver, which then converts them to glucose. This process of glucose synthesis is called gluconeogenesis. Glucagon also stimulates adipose (fat) cells to release fatty acids into the blood. These actions mediated by glucagon result in an increase in blood glucose levels to normal homeostatic levels. Rising blood glucose levels inhibit further glucagon release by the pancreas via a negative feedback mechanism. In this way, insulin and glucagon work together to maintain homeostatic glucose levels, as shown in Figure 11.3.5.

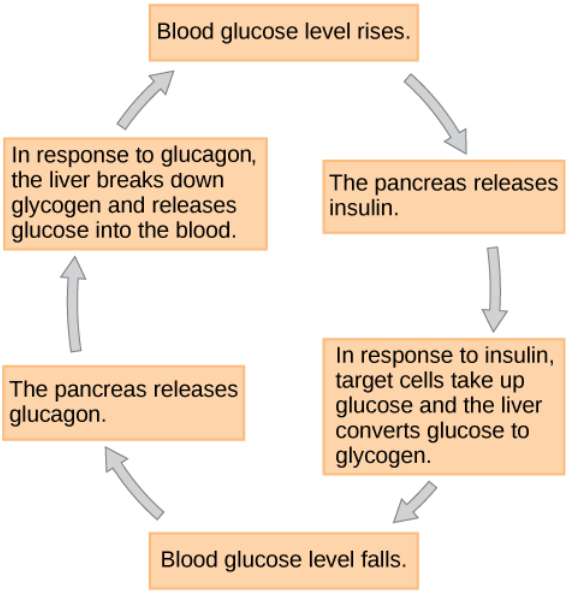


Figure 11.3.5: Insulin and glucagon regulate blood glucose levels. (credit: modification of OpenStax image)

11.3.5 Long-Term Energy Stores

"Fat" is composed of triglycerides, glycerol and fatty acids. Fat, or adipose, tissue is found beneath the skin and in various areas around the abdominal cavity. The cells in this tissue are able to absorb nutrients from the blood and are quite versatile - changing dramatically in size as the levels of stored triglycerides change. Once the short-term carbohydrate reserve is depleted, triglycerides begin to be converted to a form that cells can use and are released. Free fatty acids can be used for energy by all cells, except those of the central nervous system. Where does the brain get energy in this case? While the cells in the body are using free fatty acids, the liver is taking up the glycerol and converting it to glucose. As discussed earlier, when glucose is gone, we get the release and action of glucagon - a hormone that converts stored fuels to those that can be readily used, like glucose.

What happens when glucagon is high and insulin is low, when stored fuels are being made available? The available free fatty acids (previously stored in adipose tissue) are converted to ketones which can be used by muscles. The breakdown of fat for energy results in a high level of ketones, a phenomenon that can also occur when one is starving. Normally, ketones are excreted in the urine. When the body is not able to process excess ketones, ketoacidosis occurs. Ketoacidosis literally leads to an increase in the acidity of the body which creates a whole host of problems - even death. Dehydration occurs as the body tries to adjust. What you have is also the movement of water out of cells - which will make more sense once we cover thirst.

11.3.6 The Three Phases of Digestion

When we look at the process of digestion, we can recognize three different phases. Each has its own unique hormonal profile.

- Cephalic - During the cephalic or "head" phase, the body is preparing to eat. The expectation of food, the anticipation of food, leads to the release of insulin. If the smell or sight of food leads to a hunger pang, this just might be a consequence of insulin causing any available glucose to be used or stored. This phase ends when those ingested nutrients are absorbed into the blood stream. So the cephalic phase begins when the body prepares for food ingestion and ends when that ingested food impacts fuel levels in the bloodstream.

- Absorptive - During the absorptive phase, insulin is actively promoting the use - and storage - of ingested fuels. This phase ends when the unstored energy from the meal has been used.
- Fasting Phase - When the fuel from the meal is gone, glucagon levels rise and energy stores are converted into usable fuels.

When there is no fuel available in the blood, when glucose levels drop, energy must be mobilized (removed) from energy stores. What part of the nervous system makes energy available? The sympathetic nervous system, the fight or flight component of the autonomic branch of the peripheral nervous system, causes the secretion of glucagon when there is a lack of fuel in the blood.

11.3.7 Summary

The process of digestion begins in the mouth where food begins to be broken down both chemically and physically into the lipids, amino acids, and glucose that are used by the body. Digestion begins in the mouth and ends when fuels are absorbed into the blood stream. Digestion consists of three phases: cephalic, absorptive, and fasting.

Metabolism, a process controlled by the hormones insulin and glucagon, makes energy available for use. Insulin is produced by the pancreas in response to rising blood glucose levels and allows cells to use the available blood glucose and store excess glucose as glycogen for later use. Diabetes mellitus is caused by reduced insulin activity and causes high blood glucose levels, or hyperglycemia. Glucagon is released by the pancreas in response to low blood glucose levels and stimulates the breakdown of glycogen into glucose, which can be used by the body.

11.3.8 Attributions

"The Human Digestive System" and "Nutrition" adapted from Samantha Fowler, S., Roush, R. & Wise, J, (2013). *16.2 Digestive System - Concepts of Biology.* OpenStax. Retrieved April 24, 2022, from https://openstax.org/books/concepts-biology/pages/16-2-digestive-system (CC BY)

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"Regulation of Blood Glucose Levels by Insulin and Glucagon" adapted from Rye, C., Wise, R., Jurukovski, V., DeSaix, J., Choi, J., & Avissar , Y. (2016, October 21). *37.3 Regulation of Body Processes - Biology*. OpenStax. Retrieved February 6, 2022, from https://openstax.org/books/biology/p...body-processes (CC BY)

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11.4: Ingestive Behavior in Context- Diabetes and Obesity

Learning Objectives

1. Describe the elements of Diabetes and the role of insulin in its development
2. Differentiate Type 1 and Type 2 Diabetes.
3. Explain the role of obesity in both types of Diabetes.

11.4.1 Overview

Eating and drinking are complicated behaviors that are intended to meet biological needs. As already discussed, complex biological mechanisms serve to initiate and terminate these behaviors. As with many behaviors, humans make choices and they may make choices that are not consistent with their biological needs. We end this chapter with a discussion of diabetes and obesity. Both are conditions that were noted previously in this chapter. Here we consider them - and what we know about them - in greater detail.

11.4.2 Diabetes

Diabetes mellitus (diabetes) is a chronic disorder that can alter carbohydrate, protein, and fat metabolism. It is caused by the absence of **insulin** secretion due to either the progressive or marked inability of the islet cells of the pancreas to produce insulin, or due to defects in insulin uptake in the peripheral tissue. Diabetes is broadly classified under two categories, which include type 1 and type 2 diabetes (Mathieu & Badenhoop, 2005).

Type 1 diabetes occurs most commonly in children, but it can sometimes also appear in adult age groups, particularly in those in their late thirties and early forties. Patients with type 1 diabetes are generally not obese and frequently present with an emergency status known as diabetes ketoacidosis, a condition that develops when the body begins using fat for energy (American Diabetes Association, 2007).

The development of type 1 diabetes can be explained by damage to the pancreatic cells due to environmental or infectious agents. In individuals who are susceptible to genetic alterations, the immune system is triggered to produce an immune response against the altered islet cells that product insulin, or against molecules in those cells (Hutton & Davidson, 2010). Approximately 80% of patients with type 1 diabetes show circulating islet cell antibodies, and most of these patients have anti-insulin antibodies before receiving insulin therapy (van Belle, Coppieters, & von Herrath, 2011).

The major factor in the pathophysiology of type 1 diabetes is considered to be **autoimmunity** (Mathieu & Badenhoop, 2005).There is a strong relationship between type 1 diabetes and other autoimmune diseases such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease. When these diseases are present, the prevalence rates of type 1 diabetes increase (Philippe, 2011).

Type 2 diabetes has a different pathophysiology and origin as compared to type 1 diabetes. The existence of many new factors – for example, the increased prevalence of **obesity** among all age groups and both sexes, **physical inactivity**, **poor diet**, and **urbanization** – means that the number of patients diagnosed with type 2 diabetes is rising (Ershow, 2009) . This finding is significant because it will allow health planners to make rational plans and reallocate health resources accordingly (Wild et al., 2004).

Type 2 diabetes is described as a combination of low amounts of insulin production from pancreatic islet cells and peripheral insulin resistance (Kasuga, 2006). Insulin resistance leads to elevated fatty acids in the plasma, causing decreased glucose transport into the muscle cells, as well as increased fat breakdown, subsequently leading to elevated liver glucose production. Insulin resistance and pancreatic cell dysfunction must occur simultaneously for type 2 diabetes to develop. Anyone who is overweight and/or obese has some kind of insulin resistance, but diabetes only develops in those individuals who lack sufficient insulin secretion to match the degree of insulin resistance. Insulin in those people may be high, yet it is not enough to normalize the level of blood glucose (Røder, Porte, Schwartz, & Kahn, 1998).

Dysfunction of insulin-producing islet cells is a main factor across the progression from prediabetes to diabetes. After the progression from normal glucose tolerance to abnormal glucose tolerance, post-meal blood glucose levels increase initially. Thereafter, fasting hyperglycemia may develop as the suppression of hepatic (liver) gluconeogenesis fails (Porte, 1991). Despite the fact that the pathophysiology of diabetes differs between type 1 and type 2 diabetes, most of the complications are similar.

11.4.3 Obesity

Overweight and obesity are defined by an excess accumulation of adipose tissue to an extent that impairs both physical and psychosocial health and well-being (Naser, Gruber, & Thomson, 2006). Obesity is considered a health disaster in both Western and non-Western countries (Gallagher, 2000)

The prevalence is escalating significantly in many nations worldwide. This pandemic needs to be stopped if the economic costs, social hazards, morbidity, and mortality of the disease are considered.

11.4.4 Obesity and Type 1 Diabetes

The rising incidence of type 2 diabetes among children and adults is related to the epidemic of obesity. An increase in type 1 diabetes is thought to have similar origins (Arora, 2014). While the underling pathophysiology of type 1 diabetes, which is autoimmune in nature, continues to be investigated and studied, the exact mechanism causing the rise in the incidence of type 1 diabetes remains unclear, particularly in young age groups. One study, which collected data on childhood diabetes from 112 centers around the world, demonstrated an approximate 2.8% annual increase in type 1 diabetes over the period from 1989–2000 (Diamond Project Group, 2006).

The origin of type 1 diabetes, according to twin studies, indicates a joint contribution of environmental and genetic factors (Ershow, 2009). Furthermore, the importance of environmental factors in the development of diabetes is indicated by a significant rise in type 1 diabetes incidence in immigrants from lower to higher incidence regions. Multiple triggers for the development of type 1 diabetes have been investigated, including short-duration or the absence of breastfeeding, exposure to cow's milk protein, and exposure to some kind of infection such as enterovirus or rubella. However, none of these triggering factors has been shown to be the definitive cause (Harder, 2009).

The association between type 1 diabetes and weight gain was first investigated in 1975. The work of Baum and colleagues suggested that there was an association related to overfeeding or to hormonal dysregulation (Baum JD, Ounsted, & Smith, 1975).

The "accelerator hypothesis" proposed by Wilkin (2001) is considered one of the most accepted theories that demonstrates the association between body mass and type 1 diabetes. The authors of this theory suggested that increasing body weight in young age groups increases the risk of developing type 1 diabetes. There is an inverse relationship between body mass index and age at diagnosis. In other words, the higher the body mass index, the younger the age of diagnosis. Furthermore, as young children gain more weight, diabetes can be diagnosed earlier. This is explained by the fact that more weight accelerates insulin resistance, leading to the development of type 1 diabetes in individuals who are predisposed genetically to diabetes. Following this study, many papers were published supporting Wilkin's accelerator hypotheses. One study conducted in the United States in 2003 showed a significant increase in the prevalence of being overweight in children with type 1 diabetes, from 12.6% in the period 1979–1989 to 36.8% in the period 1990–1998. To date, the exact mechanism and relationship between type 1 diabetes and obesity remains inconclusive and needs further explanation (Wilkin, 2001).

11.4.5 Obesity and Type 2 Diabetes

The increased prevalence of obesity these days has drawn attention to the worldwide significance of this problem (Arora, 2014). In the United States, approximately two-thirds of the adult population is considered to be overweight or obese. Similar trends are being noticed worldwide (Tsai, Williamson, & Glick, 2011). Obesity is linked to many medical, psychological, and social conditions, the most devastating of which may be type 2 diabetes. At the start of this century, 171 million people were estimated to have type 2 diabetes, and this figure is expected to increase to 360 million by 2030 (McKeigue, Shah, & Marmot MG, 1991).

Both type 2 diabetes and obesity are associated with insulin resistance. Most obese individuals, despite being insulin resistant, do not develop hyperglycemia. Pancreatic cells release adequate amounts of insulin that are sufficient to overcome insulin level reductions under normal circumstances, thus maintaining normal glucose tolerance (Røder, Porte, Schwartz, & Kahn, 1998).

11.4.6 Obesity and Insulin Resistance

Insulin sensitivity fluctuation occurs across the natural life cycle. For example, insulin resistance is noticed during puberty, in pregnancy, and during the aging process (Kahn, Hull , & Utzschneider, 2006). In addition, lifestyle variations, such as increased carbohydrate intake and increased physical activity, are associated with insulin sensitivity fluctuations (Kasuga, 2006). Obesity is considered the most important factor in the development of metabolic diseases. Adipose tissue affects metabolism by secreting hormones, glycerol, and other substances including leptin, cytokines, adiponectin, and proinflammatory substances, and by

releasing nonesterified fatty acids (NEFAs). In obese individuals, the secretion of these substances will be increased (Karpe, Dickmann, & Frayn, 2011).

The cornerstone factor affecting insulin insensitivity is the release of NEFAs. Increased release of NEFAs is observed in type 2 diabetes and in obesity, and it is associated with insulin resistance in both conditions (Jelic, 2007). Shortly after an acute increase of plasma NEFA levels in humans, insulin resistance starts to develop. Conversely, when the level of plasma NEFA decreases, peripheral insulin uptake and glucose monitoring will be improved (Roden et al., 1996).

Insulin sensitivity is determined by another critical factor, which is body fat distribution. Insulin resistance is associated with body mass index at any degree of weight gain. Insulin sensitivity also differs completely in lean individuals because of differences in body fat distribution. Individuals whose fat distribution is more peripheral have more insulin sensitivity than do individuals whose fat distribution is more central (ie, in the abdomen and chest area) (Karpe, Dickmann, & Frayn, 2011).

Differences in adipose tissue distribution help explain, to some extent, how the metabolic effects of subcutaneous and intra-abdominal fat differ. Intra-abdominal fat is more related to the genes that secrete proteins and the specific types of proteins responsible for the production of energy. Adiponectin secretion by omental adipocytes is larger than the amount secreted by subcutaneous-derived adipocytes. Moreover, the quantity secreted from these omental adipocytes is negatively associated with increased body weight (Jelic, 2007). The secretion of NEFAs to different tissue may be affected by their source.

Furthermore, abdominal fat is considered more lipolytic than subcutaneous fat, and it also does not respond easily to the antilipolytic action of insulin, which makes intra-abdominal fat more important in causing insulin resistance, and thus diabetes.[27,28]

Marcial et al[29] further explained the molecular mechanisms of insulin resistance, inflammation, and the development of diabetes. One of the mechanisms of insulin is its effect as an anabolic hormone that enhances glycogen synthesis in liver and muscle. This in turn augments protein synthesis inhibiting the process of proteolysis. Insulin resistance is indeed an important factor in disease process. Fat storage and mobilization are other important factors causing insulin resistance.

11.4.7 Obesity and β-cell dysfunction

β-cells are cells of the pancreas that release insulin in response to changing blood glucose levels. These cells play a vital role in regulating insulin release, despite their fragility. The quantity of insulin released by β-cells fluctuates and changes according to the quantity, nature, and route of administration of the stimulus. Therefore, β-cells play a very important role in ensuring that in healthy subjects, concentrations of blood glucose are stable within a relatively normal physiological range. In obesity, insulin sensitivity, as well as the modulation of β-cell function, decreases.[30]

Insulin-resistant individuals, whether slim or fat, have more insulin responses and lower hepatic insulin clearance than those who are insulin sensitive. In a normal healthy subject, there is a continuous feedback relationship between the β-cells and the insulin-sensitive tissues.[10] If the adipose tissue, liver, and muscles demand glucose, this will lead to increased insulin supply by the β-cells. If the glucose levels require stability, changes in insulin sensitivity must be matched by a relatively opposite change in circulating insulin levels. Failure of this process to take place results in a deregulation of glucose levels and the development of DM. If the β-cells are healthy, there is an adaptive response to insulin resistance, which leads to the maintenance of normal levels of glucose. By contrast, when pancreatic β-cells are impaired, abnormal glucose tolerance or abnormal fasting glucose may develop, and it may even be followed by the development of type 2 diabetes.[30] A continued decline in β-cell function is one of the main causes leading to type 2 diabetes.

11.4.8 Summary

Diabetes and obesity are chronic disorders that are on the rise worldwide. Body mass index has a strong relationship to diabetes and insulin resistance. In an obese individual, the amount of NEFA, glycerol, hormones, cytokines, proinflammatory substances, and other substances that are involved in the development of insulin resistance are increased. Insulin resistance with impairment of β-cell function leads to the development of diabetes. Gaining weight in early life is associated with the development of type 1 diabetes. NEFA is a cornerstone in the development of insulin resistance and in the impairment of β-cell function. New approaches in managing and preventing diabetes in obese individuals must be studied and investigated based on these facts.

11.4.9 Attributions

FROM Al-Goblan, A. S., Al-Alfi, M. A., & Khan, M. Z. (2014). Mechanism linking diabetes mellitus and obesity. *Diabetes, metabolic syndrome and obesity : targets and therapy*, *7*, 587–591. https://doi.org/10.2147/DMSO.S67400 (CC BY-NC)

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11.5: Maintaining Water Balance

Learning Objectives

- Discuss the importance of water balance.
- Explain the role of hormones in maintaining water balance.
- Describe the renin-angiotensin-aldoesterone system and how it impacts blood volume and pressure.

11.5.1 Overview

As with eating behavior, environmental factors also impact our intake of fluids. But while we have varied sources of energy and mechanisms for storing that energy, the need to drink is triggered by a disruption in water balance. What makes thirst and drinking more complicated is the fact that water imbalances can be created by either a loss of fluids or an increase in solutes that causes water to move out of calls. In other words, just as it appears that we monitor both short-term and long-term energy stores to trigger hunger, we also monitor two different water stores to determine a need to drink. We'll explore this in more detail following an overview of the biological controls of water balance and the brain mechanisms that trigger thirst.

11.5.2 Maintaining Water Balance - Physiological Mechanisms

Maintaining a proper water balance in the body is important to avoid dehydration or over-hydration. The water concentration of the body is monitored by osmoreceptors in the hypothalamus, which detect the concentration of electrolytes in the extracellular fluid. The concentration of electrolytes in the blood rises when there is water loss caused by excessive perspiration, inadequate water intake, or low blood volume due to blood loss. An increase in blood electrolyte levels results in a neuronal signal being sent from the osmoreceptors in hypothalamic nuclei.

The hypothalamus produces a polypeptide hormone known as **antidiuretic hormone** (**ADH,** also known as **vasopressin**), which is transported to and released from the posterior pituitary gland. The principal action of ADH is to regulate the amount of water excreted by the kidneys. As ADH causes direct water reabsorption from the kidney tubules, salts and wastes are concentrated in what will eventually be excreted as urine. The hypothalamus controls the mechanisms of ADH secretion, either by regulating blood volume or the concentration of water in the blood. Dehydration or physiological stress can cause an increase in solute concentration which leads to ADH secretion and the retention of water, causing an increase in blood pressure. ADH travels in the bloodstream to the kidneys. Once at the kidneys, ADH changes the kidneys to become more permeable to water by temporarily inserting water channels, aquaporins, into the kidney tubules. Water moves out of the kidney tubules through the aquaporins, reducing urine volume. The water is reabsorbed into the capillaries returning the blood's solute levels back toward normal. As the blood solute concentration decreases, a negative feedback mechanism reduces osmoreceptor activity in the hypothalamus, and ADH secretion is reduced. ADH release can be reduced by certain substances, including alcohol, which can cause increased urine production and dehydration.

Chronic underproduction of ADH or a mutation in the ADH receptor results in diabetes insipidus, a condition characterized by the rapid loss of water following intake. If the posterior pituitary does not release enough ADH, water cannot be retained by the kidneys and is lost as urine. This causes increased thirst, but water taken in is lost again and must be continually consumed. If the condition is not severe, dehydration may not occur, but severe cases can lead to electrolyte imbalances due to dehydration.

Another hormone responsible for maintaining electrolyte concentrations in extracellular fluids is aldosterone, a steroid hormone that is produced by the adrenal cortex. In contrast to ADH, which promotes the reabsorption of water to maintain proper water balance, aldosterone maintains proper water balance by enhancing sodium (Na^+) reabsorption and potassium (K^+) secretion from extracellular fluid of the cells in kidney tubules. Because it is produced in the cortex of the adrenal gland and affects the concentrations of minerals Na^+ and K^+, aldosterone is referred to as a mineralocorticoid, a corticosteroid that affects ion and water balance. Aldosterone release is stimulated by a decrease in blood sodium levels, blood volume, or blood pressure, or an increase in blood potassium levels. It also prevents the loss of Na^+ from sweat, saliva, and gastric juice. The reabsorption of Na^+ also results in the osmotic reabsorption of water, which alters blood volume and blood pressure.

Aldosterone production can be stimulated by low blood pressure, which triggers a sequence of chemical release, as illustrated in Figure 11.5.1. When blood pressure drops, the renin-angiotensin-aldosterone system (RAAS) is activated. Cells in the juxtaglomerular apparatus, which regulates the functions of the nephrons of the kidney, detect this and release renin. Renin, an enzyme, circulates in the blood and reacts with a plasma protein produced by the liver called angiotensinogen. When

angiotensinogen is cleaved by renin, it produces angiotensin I, which is then converted into angiotensin II in the lungs. Angiotensin II functions as a hormone and then causes the release of the hormone aldosterone by the adrenal cortex, resulting in increased Na^+ reabsorption, water retention, and an increase in blood pressure. Angiotensin II in addition to being a potent vasoconstrictor also causes an increase in ADH and increased thirst, both of which help to raise blood pressure.

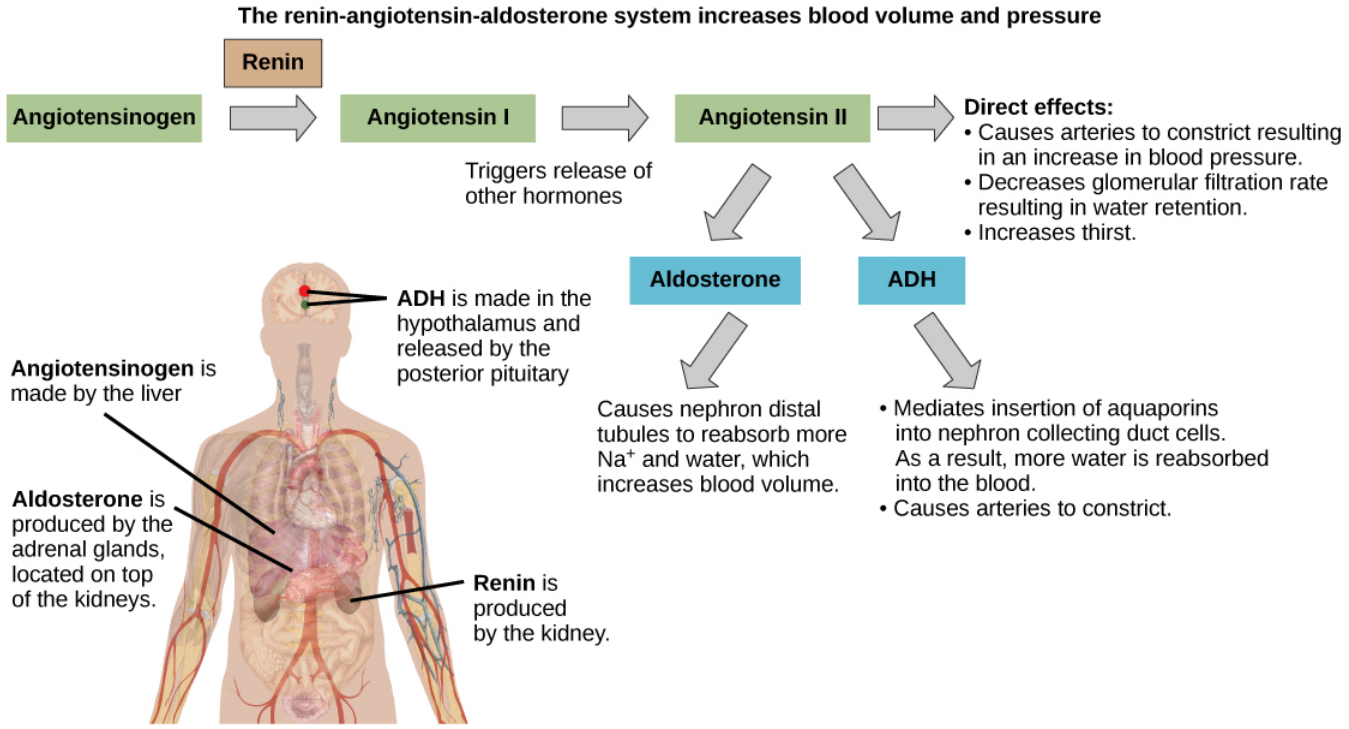


Figure 11.5.1: ADH and aldosterone increase blood pressure and volume. Angiotensin II stimulates release of these hormones. Angiotensin II, in turn, is formed when renin cleaves angiotensinogen. (From *Biology*. OpenStax. https://openstax.org/books/biology/p...body-processes (CC BY)credit: modification of work by Mikael Häggström).

11.5.3 Maintaining Water Balance - The Lamina Terminalis and Thirst

When your body starts to run low on water, a number of changes take place: for one, the volume of your blood decreases, causing a change in blood pressure. Because the amount of salt and other minerals in your body is staying constant as the volume of liquids decreases, their relative concentration increases (the same number of particles in a smaller volume means that the particles are more concentrated). This concentration of particles in bodily fluids relative to the total amount of liquid needs to be kept in a narrow range to keep the cells in your body functioning properly. Your body also needs a steady supply of fluids to transport nutrients, eliminate waste, and lubricate and cushion joints. To some extent, the body can compensate for water depletion by altering heart rate and blood pressure and by modifying kidney function to retain more water. For you, though, the most noticeable indication that your body is running low on fluids is likely the feeling of thirst, as you increasingly feel like you need to drink some water.

So how does your body know that these responses are necessary, and how are they coordinated across so many different organ systems? Research indicates that a highly specialized part of the brain called the **lamina terminalis** is responsible for guiding many of these thirst responses (Figure 11.5.2). Brain cells within the lamina terminalis can sense when the body is running low on water and whether you've had anything to drink recently. When researchers manipulate this brain region, they can also drive animals to seek out or avoid water, regardless of how hydrated that animal might be.

Two of the key subareas of the lamina terminalis that play a role in two different types of thirst are the **organum vasculosum laminae terminalis (OVLT)** and the **subfornical organ (SFO).** We will return to the distinct roles of these two areas in the discussion of Osmotic and Hypovolemic thirst in the next section of this chapter.

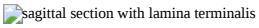


Figure 11.5.2: **Brain regions controlling thirst.** The lamina terminalis (yellow) is a series of interconnected brain structures that act as a central hub to control fluid levels in the body. Some cells in the lamina terminalis are adjacent to large, fluid-filled compartments in the brain, called ventricles (blue). When the body begins to run low on water, the composition of the body's fluids (including the fluid in the brain's ventricles) starts to change. The lamina terminalis neurons that border the ventricles can sense changes in the ventricular fluids, giving a snapshot of whether the body has enough water. These neurons also receive messages from other parts of the brain to give an even more complete picture of the body's water needs. From *The Neuroscience of Thirst: How your brain tells you to look for water.* (CC BY-NC-SA)

The lamina terminalis is located towards the front of the brain and occupies a prime location just below a fluid reservoir called the third ventricle. Unlike much of the rest of the brain, many cells in the lamina terminalis aren't guarded by a blood-brain barrier. This barrier prevents many circulating factors in the blood and other fluids from interacting with cells in the brain, offering the brain protection against potentially dangerous invaders like certain bacteria, viruses, and toxins. However, the blood-brain barrier also cuts the brain off from many circulating signals that might hold useful information about the body's overall status. Because certain cells in the lamina terminalis lie outside the blood-brain barrier, these cells can also interact with the fluid in the third ventricle to keep tabs on factors that indicate whether the body needs more or less water. In particular, these cells can monitor the fluid in the ventricle to determine its osmolality (the ratio of salt particles to a given amount of liquid) and the amount of sodium present.

When other parts of the brain detect information that's relevant to understanding the body's water needs, they frequently pass it along to the lamina terminalis, as well (Figure 11.5.2). In this way, the lamina terminalis also collects information about things like blood pressure, blood volume, and whether you've eaten recently (even before food can cause any change in circulating salt or water levels, your body tries to maintain a balance between these factors by encouraging you to drink water every time you eat). Information from the part of the brain that controls the circadian clock (the suprachiasmatic nucleus of the hypothalamus) also gets forwarded to the lamina terminalis, encouraging animals to drink more water before sleeping to avoid becoming dehydrated during long periods of sleep. Collectively, this information gives the lamina terminalis the resources needed to make a call about whether the body needs more or less water. In turn, cells in the lamina terminalis project to many other areas of the brain, sending out their verdict about current water needs. Although scientists are still trying to figure out exactly how information from the lamina terminalis affects other brain regions, it's clear that this output can influence an animal's motivation to seek out water, as well as physiological factors like kidney function and heart rate (Figure 11.5.3).

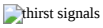


Figure 11.5.3: **Thirst signals and their effects.** Neurons in the lamina terminalis receive many different messages about the body's water needs. Thanks to their location next to ventricles in the brain, they can directly sense key indicators of water need like sodium levels and osmolality (the ratio of salt particles to a given amount of liquid). They also receive information about what time of day it is from another brain region, as well as cues from the mouth and kidneys. Neurons in the lamina terminalis can pool all of this information to determine whether the body needs more or less water. If it needs more, they can trigger feelings of thirst and appetite suppression. If it needs less, the brain will send signals telling you to stop drinking. The lamina terminalis also sends messages to a brain region called the hypothalamus. In turn, the hypothalamus can affect heart rate or urge the kidneys to retain more or less water. From *The Neuroscience of Thirst: How your brain tells you to look for water.* (CC BY-NC-SA)

11.5.3.1 What makes water so refreshing?

After a while standing outside in the hot sun, a cold drink of water tends to feel instantly refreshing. You might also find that drinking a very sugary beverage feels equally refreshing but leaves you feeling thirsty again later. In both cases, it takes tens of minutes for that drink to have any effect on attributes like osmolality or blood pressure, the body's main indicators of hydration status. Instead, the brain must rely on some other cue to tell you to stop drinking and give you that instant feeling of refreshment.

11.5.3.1.1 The Role of the Lamina Terminalis

Researchers have discovered that neurons in the lamina terminalis respond to the physical act of swallowing liquids, even before there are any changes in the amount of water in the blood. Researchers have identified a group of neurons in the lamina terminalis whose activity is required for drinking behaviors: when you artificially turn off the activity in these cells, mice no longer drink water, even when they are water deprived (Zimmerman et al., 2017). When the researchers recorded the activity of these cells as animals drank water, they found that the cellular activity decreased in lockstep with each sip of water, far before any physiological changes in blood pressure or solute concentration could have an effect. They also found that this change in activity only happened when the mice drank water, not when they drank a salt solution. This study suggests that our brains have a built-in mechanism to compare how much water we need with the amount of water we're currently drinking, telling us when we've had enough and leaving us feeling instantly hydrated. Still, scientists don't know exactly how the brain can tell water apart from other liquids, or why drinking some non-water beverages can leave you feeling instantly hydrated, as well.

11.5.3.1.2 The Role of Dopamine

Another group of researchers set out to tackle the problem of why we find drinking water so rewarding when we're thirsty (Augustine at al., 2019). Neuroscientists have long recognized the role of dopamine in determining what we find reinforcing. In order to look at the role that dopamine plays with respect to drinking behaviors, these researchers used a new kind of sensor that glows in the presence of dopamine. By putting this sensor into a mouse's brain, they were able to record dopamine levels in real time as the mouse went about its tasks (Figure 11.5.4.

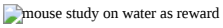


Figure 11.5.4: **Drinking water is rewarding.** Researchers in Yuki Oka's group at Caltech conducted a study to see why animals find water rewarding. By using a special kind of sensor that glows in the presence of the rewarding molecule dopamine, they could see what kinds of liquids caused dopamine release. They recorded large spikes of dopamine release when thirsty mice drank both water and salty saline solutions, indicating that mice found both of these liquids rewarding. When researchers injected water into thirsty mice, though, they found no changes in dopamine levels, even though the injected water would also hydrate the thirsty animals. From *The Neuroscience of Thirst: How your brain tells you to look for water.* (CC BY-NC-SA)

These researchers looked at dopamine levels after thirsty mice drank water and other liquids. They also recorded dopamine levels after they injected water directly into the gastrointestinal system; this procedure hydrated thirsty animals, but meant that the mice didn't actually drink any water. Oka's group found that thirsty mice had a large surge in dopamine levels after drinking either water or saline and that these dopamine changes happened even before drinking would have any effect on blood fluid levels. In contrast, the animals didn't release any dopamine after water was pumped into their gastric systems, suggesting that it's the act of drinking itself that's rewarding—not the feeling of being hydrated. This effect also starts to explain why drinking beverages other than water can be so satisfying, even when they leave you feeling thirsty later: the dopamine spike that comes from drinking liquids when animals are thirsty doesn't depend on what kind of liquid they're drinking, even though not all liquids are equally hydrating.

These two studies highlight the varying strategies the brain uses to monitor essential nutrients like water; because no single sensor can tally current water levels and predict future water needs, the brain relies on a variety of sensations and cues.

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11.5.5 Attributions

"Maintaining Water Balance - Physiological Mechanisms" adapted from Rye, C., Wise, R., Jurukovski, V., DeSaix, J., Choi, J., & Avissar , Y. (2016, October 21). *37.3 Regulation of Body Processes - Biology*. OpenStax. Retrieved February 6, 2022, from https://openstax.org/books/biology/p...body-processes (CC BY)

"Maintaining Water Balance - Triggering Thirst" adapted from Frank, M. (2019, September 26). *The Neuroscience of Thirst: How your brain tells you to look for water.* Retrieved May 9, 2022 from https://sitn.hms.harvard.edu/flash/2...ls-look-water/ (CC BY-NC-SA)

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11.6: Triggering Drinking Behavior - Osmometric and Volumetric Thirst

Learning Objectives

1. Discuss the role of solutes in determining the movement of water in the body.
2. Distinguish between intracellular and extracellular fluid.
3. Compare and contrast osmotic and volumetric (hypovolemic) thirst.

11.6.1 Overview

When talking about thirst, we are talking not just about water in the body, but also the major solute (dissolved substance) we find in this water, salt or sodium chloride (NaCl). Regulating the body's water is necessarily impacted by the substances that are dissolved in that water. Thirst is a signal to the body that there has been a loss of fluid or, more specifically, that there is a fluid imbalance. About two-thirds of the body's water is intracellular, meaning within cells. The other third, the extracellular fluid, consists of interstitial fluid (the fluid bathing cells), cerebrospinal fluid (fluid in the ventricular system), and blood plasma (intravascular).

Because we effectively have two places where water is found (intracellular and extracellular), we have two systems for monitoring the body's fluid levels - and a variety of ways of inducing thirst, as well as different types of thirst. In addition, salt appetite is necessarily associated with one form of thirst as the need created by the fluid loss requires both salt and water to restore homeostasis. One system focuses on the levels of intracellular fluid and triggers osmotic thirst. The other monitors extracellular levels - more specifically, plasma or blood volume - and triggers volumetric thirst. Volumetric thirst is associated with a need for both salt and water.

11.6.2 Intracellular Fluid Volume

Intracellular fluid volume is controlled by the concentration of solutes in the interstitial fluid (the fluid outside of cells). Under normal circumstances, the fluid outside and inside the cell is isotonic (the concentration of solutes is equal). If, however, the solute concentration is increased in the interstitial fluid (due to ingestion of solutes or loss of water), water will leave the cell by the process of osmosis. Osmosis is simply movement of water from an area of low solute concentration to an area of high concentration, water will move as needed to even out the solute concentration (Figure 11.6.1). If the interstitial fluid (the fluid outside of the cell) is hypertonic (if it has a higher solute concentration), water will leave the cell. If the interstitial fluid is hypotonic, water will enter the cell. Both conditions may be dangerous - disrupting normal neuronal function. When there is a difference between the solute concentration of the interstitial fluid and the intracellular fluid, the movement of water by osmosis causes changes in intracellular volume.

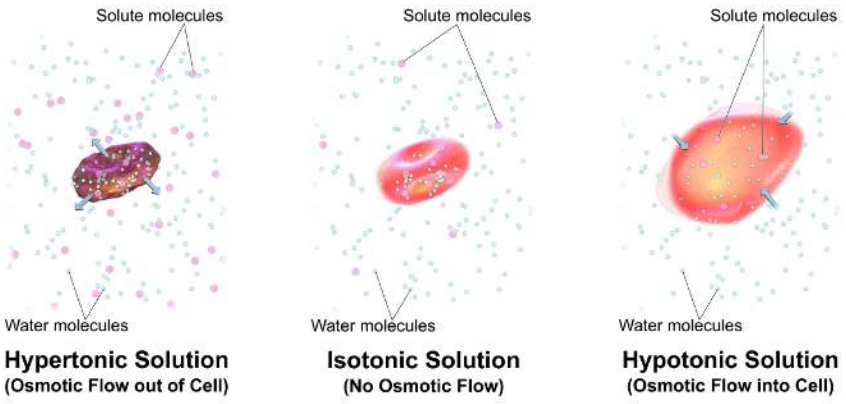


Figure 11.6.1: Water movement in hypertonic, isotonic and hypotonic solutions. (Images from Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436., CC BY 3.0 , via Wikimedia Commons)

Generally, there is no need to regulate the volume of the interstitial fluid, although we do regulate its tonicity (solute concentration) through its effects on the intracellular fluid volume. More specifically, we monitor the movement of water.

11.6.3 Plasma Volume (Extracellular)

The other important and closely regulated fluid compartment is the blood plasma. If there is a loss of plasma volume (hypovolemia), this can impair the functioning of the heart. If increased, there may be a dangerous increase in blood pressure. If hypovolemia is severe enough the heart can no longer pump effectively. The vascular system can correct for loss of volume, but only within a limited range.

11.6.4 Two Variables, Two Regulatory Mechanisms

In order to maintain optimal fluid balance, the two variables are monitored:

- Movement of water (intracellular)
- Plasma volume (extracellular)

As there are two variables being monitored, there will be two different regulatory mechanisms that underlie thirst. The monitoring of fluid levels is tied to the monitoring of sodium levels. There are two mechanisms for dealing with a need for fluid and salt or sodium - we see both physiological and behavioral mechanisms for dealing with a need for water and salt:

- Physiologically - At the kidney, the excretion (loss) of water and salt can be modified. And alterations in heart rate and blood pressure can also compensate for losses.
- Behaviorally - ingest water and salt

What is the role of the kidneys and how is kidney activity regulated? Typically, we ingest much more salt and water than we need and what we don't need is excreted. Blood is essentially filtered by the kidneys. The functional units of the kidneys, the nephrons, extract fluid from the blood and carry it (collect it into) the ureter. From the ureter, urine passes to the urinary bladder where urine is stored.

As discussed in the prior section, two hormones are involved in the excretion of sodium and water by the kidney - both hormonal signals increase retention:

- Aldosterone is secreted by the adrenal cortex.
- Vasopressin (Anti Diuretic Hormone or ADH) is secreted by the posterior pituitary, but produced by the hypothalamus. The two names by which this hormone is known reflect two aspects of its effects, "vasopressin" is a reference to its ability to cause contraction of blood vessels while ADH reflects its role in preventing excretion.

What happens without vasopressin? No water is retained. Without vasopressin, diabetes insipidus develops, leading to excessive water loss and increased thirst. Incidentally, the term diabetes insipidus literally means "a tasteless passing through". The urine is so dilute, it has little taste. It is, as you might expect, treated with vasopressin - in the form of a nasal spray. The diabetes you more commonly hear of (due to a lack of or insensitivity to insulin) is technically diabetes mellitus. Diabetes, again, means "passing through". Mellitus means "sweet" as the urine of the diabetic would be sweet with unused glucose.

11.6.5 Osmometric (Osmotic) Thirst - Detecting Water Movement Out of Cells

So, we can drink to replenish lost fluid and the kidney's function can conserve or allow fluids to be lost. As we have two variables that we are monitoring, we have two different types of thirst. **Osmotic** thirst derives its name from the word osmosis. Osmotic thirst is triggered by loss of volume from the intracellular fluid stores. This form of thirst is produced when the solute concentration or **tonicity** of the fluid **outside** of the cell is increased, causing **water to move out of the cell**. If the concentration of intracellular solutes is increased with something that passes into the cell - so the extracellular and intracellular solute concentrations remain isotonic and there's no net movement of water - drinking will not be triggered. In other words, it isn't just changes in the solute concentration that are detected, it is the loss of water from the intracellular compartment that matters (cellular dehydration).

Recall from the previous section, that antidiuretic hormone (ADH), otherwise known as vasopressin will be released by the pituitary gland in situations of cellular dehydration. Thus, the next question is what area of the brain responds to these osmotic change and the rise in hormones like vasopressin?

Osmoreceptors can be classified as central or peripheral osmoreceptors based on their location. The central receptors are primarily present in the lamina terminalis region of the anterior hypothalamus, including the **organum vasculosum laminae terminalis (OVLT)** and the **subfornical organ (SFO)** (Danziger & Zeidel, 2015; Xu et al., 2000; Muhsin & Mount, 2016). The OVLT has been shown to be sensitive to vasopressin (McKinley, et al., 2004) and, thus can influence both the physiological and behavioral

response during osmotic thirst. Since the there is an excess of extracellular salt in this situation, the thirst would be for pure water without solutes.

The receptor cells in both of the OVLT and SFO are also sensitive to angiotensin II (abbreviated as AII; Bichet, 2012; Benarroch, 2011), which is important in the control of volumetric thirst (see below). Some SFO/OVLT neurons also receive signals from peripheral arterial baroreceptors. Thus, SFO/OVLT neurons sense plasma osmolality, volume, and pressure to control thirst. These cells depolarize due to increased Na+ concentration, cell shrinkage, angiotensin II or negative suction pressure, and discharge neuronal spikes, which later initiate the sensation of thirst or vasopressin release or both (Muhsin & Mount, 2016; Gizowski & Bourque, 2018).

11.6.6 Volumetric (Hypovolemic) Thirst - Detecting Blood Loss

Volumetric thirst is triggered when there is a loss of volume from the extracellular fluid stores. Volumetric thirst is triggered by a decrease in blood volume referred to as **hypovolemia**. Hypovolemia is usually accompanied by a drop in blood pressure (hypotension). Hypovolemia and hypotension then ultimately lead to the production of **angiotensin II**. As discussed in the last section, a cascade of events is triggered when the kidneys detect a decrease in blood pressure and release the enzyme renin. This activates the renin-angiotensin-aldosterone system. Angiotensinogen, produced by the liver, is acted on by renin to produce angiotensin I, which is then converted into angiotensin II. Angiotensin II functions as a hormone and then causes the release of the hormone aldosterone by the adrenal cortex, resulting in increased sodium reabsorption, water retention, and an increase in blood pressure.

Following extracellular fluid loss - loss of plasma volume - there is a need for both salt and water. A rat will now drink a saline solution that it normally rejects. This indicates that there is a mechanism for monitoring the body's sodium concentration, so that needs are detected and then mechanisms are employed to satisfy them. Unlike osmotic thirst, volumetric thirst is accompanied by a salt appetite.

Angiotensin II, the 3rd "step" when the renin-angiotensin-aldosterone system is activated, travels through the blood stream and exerts multiple effects.

- Angiotensin II acts at the adrenal cortex to stimulate aldosterone secretion.
- Angiotensin II acts at the posterior pituitary to stimulate vasopressin (ADH) secretion.
- Angiotensin II acts at the muscles of the the small arteries to cause contraction (increasing blood pressure).
- Angiotensin II triggers drinking and salt ingestion.

Although angiotensin II is thought to produce thirst and act on other brain sites, it does not cross the blood-brain barrier. Thus, in order to cause thirst and other effects, angiotensin II must act at a part of the brain that lacks this barrier. The subfornical organ (SFO) appears to be the site at which angiotensin II acts to cause volumetric thirst.

Evidence for the role of the SFO in water ingestion:

- Very low doses of angiotensin II at the SFO cause drinking.
- Angiotensin II-induced drinking is blocked by blocking angiotensin II receptors at the SFO.
- Electrical stimulation of the SFO produces drinking.

Furthermore, neurons in the SFO increase their activity in response to angiotensin II, even when neural connections are cut - demonstrating that the neurons are responding to the AII.

The SFO has outputs to several brain regions. And these connections mediate the endocrine, autonomic, and behavioral responses associated with thirst. It is involved in a number of the effects of AII.

11.6.7 Normal Drinking

Just as we typically eat long before a physiological need for fuel would trigger hunger, we drink before change in the body's fluid stores would be detected. As with eating, we have learned elements of our drinking behavior. When do we habitually drink? Normally, we drink with meals. While eating does produce a need for fluid, we typically drink before that need would normally be detected. Food in the digestive system causes water to be diverted to these areas and absorbed food increases the solute concentration of the plasma and produces osmometric thirst.

Why do animals drink before a need is detected? Animals will actually learn to drink more if their diet is changed such that they need to drink more. With a high protein diet, more water is needed. Animals will learn to drink more with a meal in anticipation of

the need.

What signals or causes drinking with a meal? The movement of water into the digestive system produces hypovolemia. The hypovolemia causes the kidneys to secrete renin and AII levels are increased. During a normal meal the levels of renin actually double. If we then block AII production, we'll see a decrease in drinking with a meal.

11.6.8 Summary

In order to maintain an appropriate fluid balance, intracellular and extracellular fluid levels are monitored. Intracellular or osmometric thirst is triggered when water moves out of cells. In contrast, hypovolemic thirst and an appetite for salt is triggered when the loss of blood volume creates a need for salt and water.

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11.6.10 Attributions

"Osmometric Thirst - Detecting Water Movement Out of Cells" adapted from Koshy, R. & Jamil, R. (2021). Physiology, Osmoreceptors. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557510/ (CC BY)

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CHAPTER OVERVIEW

12: Intelligence, Cognition, and Language

12.1: Overview of Brain Mechanisms in Intelligence, Language, and Cognition

12.2: Cognition and Intelligence as Psychological Adaptations

12.3: High Intelligence-Nature or Nurture; Learning Disabilities

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12.1: Overview of Brain Mechanisms in Intelligence, Language, and Cognition

Learning Objectives

1. Discuss the general relationship across species between brain size, body size, and intelligence, including trends in corticalization and cortical folding
2. Discriminate the functions of glial cells
3. Distinguish the locations and functions of each of the lobes of the cerebral cortex
4. Describe lateralization and the role of split-brain research
5. Describe neuroplasticity and briefly discuss examples of it

12.1.1 Overview

We begin this chapter with a general review of the brain areas involved in complex cognitive and psychological functions, focusing on the cerebral cortex, including studies of the split brain. This foundational neuroanatomical information is critical in order to fully appreciate the neural mechanisms of human cognition.

12.1.2 **The Cerebral Cortex Creates Intelligence, Language, and Thinking: Overview of the Basics**

All animals have adapted to their environments by developing abilities that help them survive. Some animals have hard shells, others run extremely fast, and some have acute hearing. Human beings do not have any of these particular characteristics, but we do have one big advantage over other animals—we are very, very smart.

You might think that we should be able to determine the intelligence of an animal by looking at the ratio of the animal's brain weight to the weight of its entire body. But this does not really work. The elephant's brain is one thousandth of its weight, but the whale's brain is only one ten-thousandth of its body weight. On the other hand, although the human brain is one 60th of its body weight, the mouse's brain represents one fortieth of its body weight. Despite these comparisons, elephants do not seem 10 times smarter than whales, and humans definitely seem smarter than mice.

The key to the advanced intelligence of humans is not found in the size of our brains. What sets humans apart from other animals is our larger cerebral cortex—*the outer bark-like layer of our brain that allows us to so successfully use language, acquire complex skills, create tools, and live in social groups* (Gibson, 2002). In humans, the cerebral cortex is wrinkled and folded, rather than smooth as it is in most other animals. This creates a much greater surface area and size, and allows increased capacities for learning, remembering, and thinking. The increasing amount of cortex in mammals involving folding of the cerebral cortex is referred to as *corticalization*.

Although the cortex is only about one tenth of an inch thick, it makes up more than 80% of the brain's weight. The human cortex contains about 20 billion nerve cells (the entire human brain has somewhere between 100 and 200 billion neurons) and at least 300 trillion synaptic connections (de Courten-Myers, 1999). Supporting all these neurons are billions more glial cells (glia), cells that surround and link to the neurons, protecting them, providing them with nutrients, and absorbing unused neurotransmitters. The glia are essential partners of neurons, without which the neurons could not survive or function (Miller, 2005).

As you recall from the chapter on anatomy of the nervous system, the cerebral cortex is divided into two hemispheres, and each hemisphere is divided into four lobes: **frontal, parietal, occipital, and temporal.**

If we look at the cortex starting at the front of the brain and moving over the top (see Figure 12.1.1), we see first the **frontal lobe** (behind the forehead), which is responsible primarily for thinking, planning, memory, and judgment. Following the frontal lobe is the **parietal lobe**, which extends from the middle to the back of the skull and which is responsible primarily for processing information about touch and spatial perception. Other parts appear to be involved in visualization. Spatial perception is one component of intelligence measured on IQ tests. Then comes the **occipital lobe**, at the very back of the skull, which processes visual information. Surrounding the primary visual cortex is visual association cortex which is involved in higher order, more complex visual processing and perception. Finally, in front of the occipital lobe (near the temples and ears) is the **temporal lobe**, responsible primarily for hearing and language. Also located in the temporal lobe is the Inferotemporal (IT) cortex which is involved in visual recognition.

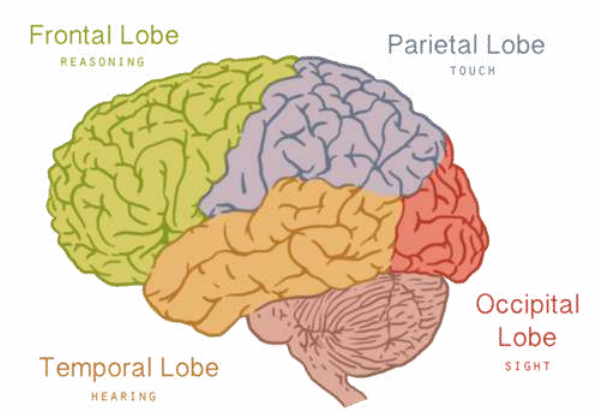


Figure 12.1.1: The brain is divided into two hemispheres (right and left), each of which has four lobes (temporal, frontal, occipital, and parietal). Furthermore, there are specific cortical areas within the lobes that control different processes. From Brain lobes by Laura Guerin, CC BY-NC 3.0 via CK-12

A relatively large portion of the cortex in each lobe is made up of **association areas** in which sensory and motor information is combined and associated with our stored knowledge. These association areas of cortex are the places in the brain that are responsible for most of the things that make human beings seem human. The association areas are involved in higher mental functions, such as learning, thinking, planning, judging, moral reflecting, figuring, and spatial reasoning.

12.1.3 The Brain Is Flexible: Neuroplasticity

The control of some specific bodily functions, such as movement, vision, and hearing, is performed in specified areas of the cortex, and if these areas are damaged, the individual will likely lose the ability to perform the corresponding function. For instance, if an infant suffers damage to facial recognition areas in the temporal lobe (FFA), it is likely that he or she will never be able to recognize faces (Farah, Rabinowitz, Quinn, & Liu, 2000). On the other hand, the brain is not divided up in an entirely rigid way. The brain's neurons have a remarkable capacity to reorganize and extend themselves to carry out particular functions in response to the needs of the organism, and to repair damage. As a result, the brain constantly creates new neural communication routes and rewires existing ones. **Neuroplasticity** refers to *the brain's ability to change its structure and function in response to experience or damage*. Neuroplasticity enables us to learn and remember new things and adjust to new experiences as discussed in chapter 10 on learning and memory.

Our brains are the most "plastic" when we are young children, as it is during this time that we learn the most about our environment. On the other hand, neuroplasticity continues to be observed even in adults (Kolb & Fantie, 1989). The principles of neuroplasticity help us understand how our brains develop to reflect our experiences. For instance, accomplished musicians have a larger auditory cortex compared with the general population (Bengtsson et al., 2005) and also require less neural activity to move their fingers over the keys than do novices (Münte, Altenmüller, & Jäncke, 2002). This is because accomplished musicians through practice have eliminated synaptic connections associated with incorrect movements, making neural control more efficient.

Plasticity is also observed when there is damage to the brain or to parts of the body that are represented in the motor and sensory cortexes. When a tumor in the left hemisphere of the brain impairs language, the right hemisphere will begin to compensate to help the person recover the ability to speak (Thiel et al., 2006). And if a person loses a finger, the area of the sensory cortex that previously received information from the missing finger will begin to receive input from adjacent fingers, causing the remaining digits to become more sensitive to touch (Fox, 1984).

Although neurons cannot repair or regenerate themselves as skin or blood vessels can, new evidence suggests that the brain can engage in **neurogenesis**, the forming of new neurons (Van Praag, Zhao, Gage, & Gazzaniga, 2004). These new neurons originate deep in the brain and may then migrate to other brain areas where they form new connections with other neurons (Gould, 2007). This leaves open the possibility that someday scientists might be able to "rebuild" damaged brains by creating drugs that help grow neurons.

12.1.3.1 Research Focus: Identifying the Unique Functions of the Left and Right Hemispheres Using Split-Brain Patients

We have seen 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 (1965) 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 (Gazzaniga, 2005).

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 (see Figure 12.1.2). The researchers had W. J. look straight ahead and then flashed, for a fraction of a second, a picture of a geometrical 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 this when the object was shown in the right visual field. On the other hand, 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.

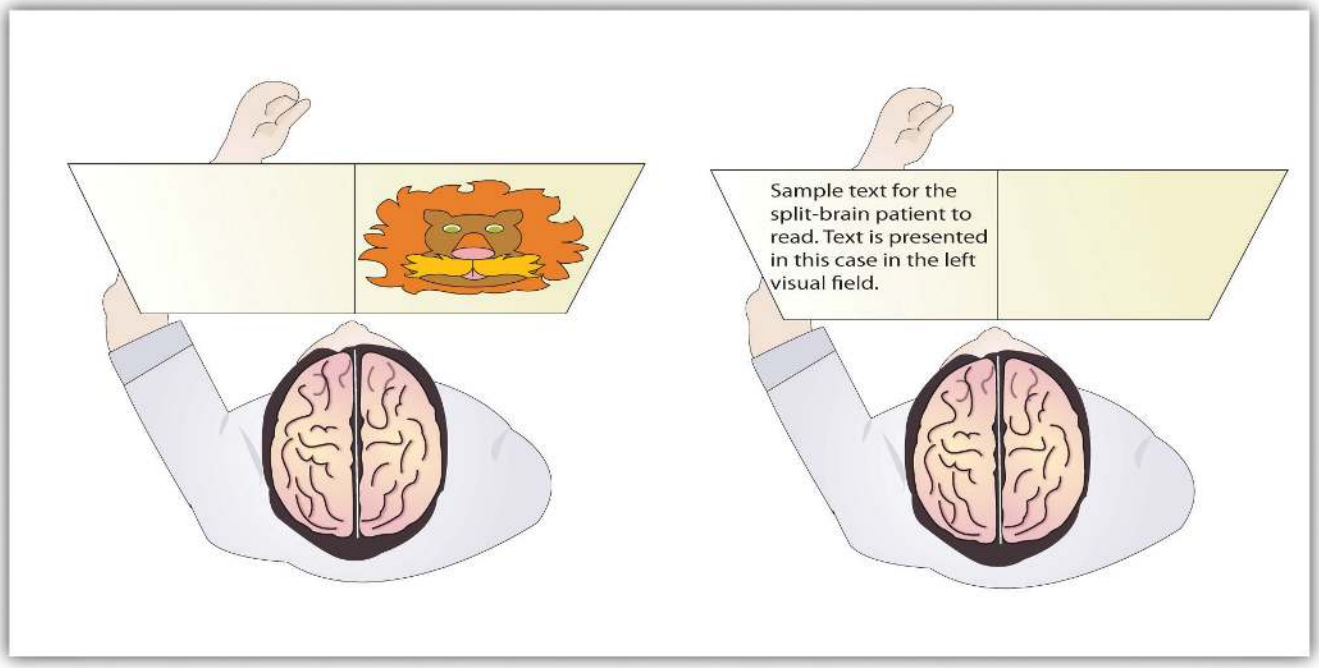


Figure 12.1.2: Visual and Verbal Processing in the Split-Brain Patient. From Introduction to Psychology, Open textbooks for Hong Kong. CC BY-SA 4.0

The information that is 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 (as it is in normal persons without brain damage), which allows researchers to learn about the functions of each hemisphere. In the perceptual test on the left, the split-brain patient could not choose which image had been previously presented because the left hemisphere cannot process visual information. In the test on the right side of Figure 12.1.2, the patient could not read the passage because the right brain hemisphere cannot process language.

This research, and many other studies following it, has 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, on the other hand, has only very 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 only using 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 (Soroker et al., 2005).

12.1.3.2 Summary

The evolutionarily old brain—including the brain stem, medulla, pons, reticular formation, thalamus, cerebellum, amygdala, hypothalamus, and hippocampus—regulates basic survival functions, such as breathing, moving, resting, feeding, emotions, and memory.

The cerebral cortex, made up of billions of neurons and glial cells, is divided into the right and left hemispheres and into four lobes. The frontal lobe is primarily responsible for thinking, planning, memory, and judgment. The parietal lobe is primarily responsible for bodily sensations and touch. The temporal lobe is primarily responsible for hearing and language. The occipital lobe is primarily responsible for vision. Other areas of the cortex act as association areas, responsible for integrating information. The motor cortex controls voluntary movements. Body parts requiring the most control and dexterity take up the most space in the motor cortex. The sensory cortex receives and processes bodily sensations. Body parts that are the most sensitive occupy the greatest amount of space in the sensory cortex.

The brain changes as a function of experience and potential damage in a process known as plasticity. Neuroplasticity allows the brain to adapt and change as a function of experience or damage. The brain can generate new neurons through neurogenesis.

The severing of the corpus callosum, which connects the two hemispheres, creates a "split-brain patient," with the effect of creating two separate minds operating in one person. Studies with split-brain patients as research participants have been used to study brain lateralization. The left cerebral hemisphere is primarily responsible for language and speech in most people, whereas the right hemisphere specializes in spatial and perceptual skills, visualization, and the recognition of patterns, faces, and melodies.

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12.1.5 Attributions

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12.2: Cognition and Intelligence as Psychological Adaptations

Learning Objectives

1. Explain what is meant by the claim that psychological processes, including intelligence, serve adaptive movement
2. Explain why intelligence and cognition are examples of psychological adaptations
3. Describe some of the environmental regularities, including several universal recurrent relational features of the world, that may have been genetically incorporated into brain organization generating intelligence, including general "fluid" intelligence
4. Describe the brain areas that are involved in intelligence, broadly defined as brain systems that guide behavior toward successful adaptation
5. Describe the role that visualization abilities play in intelligence

12.2.1 Overview

After a general review of cortical functions in the previous section, we now examine higher cognitive functions as modes of achieving biological adaptation to the environment.

Early work by psychologists interested in human intelligence took a practical approach. These psychologists in the first part of the twentieth century focused on the development of methods of measuring intelligence in humans. This approach to the study of psychological attributes is called **psychometrics**. Though early research emphasized the creation and refinement of intelligence tests, rather than the biological origins and functions of intelligence, psychometric analysis of the performance of large groups of people on intelligence tests (Spearman, 1904, 1925) ultimately led to theories of the structure of human intelligence (Carroll, 1993; Cattell, 1987). These theories are important to biological psychology because they have influenced much of the modern thinking and research on the genetic and brain mechanisms involved in human thinking and intelligence.

More recently, intelligence research by psychologists and neuroscientists has expanded to include the study of brain mechanisms underlying intelligence in humans and in other species. This approach has led to conceptions of intelligence and cognition in a broader biological and evolutionary context. On this view, thinking, intelligence, and language are products of evolution, just like other genetic traits of organisms.

One of the key evolutionary trends responsible for the evolution of intelligence and cognition was genetic incorporation of information about biologically significant regularities of the world into the circuitry and operations of the brain. As a consequence, the brain is equipped with many "**cognitive instincts**" and innate implicit knowledge about biologically important, enduring regularities of the terrestrial environment, forming the groundwork for much of our genetically evolved intelligence as a species.

This view contrasts with and rejects the "blank slate" view of the mind/brain assumed in the Standard Social Science Model (SSSM), the set of assumptions that much of psychology and the social sciences were founded upon--the view that humans lacked any innate psychological nature and that the mind and brain were essentially blank at birth, leaving it to learning and culture to form human behavior free of genetics and biological evolution. In this chapter, we take a different point of view--that biology, genes and evolution, are the primary determinants of human cognition and behavior, in interaction with learning and cultural influences, which themselves are ultimately biological in nature.

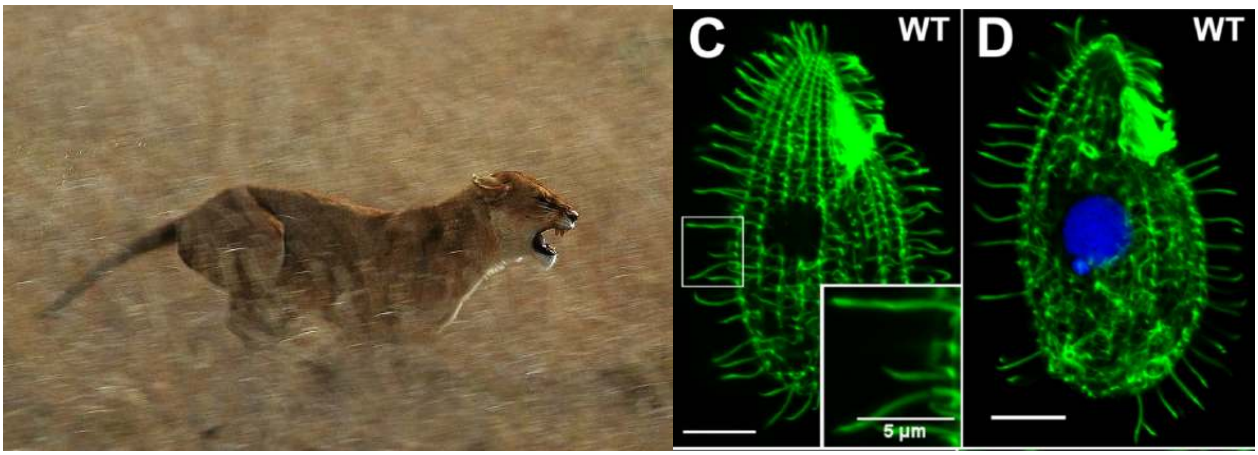


Figure 12.2.1: (Left) Lioness hunting in the Serengeti region of Tanzania. Its mechanisms of sensation and perception, emotion, and intelligence are pitted against these same guidance systems for movement found in its prey. Predator-prey interactions may have been an escalating evolutionary impetus for the development of intelligence in both predator and prey. (Right) A single-celled organism featuring its cilia which it uses to move toward favorable parts of its fluid environment and away from harmful regions, thereby facilitating its adaptation. Approach to beneficial elements of the environment and avoidance of and withdrawal from harmful elements is a primary rule governing guidance systems for movement in all motile species. (Image on left is from Wikimedia Commons, CC BY-SA 2.5 Generic. Caption by Kenneth A. Koenigshofer, PhD. Image on right is from Wikimedia Commons, CC BY SA 4.0 International. Caption by Kenneth A. Koenigshofer, PhD).

12.2.1.1 Thinking and Intelligence Serve the Adaptive Organization of Movement

When we consider thinking and intelligence from a biological and evolutionary perspective, it is important to ask what functions they perform for the organism. The brain does all kinds of complex processing, but it is important to understand that for that processing to have any effect on the environment, brain activity must ultimately converge onto motor neurons in the spinal cord ("the final common path") that stimulate the muscles to produce movement--behavior (see the chapter on movement). Like every aspect of our psychology and its corresponding brain activity, the function of thinking and intelligence is to generate adaptive behavior, movement, to successfully meet environmental challenges to survival and reproduction and to exploit opportunities, thereby increasing biological fitness.

Consider plants, for a moment. They don't have human-like intelligence or thinking--they don't need to, because they depend very little upon movement for survival and reproduction--instead, water and their source of energy, sunlight, come to them. Yes, plants can move slowly in a limited way, but contrast this with all the complex social behaviors modern humans engage in to just to get food and water--e.g. agriculture, supply chains, plumbing, dams, water companies, shopping). Neither do plants have to flee or hide from predators; they protect themselves with thorns or poisons or simply grow back if partially eaten. Neither do they need to move for reproduction--wind and insects and other animals carry the reproductive cells for them.

But none of this is true for animals. For animals, including the human animal, movement is key to survival and reproduction, and, as noted above, the movement must be guided to form patterns of action that solve adaptive problems and exploit adaptive opportunities. According to Darwin's theory of evolution, which he explained as "descent with modification," the roots of human cognition and intelligence lie deep in our species' evolutionary ancestry. Evidence for this can be found in Darwin's principle of the "continuity of species" applied to psychology, as shown by the great degrees of



Figure 12.2.2: Movement is essential for survival and reproduction in animals. The great Wildebeest migration with over 2 million animals follows the rains to lush new feeding grounds. (Image from Wikimedia Commons; CC BY SA 4.0 International. Caption by Kenneth A. Koenigshofer, PhD).

similarity in the guidance and control systems for movement and their underlying brain mechanisms across mammalian species--for example, all mammals have similar brain structures, including limbic structures and cerebral cortex. All species respond to potentially harmful stimuli with threat, attack, or escape. All mammals respond to sexual signals by moving toward and making contact with their source. Each suggests common behavioral control mechanisms evolutionarily conserved across species

But intelligence also exists in non-mammalian species. Intelligence in distantly related species including some birds, such as Corvids (e.g. ravens, jays, crows) and parrots, and in invertebrates such as the octopus and cuttlefish (Adams & Burbeck, 2012; Mather, 2019; Mather & Dickel, 2017), illustrate convergent evolution, suggesting the high adaptive utility of intelligence in diverse ecological niches. Intelligence and thinking, like all psychological processes, evolved to serve the organization of movement to make behavior adaptive, successful, in the Darwinian struggle for survival and reproduction (Koenigshofer, 2011, 2016).

12.2.1.2 Cognition and Intelligence are Psychological Adaptations

Intelligence and thinking (i.e. cognition) are **psychological adaptations** evolved by natural selection over millions of years. A psychological adaptation is a psychological or behavioral trait that has developed through evolutionary processes such as natural and sexual selection and which is encoded into a species' DNA (see Ellis & Ketelaar, 2002). Dicke and Roth (2016) offer a comprehensive definition of intelligence recognizing its role in adaptation to the environment in a wide range of animals and humans:

> According to the majority of behaviorists and animal psychologists, ‘intelligence’ can be understood as mental or behavioral flexibility or the ability
> of an organism to solve problems occurring in its natural and social environment, culminating in the appearance of novel solutions that are not
> part of the animal’s normal repertoire.

By contrast, Colom et al. (2010) define intelligence simply as "a general mental ability for reasoning, problem solving, and learning."



Figure 12.2.3: Because animals cannot photosynthesize, they must move in order to obtain their sources of energy found in plants and other animals--animals which can hide, run, and fight back--unlike the plants' source of energy, the sun. Movement is organized by brain circuitry which has been configured by natural selection over evolutionary time to solve adaptive problems. Here a hyena on the plains of Africa solves the problem of getting sufficient energy to survive and ultimately reproduce its genes. (Image from Wikimedia Commons; CC BY SA 4.0 International.).

A typical definition of general intelligence shows how intelligence and general intelligence are terms sometimes used interchangeably, even by psychologists. General intelligence is often defined as "ability to reason deductively and inductively, to think abstractly, use analogies, to synthesize information, and to apply that information to new domains" (Gottfredson, 1997; Neisser et al., 1996).

In spite of some differences in definition among researchers, there is unanimous agreement that intelligence and cognition are properties of brain processes which have been shaped and refined over millions of years of evolution. To help us understand human intelligence and cognition and their evolutionary origins, many biological psychologists study these processes in other animals, including apes, monkeys, rats, dogs, parrots, and Corvids, such as ravens, jays, and crows. Animals often surprise us with the sophistication of their emotional sensitivity and their intelligence even though they lack language (Huber & Gajdon, 2006; Wasserman, et al., 2006).

An interesting anatomical feature of the cerebral cortex is what we might call microprocessors or "chips" in the human cortex. These are columnar structures, known as **cortical columns**, containing approximately 3,000 neurons each. There are approximately 150,000 cortical columns in the human cerebral cortex (Hawkins, et al., 2017) . These structures are very similar from one part of the cortex to another and from one mammalian species to the next and suggest highly generalized computational functions in cerebral cortex, whereas specialized modules or genetically dedicated circuits for processing of emotional and motivational information are localized to subcortical regions of the brain, shared by all mammals (Panksepp & Panksepp, 2000).

Intelligence and cognition (i.e. thinking) are exceedingly complex processes. As a consequence, the brain mechanisms involved in these processes are not well understood. As you can see, even definitions of these processes vary widely in the scientific community. However, all of the definitions above include terms such as reasoning, abstract thinking, insight, or problem solving, processes which themselves are not well defined or clearly understood by psychologists and neuroscientists. This highlights the fact that psychologists and neuroscientists are still in the early stages of gaining a real understanding of how intelligence and thinking work and what neural processes in the brain produce them.

12.2.1.3 Conditions required for evolution of psychological adaptations

Understanding the evolutionary origins of intelligence and thinking may offer insights about how they work and about their underlying brain mechanisms. First of all, remember the claim made above that intelligence and cognition are psychological adaptations, or more correctly, a collection of psychological adaptations, each evolved by natural selection to process certain types of information in specific ways.

By this reasoning, long-term, across-generation regularities of the world that have adaptive significance should be expected to play a special role in the evolution of the mind/brain. As evolutionary psychologists, Tooby and Cosmides (1992, p. 69), state: “Long-term, across-generation recurrence of conditions ... is central to the evolution of adaptations." And as former Stanford psychologist, Roger Shepard, put it, there has evolved "a mesh between the principles of the mind and the regularities of the world" (Shepard, 1987a). This means that the organization of the mind reflects regularities of the world, because of the fact that natural selection

operates on conditions that repeat regularly over long periods of time. In other words, the brain is filled with circuitry that operates by genetically programmed rules derived from information about enduring environmental regularities.

Examples of such long-term regularities or enduring properties of the world are: the widespread presence of environmental stimuli that can damage body tissue; that some things in the environment contain sources of nutrition while others are poisonous; that some potential mates are more likely than others to be healthy and fertile; and so on. In response to biologically important regularities in the world such as these, neural circuitry has evolved in animal and human brains that causes withdrawal from harmful stimuli in response to pain, consumption of sources of nourishment and avoidance of foods that cause illness, and powerful innate drives to mate with sexual partners possessing features indicative of health and reproductive potential (Ellis & Ketelaar, 2002, p. 162; Gangestad & Simpson, 2000).





Figure 12.2.4: (Left) For most people, spiders like this one induce a strong aversive reaction motivating avoidance and withdrawal behavior, an example of a psychological adaptation evolved to protect us from possible poisoning from this class of stimulus. (Right) Humans have evolved a preference for fats, sweets, and salt, a psychological adaptation from the Pleistocene which can be harmful to health if followed too frequently in the modern urban environment full of fast food restaurants--a very different environment from that of our hunter-gatherer ancestors. (Image on left from Wikimedia Commons, CC BY SA 2.0 Generic license. Image on right from Wikimedia Commons, CC BY-SA 4.0 International license. Captions by Kenneth A. Koenigshofer, PhD).

Each of these innate behaviors evolved in response to specific regularities of the world, "recurrence of conditions," that consistently had important adaptive consequences--consequences for survival and reproduction--over countless generations of evolution.



Figure 12.2.5: According to evolutionary psychologists, Cosmides and Tooby (2003), forming and maintaining friendships is important to us today because this was one of many adaptive problems that our human ancestors encountered and had to solve in our Pleistocene past. Friendships led to alliances that were important in securing resources within Pleistocene bands of individuals that depended upon one another for survival. For this reason, we are motivated to find friends and having them feels good, reinforcing the behavior. Information processing by the brain necessary for formation and maintenance of relationships is one of the topics studied by biological psychologists interested in intelligence and social cognitive neuroscience. (Image from Wikimedia Commons, CC BY-SA 2.0 Generic license. Caption by Kenneth A. Koenigshofer, PhD.).

Evolutionary psychologists have identified some additional recurrent problems that had to be regularly solved by our human ancestors: " . . . winning social support from [group] members, remembering the locations of edible plants, hitting game animals with projectiles, …, recognizing emotional expressions, protecting family members, maintaining mating relationships, …, assessing the character [and social valuations] of self and others, causing impregnation, acquiring language, maintaining friendships, thwarting antagonists, and so on" (Cosmides and Tooby 2003, p. 59).

In each case, evolutionary psychologists suspect that brain mechanisms have evolved to contribute to solutions of each of these adaptive problems regularly present generation after generation. On this view, cognition is believed to consist of “many mental rules that are specialized for reasoning about various evolutionarily important domains, such as cooperation, aggressive threat, parenting, disease avoidance, predator avoidance, object permanence, and object movement” (Cosmides & Tooby, 1992, p. 179). But these are not the only kinds of recurrent, across-generation conditions that have been genetically represented by natural selection in brain circuitry. Such regularities can be much more abstract and widely distributed throughout the environment.

12.2.1.4 Innate (instinctual) Knowledge of Universal Regularities of the World: The Foundations of Intelligence

One approach to understanding the nature and origins of intelligence is the idea that natural selection incorporated information about “general—perhaps even universal—properties” of the world (Shepard, 1992, p. 500) into brain organization over evolutionary time (Shepard, 1992, 1994, 2001). The core idea is that natural selection has selected genes that equip human and animal brains with fundamental information about how the physical world is organized, information that is essential for intelligent adaptation to the environment. This approach also may explain fundamental principles of how our thinking processes are organized and how they evolved.

Consequently, information about these enduring environmental regularities, such as the fact that the sun rises and sets approximately every 24 hours, becomes genetically encoded into genes which organize specific brain circuitry or other properties of the brain. Recall the innate mechanisms of this circadian rhythm in the hypothalamus and pineal glad from the previous discussion of the rest/activity cycle. These rhythms have originated from "genetic or evolutionary internalization" of information about the repeating daily cycle of light and dark into brain organization as a result of natural selection.



Figure 12.2.6: A woman sleeping. She does not know that daily cycles of sleep and wakefulness and other circadian rhythms are the result of genetic internalization over the course of evolution of an enduring regularity of the physical environment, the rotation of Earth on its axis (see text below and the chapter on sleep). (Image from Wikimedia Commons; CC BY-SA 2.0 Generic license. Caption by Kenneth A. Koenigshofer, PhD.).

The genetic internalization of information also exists for spatial intelligence. For example, there are "**place cells**" and spatial cognitive maps in the **hippocampus** along with areas of the **parietal cortex** which play a role in spatial processing. And our internalized concept of time is related to the functional organization of the **cerebellum** where cells which monitor time have been identified (Irvy, et al., 1989; Irvy & Spencer, 2004; Hayashi, et al., 2014). Other biologically significant regularities of the world, including regularities of the social environmenthave led to the evolution of specific components of social intelligence.

12.2.1.5 Natural Selection Favored Representations of Abstract Relational Regularities: Evolution of General Intelligence

12.2.1.5.1 Causality

Because the world is governed by natural causal laws, **cause-effect** relations between things regularly occur everywhere in the environment and have consistently existed since the beginning of evolutionary time. Such regularities, though abstract and relational, can drive natural selection (Koenigshofer, 2017; see Cosmides & Tooby, 1992, p. 48; Kaufman et al., 2011, p. 213). From the standpoint of biological adaptation, implicit knowledge about causality allows intelligent creatures to navigate and exploit an enormous variety of complex causal relations which benefit adaptation to the problems and opportunities presented by the environment. A chimpanzee who understands that putting a long stick into a termite hill will cause termites to bite onto the stick gets a lot more juicy termites to eat than a chimpanzee who does not understand this causal relationship (Goodall, 2000). Human understanding of complex causes led to the control of fire, the invention of cooking and agriculture, the construction of shelters and tools, and other innovations making it possible for our species to successfully occupy every region of the planet. At least for the time being.

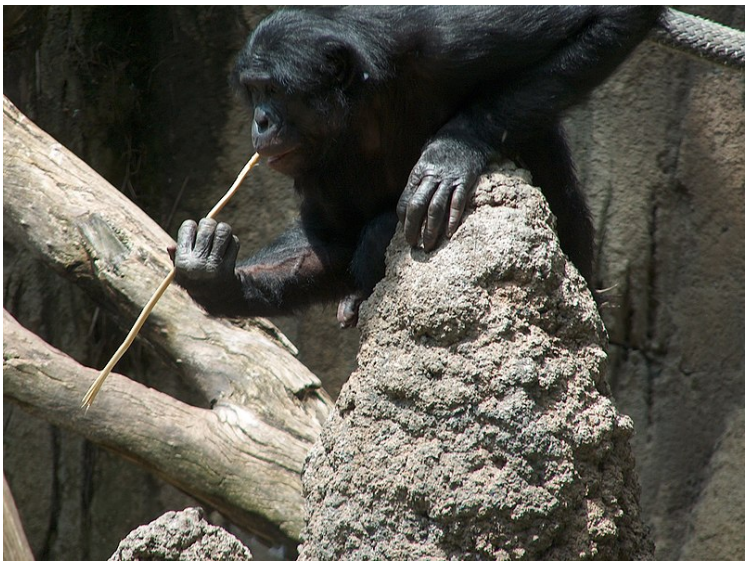


Figure 12.2.7: Bonobo chimpanzee termite fishing. (Image from Wikimedia Commons; CC BY-SA 3.0 Unported license. Caption by Kenneth A. Koenigshofer, PhD.).

If humans and at least some animals are born with an innate disposition to understand cause and effect, we should expect to find brain structures that play a role in this understanding. In fact, brain imaging studies show that "specific brain networks are involved in the extraction of causal structure from the world" (Fugelsang, et al., 2005, p.45). Some of these studies using fMRI techniques implicate several brain structures including areas in the **frontal, parietal, and temporal lobes** (Fugelsang, et al., 2005). **Bilateral prefrontal cortex** activation was seen with tasks requiring **logical inference** to make a judgement of causation. T

Several other studies also support the hypothesis that **extraction of causal structure** is an **innate** property of the brain structures of the visual system (Blakemore, et al., 2001; Fonlupt, 2003; Roser et al., 2005). Perception of causality is immediate like perception of motion or perception of faces suggesting innate mechanisms for perception of causation. Some authors have suggested that the detection of causality may even be served by a specialized brain module for recognizing and understanding causality (Leslie & Keeble, 1987; Scholl & Nakayama, 2002).

The exact brain areas activated during detection of causation depends on a number of factors. Judgments of causality that require integration of a working hypothesis with relevant data activate neural tissue in **prefrontal and occipital cortices**. Empirical studies, such as those cited above support the theory that information about cause-effect relations has been genetically internalized into the brain and this innate understanding of causality is a highly adaptive component of intelligence.

12.2.1.5.2 Predictive Relations (Predictive Co-occurrence of Events)

In addition to causality, it is also an enduring property of the world that some things regularly predict the occurrence of other things (i.e. a growling bear predicts an impending attack, sudden heavy rainfall predicts possible flash flooding, an approaching range fire predicts potential danger). Clearly, **predictive relations** are present everywhere in the environment. Thus, we should expect that natural selection must have organized internalized brain systems that capture predictive relations between events in the world.

The brain can be characterized as "a probabilistic prediction engine" (Nave, et al., 2020, p. e1542). It is not only evolved for prediction, but to implicitly make probability assessments about how likely its predictions about future are to be true. Predictive relations exist whenever specific events, objects, or situations consistently co-vary or correlate--whenever one thing consistently follows another; for example, think of the CS and US in classical conditioning. After conditioning has occurred, the CS predicts the US. This implicit prediction then controls behavior--the dog salivates immediately after the CS is presented in anticipation of coming food, a response that prepares the dog for the expected arrival of the US. As discussed in the chapter on learning and memory *classical conditioning* specifically involves the **cerebellum**, whereas associations, in general, between co-occurring events appears to depend on **long-term potentiation (LTP)**, and corresponding changes at synapses in **hippocampus** (Oishi, et al., 2019), **cerebral cortex** (Daw, et al., 2009; De Pasquale, et al., 2014) and other brain regions.

The adaptive significance of this property of general intelligence is hard to overestimate. An innate predisposition built into the brain to search for predictive relations in the environment and to exploit the adaptive information in those relations is an exceedingly powerful cognitive tool for understanding the world.



Figure 12.2.8: Contrasting behaviors to satisfy water needs in two species. The woman uses invention and technology, two products of human intelligence, to provide a more consistent and higher quality water source. (Images from Wikimedia Commons; Elephants drinking; https://commons.wikimedia.org/wiki/F...k,_Kenya_4.jpg ; by CT Cooper; licensed under the Creative Commons Attribution 3.0 Unported license. Woman pumping well; https://commons.wikimedia.org/wiki/F...an_Working.jpg; by Osaba Gerald; licensed under the Creative Commons Attribution-Share Alike 4.0 International license; caption by Kenneth A. Koenigshofer, PhD).

12.2.2 What makes humans so smart?

What makes humans so smart compared to other species on the planet? One key difference between human intelligence and intelligence in non-human animal species is the much higher degrees of **abstraction** that humans are capable of representing, compared to other animals. The ability of the human brain for high levels of abstraction, setting it apart from the brains of other species, is likely due to the greater complexity of circuits in human cerebral cortex compared to other mammals (recall that only mammals have six layered cerebral cortex and approximately 150,000 cortical columns--discussed above--while non-human mammals have significantly fewer). Humans easily detect highly abstract similarities in the environment compared to non-human animals and are capable of forming highly abstract categories and concepts based on these abstract similarities in properties or functions (Koenigshofer, 2017; Penn et al., 2008).

Research in molecular genetics suggests one possible explanation for how human ability for high levels of abstraction may have come about. Pollard (2009), comparing human and chimpanzee genomes, found “massive mutations” in humans in the “DNA switches” controlling size and complexity of cerebral cortex, extending the period of prenatal cell division in human cerebral cortex by several days compared to our closest primate relatives. Research using **artificial neural networks** suggests that increasing cortical complexity leads to sudden leaps in ability for abstraction and rule-like understanding of general principles (Clark, 1993), lending further support to the hypothesis that **superior ability for abstraction due to cortical complexity** may be the key component explaining differences in general intelligence between humans and nonhuman animals (see module on artificial neural networks in this chapter).

The frontal cortex is involved in concrete rule learning. **More anterior regions of frontal cortex support rule learning at higher levels of abstraction.** These abilities for high levels of abstraction may involve **anterior dorsolateral prefrontal cortex** in humans (Kroger et al., 2002; Reber, Stark, and Squire, 1998). Along with human language, the exceptional capacity of the human brain for abstraction may explain the unusual achievements of the human species ranging from agriculture, technology and science, to the invention of complex economies and governments (Koenigshofer, 2016, 2017).

Furthermore, **cultural transmission** of learned information in humans, ranging from books and educational institutions to film and the internet, allows each generation to profit from the accumulated knowledge of prior generations. Cultural transmission, along with cooperative problem solving and development of experts in different fields, creates a kind of **group intelligence** not typically possible in other species. Of course, human language, spoken and written, plays an enormous role in these shared cognitive processes among humans, perhaps explaining at least in part why language evolved. These considerations bring to the forefront the role of culture in human genetic evolution. **Gene-culture coevolution theory** proposes a multidirectional coevolution between genes and culture in which culture and human created artifacts such as tools, weapons, clothing, and pottery have driven the last 100,000 years of human evolution (Lloyd & Feldman, 2002; Durham, 1991). This theory also assumes an important role for

language in cultural transmission of learned knowledge and behavior. It also postulates existence of hominin biological changes that facilitated development of sophisticated language in humans (Lloyd & Feldman, 2002).

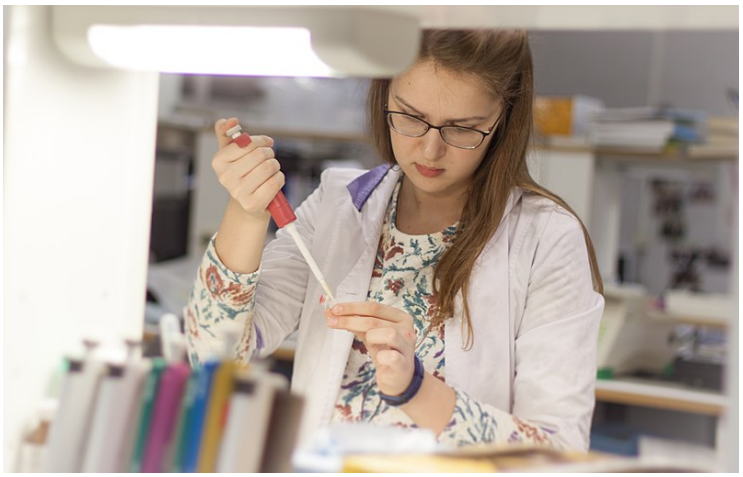


Figure 12.2.9: Scientists seek cause-effect, similarity, and predictive relations between variables. Scientific methods are an example of human general intelligence at its best. Alison Gopnik (2010, 2012) at UC Berkeley has found that young children engage in logical analysis of causation, teasing out causes from non-causal factors, in much the same way that scientists do. (Image from Wikipedia, https://commons.wikimedia.org/wiki/F..._reaction).jpg; by Alenakopytova; licensed under the Creative Commons Attribution-Share Alike 4.0 International license).

Another factor that may contribute to the superior intellectual capacities of humans is the sophisticated control systems in the human prefrontal cortex. Miller and Cohen (2001) proposed that “cognitive control stems from the active maintenance of patterns of activity in the **prefrontal cortex** that represents goals and means to achieve them. They provide bias signals to other brain structures whose net effect is to guide the flow of activity along neural pathways that establish the proper mappings between inputs, internal states, and outputs needed to perform a given task.” On their view, the prefrontal cortex (PFC) guides the flow of neural activity in relevant brain areas, which allows for cognitive control of behavior. As they state: "depending on their target of influence, representations in the PFC can function variously as attentional templates, rules, or goals by providing top-down bias signals to other parts of the brain that guide the flow of activity along the pathways needed to perform a task" (Miller & Cohen, 2001).

Goldman-Rakic (1996) proposed that the **prefrontal cortex** represents information not currently in the environment, creating a "**mental sketch pad**," to hold visual images in working memory, to represent plans, and to focus attention to intelligently guide thought, action, and emotion. This includes the inhibition of distracting thoughts, actions, and feelings. Although such control does exist to some degree in some non-human animals it is less developed and less influential over behavior than in our own species. The prefrontal cortex is highly interconnected with much of the brain, including extensive connections with other cortical, subcortical and brain stem sites. The **dorsal prefrontal cortex** is especially interconnected with brain regions involved with attention, cognition and action, while the **ventral prefrontal cortex** interconnects with brain regions involved with emotion.

12.2.2.1 Brain Mechanisms, Mental Representations, Relational Reasoning and Intelligence

Research suggests that reasoning requires coding involving neurons in **prefrontal cortex**. "Reasoning depends on the ability to form and manipulate mental representations of relations between objects and events. . . [and] the integration of multiple relations between mental representations . . .[However,] patients with **prefrontal damage** exhibited a selective and catastrophic deficit in the integration of relations. . . . The integration of relations may be the fundamental common factor linking the diverse abilities that depend on prefrontal function, such as planning, problem solving, and fluid intelligence" (Waltz et al., 1999, p. 119; **fluid intelligence** is another term for **general intelligence**, and is separate from one's store of learned knowledge). These results suggest that although mental models may involve many different brain areas acting together, the **prefrontal cortex** appears to play a special role in high level abstract reasoning requiring the integration of multiple relations. This may explain why **damage in prefrontal cortex** "leads to selective decrements in performance on tasks involving hypothesis testing, categorization, planning, and problem solving, all of which involve relational reasoning" (Waltz et al., 1999, p. 119).

Recent research has identified a number of brain structures involved in mental representations of future states of the world, specifically of one's own personal future, goals, and plans, essential for intelligent control of behavior. **Prospection** is the ability to

mentally represent the future. Behaviors controlled by mental anticipation of imagined futures can be called prosponses to distinguish them from responses to stimuli in the present or recent past (such as a CS in conditioning) (Koenigshofer, 2016). According to Spreng et al. (2015), autobiographical planning involves personal plans directed toward real-world goals. These researchers found that autobiographical planning involves "synchronized activity of **medial temporal lobe memory structures** as well as **frontal executive regions**, . . . specifically, of the **default** and **frontoparietal control networks**. [The **default network** consists of] the **medial prefrontal cortex** (PFC), **medial parietal cortex**, **including posterior cingulate cortex** (PCC) and **retrosplenial cortex** (RSC), the **posterior inferior parietal lobule** (IPL), **medial temporal lobes** (MTL) [**including hippocampus, amygdala, and parahippocampal** regions], and **lateral temporal cortex**. . . [This network is activated] by self-generated thought and active across multiple functional domains including memory, future-thinking, and social cognition" (Spreng et al., 2015).

Functional MRI (fMRI) studies "reveal striking overlap in the brain activity associated with remembering actual past experiences and imagining or simulating possible future experiences" (Schacter, et al., 2012, p. 677-678). Clinical observations are consistent with this hypothesis from fMRI studies. For example, amnesic patients have difficulty imagining the future. Another study of amnesic patients with **hippocampal damage** revealed impairments when these patients were asked to imagine novel experiences (Schacter, et al., 2012). The abilities for imagining and future-thinking are very important components of human intelligence.

12.2.3 General Intelligence in Humans and Non-human Animals: Neural Correlates

Historically, psychologists have focused on ways of measuring intellectual abilities that are important for success in school. Traditional IQ tests were designed to measure these abilities. As discussed above, one important observation from research based on these intelligence tests is that measures of different intellectual skills are correlated: individuals that do well in one type of intellectual ability tend to do well in all types. These positive correlations among measures of different types of intellectual activity are known among psychologists as "the positive manifold." The "positive manifold" has been interpreted by many psychologists as strong statistical evidence (from the mathematical method, factor analysis; Spearman, 1904) for the general intelligence factor, "g," which exists in addition to more specific intelligences such as verbal fluency and visual-spatial abilities (see models of human intelligence in the next module).

Perhaps unexpectedly, recent research shows that general intelligence (ability to recognize "relations and correlates," according to Spearman,1904, 1925, who originated the concept) is found to some degree in many mammals and even in some birds (Emery & Clayton, 2004). Recent research shows that degrees of general intelligence among mammals is most strongly associated with "the **number of cortical neurons, neuron packing density, interneuronal distance and axonal conduction velocity**—factors that determine general information processing capacity (IPC), as reflected by general intelligence" (Dicke & Roth, 2016). These researchers compare IPC in various species. They report that: "The highest IPC is found in humans, followed by the great apes, Old World and New World monkeys. The IPC of cetaceans and elephants is much lower because of a thin cortex, low neuron packing density and low axonal conduction velocity. By contrast, corvid [rooks, crows, ravens] and psittacid birds [parrots] have very small and densely packed pallial neurons and relatively many neurons, which, despite very small brain volumes, might explain their high intelligence."

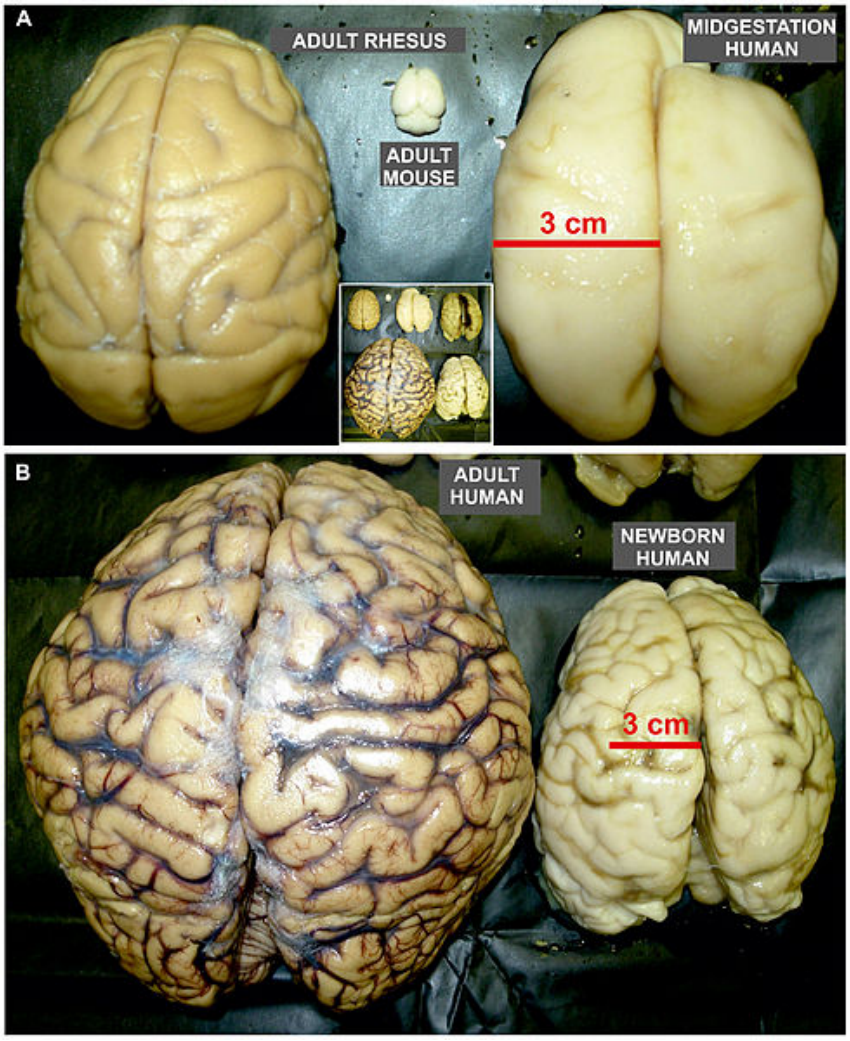


Figure 12.2.11: Size proportion of mature rodent and non-human primate brain as well as developing and mature human brains. Dorsal view of adult mouse (A), rhesus monkey (A), and human brain (B), as well as human fetal brain around mid-gestation (A) and at term (B). (A) The size of human fetal brain already at mid-gestation has reached the size of the adult rhesus monkey brain. Nevertheless, adult rhesus monkey brain is almost 100 times larger than brain of adult mouse. (B) The adult human brain is around 3–4 times larger than newborn brain which size reaches the size of adult chimpanzee brain. Note that the pattern of gyrification (cerebral gyri--the hill portions of the cortical folds) in human newborn brain is close to the one observed in adult. The inlet in the middle of the figure is the integrative photo of all brains shown in A and B that demonstrate their actual proportions (the right brain in the upper row of insertion is from fetus at the beginning of third trimester of gestation). Image and caption from Wikimedia. https://commons.wikimedia.org/wiki/F...00050-g004.jpg; by Ana Hladnik, Domagoj Džaja, Sanja Darmopil, Nataša Jovanov-Milošević and Zdravko Petanjek; licensed under the Creative Commons Attribution 3.0 Unported license).

An approach to individual differences among humans in intelligence involves **efficiency of neural processing**--higher IQ people show greater processing efficiency (Haier et al., 1992; Van Den Heuvel et al., 2009). Brain imaging studies show that higher IQ individuals show lower brain activation (as indicated by glucose metabolism) than lower IQ individuals when completing the same cognitive task, indicating that individuals with higher intelligence, as measured by IQ tests, do information processing more efficiently, with less expenditure of metabolic energy by the brain, compared to lower IQ individuals whose brains work harder. Haier, et al. (1992, p. 415-416) conclude: "Intelligence is not a function of how hard the brain works but rather how efficiently it works."

Brain processing efficiency may be related to any number of factors: inherited brain circuitry configurations which are more "streamlined" as a result of more efficient neural pruning during brain development (Koenigshofer, 2011, 2016); better conduction over pathways connecting multiple regions of brain; "more long-distance connections that ensure a high level of global

communication efficiency within the overall network" (Van Den Heuvel, et al., 2009, p. 7619) and many more. Resting state functional connectivity between bilateral prefrontal cortices encompassing the dorsal attention network and the **right insula (salience network)** was also associated with intelligence scores."

In humans, **general intelligence** is heritable and is dependent upon **many genes interacting** together (Bouchard, 2014). One can wonder whether some of these many genes determining intelligence might hold information about some of the environmental regularities in the world discussed above, including relational regularities such as causality and similarity. This is an area of research wide open for researchers in behavior genetics or cognitive genetics.

When considering human intelligence, the role of language is a significant factor. Much of human thinking involves the use of words. As Dicke and Roth (2016) state, "The evolution of a syntactical and grammatical language in humans most probably has served as an additional intelligence amplifier, which may have [also] happened in songbirds and psittacids" [parrots] as a consequence of convergent evolution--the evolution of similar characteristics in unrelated or distantly related species because of common selection pressures. As mentioned above, the **precuneus** of the parietal lobe may have played a significant role in the evolution of language by having involvement in the combination of ideas and concepts from different semantic domains (Rabini, et al., 2021).

Studies of brain damaged patients supply further insight into brain mechanisms involved in abstract concept formation and thinking dependent upon language. Patients with one type of **frontotemporal** dementia (FTD) are particularly impaired "in verbal concept formation (i.e. categorization based on abstract similarities between items). . . [with] especially the **left frontal lobe**, thought to be involved in abstract word processing (Lagarde, et al., 2015, p. 456).

12.2.4 Another Component of General Intelligence: Visual Imagery and Imagination

Significantly, visual imagery in the mind's eye can also be employed to mentally test novel combinations of causes and effects, similarity relations, and predictive relations (covariations) to discover new knowledge about hidden causes of events in the world, eventually leading to the creation of sophisticated scientific models of how the world works—human general intelligence at its best (Koenigshofer, 2017). For example, the famous theoretical physicist, Albert Einstein, used mental imagery extensively to do "thought experiments" that played a large role in his formulation of the theories of general and special relativity. Brain imaging studies using fMRI implicate **parietal cortex** in the use of imagination (Nair et al., 2003). Bruner (2010, p. S84) suggests that "the **parietal lobe system** 'forms a neural image of surrounding space' (Mountcastle, 1995 p. 389)," and perhaps of one's potential future action in that space. Significantly, parietal cortex has strong linkages with **prefrontal cortex** forming a **frontoparietal network:** the **inferior parietal lobule** (further subdivided into the **supramarginal gyrus**, the **temporoparietal junction**, and the **angular gyrus**, see Figure 14.2.8) is primarily connected with **dorsolateral prefrontal cortex** (Bruner, 2010; see Figure 14.2.7), associated, in part, with abilities for abstract thought, while upper parietal regions, according to Bruner, are associated in the scientific literature with functions such as abstract representation, internal mental images, "imagined world[s],. . . and thought experiment" (i.e., imagination). Significantly, a number of other research groups using fMRI brain imaging techniques in humans also find evidence of a critical role of the **frontoparietal network** in human intelligence and general cognitive ability (Colom, et al., 2010; Jung & Haier, 2007; Sripada, et al., 2020; Vendetti & Bunge, 2014; Wendelken, et al., 2017; Yeo et al., 2016).

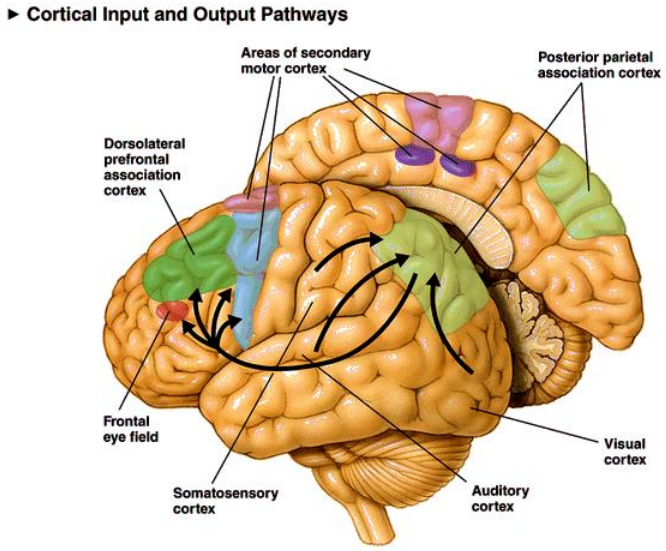


Figure 12.2.13: Connections of posterior parietal association cortex with dorsolateral prefrontal association cortex. (Image from Wikipedia; https://commons.wikimedia.org/wiki/F...ietal_Lobe.jpg; by Paskari; licensed under the Creative Commons Attribution-Share Alike 2.5 Generic, 2.0 Generic and 1.0 Generic license. Caption by Kenneth A. Koenigshofer, PhD.).

The emergence during human evolution of this visualization ability may help account for the development of modern human cognition, first appearing some 60,000-100,000 years ago (Mellars, 2005). Speculatively, superior abilities for imagination of the type described above might account, at least in part, for human competitive advantage over Neanderthals (Koenigshofer, 2017) perhaps contributing to Neanderthal extinction about 30,000 years ago (Watson and Berry, 2009). Consistent with this view, morphological studies suggest enhanced **parietal lobe** development in modern humans compared to Neanderthals (Bruner, 2010); by contrast, recent studies show little relative enlargement of the frontal lobes in humans compared to apes (Barton and Venditti, 2013). At least one post-mortem anatomical study of Einstein's brain suggested unusual enlargement of the **inferior parietal lobules** in parietal lobes along with a number of other atypical features in the **occipital lobes**, and throughout the cerebral cortex (Chen et al., 2014; see Carrillo-Mora et al., 2015). Another study of Einstein's brain by Falk et al. (2013, p. 1304) reports "Einstein’s brain has an extraordinary prefrontal cortex, which may have contributed to the neurological substrates for some of his remarkable cognitive abilities. The primary somatosensory and motor cortices near the regions that typically represent face and tongue are greatly expanded in the left hemisphere. Einstein’s parietal lobes are also unusual and may have provided some of the neurological underpinnings for his visuospatial and mathematical skills, as others have hypothesized. Einstein’s brain has typical frontal and occipital shape asymmetries (petalias) and grossly asymmetrical inferior and superior **parietal lobules**" with relative enlargement of the left inferior parietal module. Chen et al., referred to above, found exceptional enlargement of both **inferior parietal lobules** (which include the **supramarginal gyrus and angular gyrus** (Figure 14.2.8), involved in multiple functions including number processing, "mentalizing," and spatial cognition) in Einstein's brain compared to controls. Einstein was famous for his use of visualization to explore his ideas in theoretical physics through "thought experiments" in his "mind's eye." Additional evidence regarding Einstein's exceptional parietal lobes was provided by studies of cortical glial cells. A study by Diamond et al. (1985) of Einstein's brain found that the only cortical area of the four cortical areas examined with a greater number of glial cells per neuron, compared to controls, was the **left posterior parietal cortex**, a finding interpreted by the authors to mean that this area of Einstein's brain must have been exceptionally active during his lifetime.



Figure 12.2.14: Cortical gyri, including the left inferior parietal lobule composed of the supramarginal and angular gyri. (Image from Wikimedia Commons; https://commons.wikimedia.org/wiki/F...al_Surface.png; by John A. Beal, Ph.D.; licensed under the Creative Commons Attribution 2.5 Generic license.

This capacity for visualization permitting mental trial and error likely occurs to some degree in non-human animal species as well. Kohler's (1925/1959) classic work showing the use of "insight" by chimpanzees in problem solving offers evidence for this hypothesis, assuming that insight involves mental trial and error. Additional evidence suggesting mental trial and error in imagination in a variety of animals is provided by experiments showing insight in some orangutans, gorillas, and chimpanzees

(Mendes, et al., 2007; Hanus, et al., 2011) and in rooks--birds in the same Corvid family as ravens and crows (Bird & Emery, 2009a, 2009b).

One key feature of more traditional approaches to the study of human intelligence is that they emphasize aspects of human intelligence and thinking, such as language and computation, that are especially important for life in complex modern society. As described in the next module, some psychologists have hypothesized multiple kinds of human intelligence. Others focus primarily on how to measure intelligence, and still others study individual differences in intelligence among people. Because these psychologists tend to be interested in practical application of their tests in school and work settings, they tend to give relatively little attention to theories about the evolutionary origins or biological functions of intelligence. Nevertheless, intelligence tests are very useful predictors of success in environments such as school, military, and work settings. All involve measurement of mental skills important to successful adaptation to the demands of the physical and social environments typical of modern, industrialized societies.

12.2.5 Summary

Intelligence and cognition are complex psychological adaptations involving many different areas of the brain interacting together. Intelligence in the broadest sense involves the formation of sophisticated mental models of the world and how it works. These models include representations of things, events, and the predictive, similarity, and causal relations among them, as well as representations of space and time. Mental models of the physical and social environments permit prediction of future events, providing powerful evolutionary advantage. Mental models include the formation of categories, based on similarities, which allow inferences based on assignment of newly encountered things and events to previously formed categories. Mental models exploit the innate disposition to understand cause-effect relations in the environment, leading to knowledge about what causes what. This knowledge allows manipulation of causes to affect future environmental outcomes toward better adaptation. General intelligence emerges during evolution from genetic internalization of universal, abstract relational features of the world including cause-effect, event covariation, and similarity, each of which plays a role in thought and reasoning about the environment (Koenigshofer, 2017). Spearman (1904, 1925) discovered and was first to describe general intelligence, which he believed consisted of ability to recognize "relations and correlates" in the environment. Another aspect of general intelligence is ability to visualize, to form and manipulate visual images in imagination. This ability may have developed as an exaptation or recruitment of portions of the visual and motor systems, including parietal association cortex. This would allow some visual and motor circuits to form internally generated mental images that can be mentally manipulated to test out probable effects of possible future behaviors before committing to them in the physical world. Because this ability to visualize outcomes in the "mind's eye" is much safer and saves time and calories compared to testing outcomes in actual physical behavior, it is likely that there has been strong selection pressure for ability to manipulate mental images to plan future action. This component of intelligence provides a powerful mechanism for maximizing the adaptive outcomes of behavior and therefore provides enormous selective advantage--a strong impetus for its evolution as a central feature of intelligence (Koenigshofer, 2017).

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12.2.7 Attributions

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12.3: High Intelligence-Nature or Nurture; Learning Disabilities

12.3.1 Learning Objectives

1. Describe how genetics and environment affect intelligence
2. Explain the relationship between IQ scores and socioeconomic status
3. Describe the difference between a learning disability and a developmental disorder

12.3.2 Overview

A young girl, born of teenage parents, lives with her grandmother in rural Mississippi. They are poor—in serious poverty—but they do their best to get by with what they have. She learns to read when she is just 3 years old. As she grows older, she longs to live with her mother, who now resides in Wisconsin. She moves there at the age of 6 years. At 9 years of age, she is raped. During the next several years, several different male relatives repeatedly molest her. Her life unravels. She turns to drugs and sex to fill the deep, lonely void inside her. Her mother then sends her to Nashville to live with her father, who imposes strict behavioral expectations upon her, and over time, her wild life settles once again. She begins to experience success in school, and at 19 years old, becomes the youngest and first African-American female news anchor ("Dates and Events," n.d.). The woman—Oprah Winfrey—goes on to become a media giant known for both her intelligence and her empathy.

12.3.3 High Intelligence: Nature or Nurture?

Where does high intelligence come from? Some researchers believe that intelligence is a trait inherited from a person's parents. Scientists who research this topic typically use twin studies to determine the heritability of intelligence. The Minnesota Study of Twins Reared Apart is one of the most well-known twin studies. In this investigation, researchers found that identical twins (100% of their DNA is identical) raised together and identical twins raised apart exhibit a higher correlation between their IQ scores than siblings (50% of their DNA in common) or fraternal twins (50% of their DNA in common) raised together (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990). The findings from this study reveal a genetic component to intelligence (Figure 12.3.1). At the same time, other psychologists believe that intelligence is shaped by a child's developmental environment. If parents were to provide their children with intellectual stimuli beginning from before they are born, it is likely that they would absorb the benefits of that stimulation, and it would be reflected in intelligence levels.

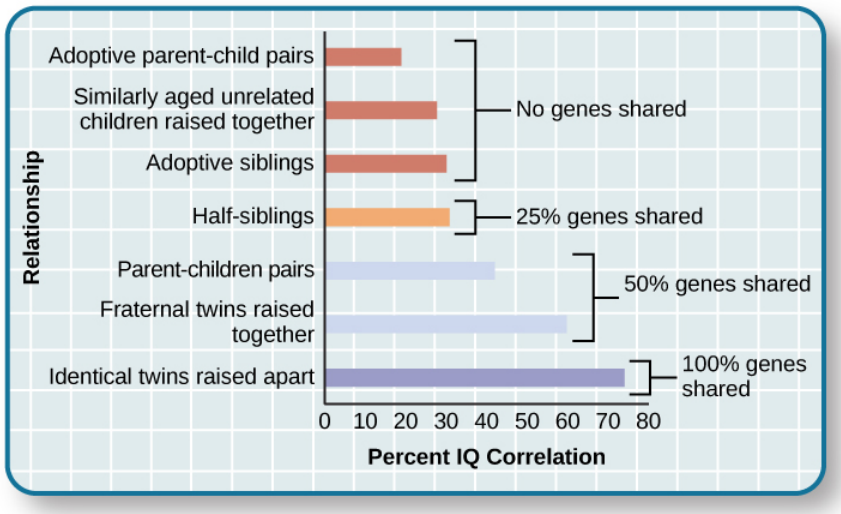


Figure 12.3.1: The correlations of IQs of unrelated versus related persons reared apart or together suggest a genetic component to intelligence. (From OpenStax, Psychology 2ed. Chap. 7.6, CC BY 4.0)

The reality is that aspects of each idea are probably correct. One study suggests that genetics seem to be in control of the level of intelligence, environmental influences are also involved (Bartels, Rietveld, Van Baal, & Boomsma, 2002). Certainly, there are behaviors that support the development of intelligence, but the genetic component of high intelligence can not be ignored. As with all heritable traits, however, it is not always possible to isolate how and when high intelligence is passed on to the next generation.

Range of Reaction is the theory that each person responds to the environment in a unique way based on his or her genetic makeup. According to this idea, your genetic potential is a fixed quantity, but whether you reach your full intellectual potential is dependent upon the environmental stimulation you experience, especially in childhood. Think about this scenario: A couple adopts a child who has average genetic intellectual potential. They raise her in an extremely stimulating environment. What will happen to the couple's new daughter? It is likely that the stimulating environment will improve her intellectual outcomes over the course of her life. But what happens if this experiment is reversed? If a child with an extremely strong genetic background is placed in an environment that does not stimulate him: What happens? Interestingly, according to a longitudinal study of highly gifted individuals, it was found that "the two extremes of optimal and pathological experience are both represented disproportionately in the backgrounds of creative individuals"; however, those who experienced supportive family environments were more likely to report being happy (Csikszentmihalyi & Csikszentmihalyi, 1993, p. 187).

Another challenge to determining origins of high intelligence is the confounding nature of our human social structures. It is troubling to note that some ethnic groups perform better on IQ tests than others—and it is likely that the results do not have much to do with the quality of each ethnic group's intellect. The same is true for socioeconomic status. Children who live in poverty experience more pervasive, daily stress than children who do not worry about the basic needs of safety, shelter, and food. These worries can negatively affect how the brain functions and develops, causing a dip in IQ scores. Mark Kishiyama and his colleagues determined that children living in poverty demonstrated reduced prefrontal brain functioning comparable to children with damage to the lateral prefrontal cortex (Kishyama, Boyce, Jimenez, Perry, & Knight, 2009).

The debate around the foundations and influences on intelligence exploded in 1969, when an educational psychologist named Arthur Jensen published the article "How Much Can We Boost I.Q. and Achievement" in the Harvard Educational Review. Jensen had administered IQ tests to diverse groups of students, and his results led him to the conclusion that IQ is determined by genetics. He also posited that intelligence was made up of two types of abilities: Level I and Level II. In his theory, Level I is responsible for rote memorization, whereas Level II is responsible for conceptual and analytical abilities. According to his findings, Level I remained consistent among the human race. Level II, however, exhibited differences among ethnic groups (Modgil & Routledge, 1987). Jensen's most controversial conclusion was that Level II intelligence is prevalent among Asians, then Caucasians, then African Americans. Robert Williams was among those who called out racial bias in Jensen's results (Williams, 1970).

Obviously, Jensen's interpretation of his own data caused an intense response in a nation that continued to grapple with the effects of racism (Fox, 2012). However, Jensen's ideas were not solitary or unique; rather, they represented one of many examples of psychologists asserting racial differences in IQ and cognitive ability. In fact, Rushton and Jensen (2005) reviewed three decades worth of research on the relationship between race and cognitive ability. Jensen's belief in the inherited nature of intelligence and the validity of the IQ test to be the truest measure of intelligence are at the core of his conclusions. If, however, you believe that intelligence is more than Levels I and II, or that IQ tests do not control for socioeconomic and cultural differences among people, then perhaps you can dismiss Jensen's conclusions as a single window that looks out on the complicated and varied landscape of human intelligence.

12.3.4 Learning Disabilities

Learning disabilities are cognitive disorders that affect different areas of cognition, particularly language or reading. It should be pointed out that learning disabilities are not the same thing as intellectual disabilities. Learning disabilities are considered specific neurological impairments rather than global intellectual or developmental disabilities. A person with a language disability has difficulty understanding or using spoken language, whereas someone with a reading disability, such as dyslexia, has difficulty processing what he or she is reading.

Often, learning disabilities are not recognized until a child reaches school age. One confounding aspect of learning disabilities is that they often affect children with average to above-average intelligence. At the same time, learning disabilities tend to exhibit comorbidity with other disorders, like attention-deficit hyperactivity disorder (ADHD). Anywhere between 30–70% of individuals with diagnosed cases of ADHD also have some sort of learning disability (Riccio, Gonzales, & Hynd, 1994). Let's take a look at two examples of common learning disabilities: dysgraphia and dyslexia.

12.3.4.1 Dysgraphia

Children with dysgraphia have a learning disability that results in a struggle to write legibly. The physical task of writing with a pen and paper is extremely challenging for the person. These children often have extreme difficulty putting their thoughts down on paper (Smits-Engelsman & Van Galen, 1997). This difficulty is inconsistent with a person's IQ. That is, based on the child's IQ

and/or abilities in other areas, a child with dysgraphia should be able to write, but can't. Children with dysgraphia may also have problems with spatial abilities.

12.3.4.2 Dyslexia

Dyslexia is the most common learning disability in children that causes difficulties in learning to read. An individual with dyslexia exhibits an inability to correctly process letters. The neurological mechanism for sound processing does not work properly in someone with dyslexia. As a result, dyslexic children may not understand sound-letter correspondence. A child with dyslexia may mix up letters within words and sentences—letter reversals, such as those shown in Figure 12.3.2, are a hallmark of this learning disability—or skip whole words while reading. A dyslexic child may have difficulty spelling words correctly while writing. Because of the disordered way that the brain processes letters and sound, learning to read is a frustrating experience. Some dyslexic individuals cope by memorizing the shapes of most words, but they never actually learn to read (Berninger, 2008).

12.3.4.3 The Brain, Dyslexia, and **Dysgraphia**

Developmental dyslexia is a heritable neurodevelopmental disorder that impairs reading in individuals with normal intelligence and educational opportunities. Reading requires the coordination of many brain systems. This "reading circuit" includes language mechanisms in Broca's and Wernicke's areas in the frontal and temporal lobes, respectively, as well as systems involved in vision, working memory, attention, movement and cognition. Processing of printed words takes place within "the visual word form area" located in the fusiform gyrus (also involved in object and face recognition) of the left hemisphere.

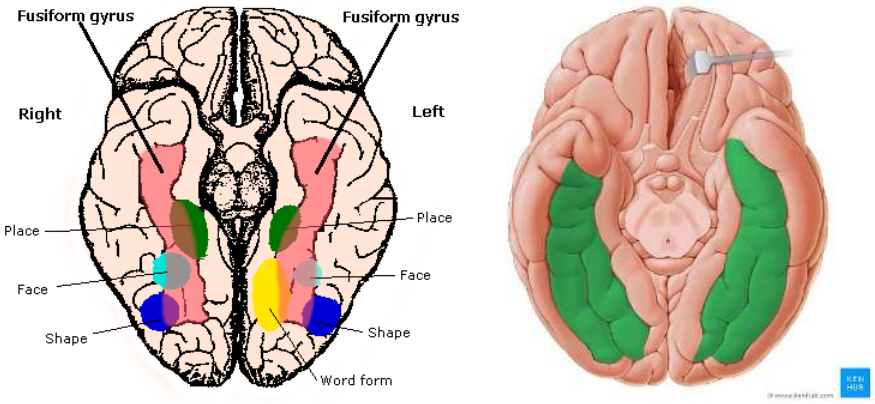


Figure 12.3.2: Fusiform gyrus viewed from bottom of human brain. Note an area for "word form" located in the left fusiform area. (Images from Wikimedia Commons, CC BY-SA 3.0).

Next, a large circuit in the left hemisphere is activated. This circuit includes the **supramarginal gyrus** (mapping of spelling and other writing conventions to language sounds), the **superior temporal gyrus** (phonological sound processing), the **inferior parietal lobule** and the **angular gyrus** (word-meaning processing) and the **inferior frontal gyrus** (phonological sound and semantic meaning processing, working memory). In addition, **subcortical regions** implicated in long-term and working memory, procedural learning and rapid sequential auditory processing (thalamus, basal ganglia and hippocampus) also appear to be involved in reading.

In addition, there is strong evidence for a role of the **visual magnocellular (M) system** in reading and research suggests a significant role of deficits in the visual magnocellular (M) system in **developmental dyslexia** (DD). The M and parvocellular (P) pathways are major parallel visual system streams feeding to lateral geniculate nucleus (visual area) of the thalamus, then onto primary visual (striate) cortex, and then to the extrastriate regions of the occipital lobe (i.e., the 'dorsal' and the 'ventral' visual streams). The **ventral stream (the "what" pathway)** which involves the inferior temporal cortex is associated with color, form perception, and the discrimination and recognition of objects). The **visual magnocellular or dorsal system (the "where" pathway**; depth and motion perception) contributes to rapid recognition and sequencing of letters by quickly focusing the **ventral attention network** (VAN) on the letter to be identified. Finally, left and right fronto-parietal (attentional) networks critically modulate visual and auditory word pathways by selective attention in both temporal and spatial dimensions. The **visual magnocellular system (the "where" pathway) is related to the fronto-parietal attentional network**. Previous neuroimaging studies have revealed reduced or absent activation within the visual M pathway in DD. Considering the complexity of the circuitry involved in reading, it is likely that a wide range of patterns of neurological deficit in the above mentioned brain areas may contribute to reading difficulties in different individuals (Mascheretti, et al., 2021).

Dysgraphia appears to involve disorder in some **brain areas** which are **not involved in dyslexia**. Richards, et al. (2015) used fMRI to study structural white matter integrity and functional connectivity in children with dysgraphia and dyslexia and found significant differences between control group and both the dysgraphic and dyslexic groups in functional connectivity. Left **occipital temporal gyrus**, supramarginal gyrus, **precuneus**, and **inferior frontal gyrus** were used in these analyses because these brain areas were shown in an analysis of prior research to be related to written word production. Dysgraphia and dyslexia differ in white matter integrity, fMRI functional connectivity, and white matter–gray matter correlations.



Figure 12.3.3: These written words show variations of the word “teapot” as written by individuals with dyslexia. (From The Source of Intelligence. Licensed CC BY-NC 4.0).

12.3.5 Summary

Genetics and environment affect intelligence and the challenges of certain learning disabilities. The intelligence levels of all individuals seem to benefit from rich stimulation in their early environments. Highly intelligent individuals, however, may have a built-in resiliency that allows them to overcome difficult obstacles in their upbringing. Learning disabilities can cause major challenges for children who are learning to read and write. Unlike developmental disabilities, learning disabilities are strictly neurological in nature and are not related to intelligence levels. Students with dyslexia, for example, may have extreme difficulty learning to read, but their intelligence levels are typically average or above average.

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12.3.7 Attributions

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CHAPTER OVERVIEW

13: Sexuality and Sexual Development

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13.1: Sex Hormones, Sexual Motivation, and Reproductive Behaviors
13.2: Sexual Development, Anatomy and Physiology
13.3: Differences of Sexual Development
13.4: Gender
13.5: Sexual Orientation
13.6: Sex Differences and Evolutionary Interpretations

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13.1: Sex Hormones, Sexual Motivation, and Reproductive Behaviors

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Distinguish between the organizational and activational effects of sex hormones
2. Describe some reciprocal interactions between sex hormones and reproductive behavior
3. Understand basic biological mechanisms regulating sexual behavior and motivation
4. Identify the role of the brain in responding to sexual stimuli
5. Explain the role of hormones in parental behavior

13.1.1 Overview

This module discusses the relationship between sex and hormones (including organizational and activational effects, maturation of the reproductive systems, interactions between hormones and behavior, and anabolic steroids), sexual behavior as a form of motivation (including physiological mechanisms and human sexual behavior and motivation), sex and the brain (including erogenous zones, and the role of the hypothalamus and the pituitary gland), and parental behavior (including hormones and rodent maternal behavior, maternal aggression, and hormones and human maternal behavior).

13.1.2 Human Sexuality in Context

Human sexuality refers to people's sexual interest in and attraction to others, as well as their capacity to have erotic experiences and responses. Sexuality may be experienced and expressed in a variety of ways, including (but not limited to) thoughts, desires, practices, roles, and behaviors. This chapter mostly focuses on the biological and physical aspects of sexuality- human reproductive anatomy and functions, including the human sexual response cycle and the basic biological drive that exists in all species- but also addresses the psychological domains of gender identity and sexual orientation. We begin with hormones, as they play such an integral role in the development and expression of human sexuality.

13.1.3 Sex and Hormones

Because of their inextricable link to the development and maturation of reproductive anatomy (both prenatally and during puberty), as well as the promotion and maintenance of adult reproductive functions, Biological Psychology textbooks often include hormones in the chapter on sex and reproductive behaviors. However, many other bodily functions (such as growth, sleep, hunger, satiation, and maintenance of blood pressure, to name a few) are regulated by hormones, so we have opted to cover basics of the endocrine system (the organs which produce and secrete hormones) in the Nervous System Anatomy chapter. Please refer to that chapter if you need a brief overview of hormones and the endocrine system.

13.1.3.1 Organizational and Activational Effects of Sex Hormones

Although the dichotomy cannot be strictly applied, the effects of steroid sex hormones have typically been characterized as organizational versus activational. Organizational effects result in permanent changes that usually occur early in development, such as the prenatal development of human reproductive structures (also known as **primary sex characteristics**- differences in male and female bodies that are present at birth). Activational effects are usually temporary and occur throughout life, dependent on specific conditions. Thus, structures in the body, brain, and nervous system are thought to be *organized* (in a male-typical or female-typical manner) through the action of steroid hormones early in development, and then later on *activated* by steroid hormones, resulting in structures and behaviors that differ between the sexes (Arnold and Breedlove, 1985). While this simple dichotomy works well with animals with very distinct sexual dimorphism in behavior (such as rats, where only males attempt to mount other rats and only females exhibit a sexually receptive posture called lordosis), it cannot be applied in such a straightforward manner to people. For one thing, humans do not exhibit any sexual behaviors that are strictly stereotyped and unique to either males or females. Nonetheless, some of the differences between human males and females can be attributed, at least in part, to either the organizational or activational effects of sex hormones.

One example of a permanent organizational effect is the difference between males and females in the secretion of certain hormones (related to reproductive function) by the hypothalamus; adult females follow a pattern of cyclical hormone release (related to their fertility cycles), whereas males do not. Changing the hormones that are present in the body later in life will not change the capacity of the hypothalamus to cycle the release of these hormones. Some **secondary sex characteristics** (changes that occur in male and female bodies during the sexual maturation that occurs with puberty) are also permanent changes- requiring surgery to alter- such as the development of breasts and wider hips in women or a prominent Adam's apple (cartilage around the thyroid in the neck area) and broader shoulders in men. In contrast, some secondary sex characteristics, like the presence of facial hair in men (but not in women), can be modified with changes to hormone levels in the adult body of either sex.

One example of a temporary activational effect is lactation, or the production and secretion of milk from the mammary glands (breasts). Normally this only occurs in females after childbirth, when the necessary combination of the hormones estrogen, progesterone, and prolactin are present. "However, if a man is treated with this hormone combination, his mammary glands not only can produce milk, but he can nurse a baby! Thus, lactation is an "activated-only" action of hormones, and there is no organized sex difference in the mammary gland tissue itself." (Jones and Lopez, 2006, page 466). So, while modern science cannot yet assist transgender women (whose biological birth sex was male) in carrying and giving birth to an infant, they can nonetheless participate in nursing the baby.

13.1.3.2 Sex Hormones and Maturation

The main categories of sex hormones are **androgens** (more prevalent in biological males), of which **testosterone** is a primary example, and **estrogens** (more prevalent in biological females), of which **estradiol** is a primary example. It is important to note that *all* individuals have both androgens ("male hormones") and estrogens ("female hormones"), but the relative proportion of the hormones present in a given body varies, usually correlated with biological sex. Testosterone is secreted by the testes in males and in small amounts by the ovaries in females (although most is converted to estradiol). A small amount of testosterone is also secreted by the adrenal glands (endocrine glands positioned on top of the kidneys) in both sexes. Estrogens are secreted by the ovaries in females and by fat cells in both sexes.

Male and female reproductive systems are different at birth (due to differences in primary sex characteristics), but the gonads (testes in males and ovaries in females) are immature and incapable of producing gametes (sperm in males and eggs in females) or sex hormones. Maturation of the reproductive system occurs during puberty when hormones from the hypothalamus and pituitary gland stimulate the testes or ovaries to start producing sex hormones again. Sex hormones, in turn, lead to the growth and maturation of the reproductive organs, rapid body growth, and the development of secondary sex characteristics, such as pubic and underarm hair in both sexes, facial hair in males and breasts in females.

13.1.3.3 Interactions Between Sex Hormones and Reproductive Behaviors

As discussed in Chapter 4.6, the interaction between hormones and behavior is bidirectional: hormones can influence behavior, and behavior can sometimes influence hormone concentrations. Hormones travel through the blood, influencing the nervous system to regulate an individual's behaviors, some of which are related to sexuality and reproduction (such as aggression, mating, and parenting). Some hormone-behavior interactions that are related specifically to reproductive behaviors are described below.

13.1.3.3.1 Hormonal Influence on Reproductive Behaviors

Hormones coordinate the physiology and behavior of individuals. Over evolutionary time, hormones have 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. Similarly, during pregnancy estrogens and progesterone concentrations are elevated, and these hormones are also involved in maternal behavior in the mothers.

How might hormones affect behavior? While hormones do not *cause* behavioral changes, they influence the components that interact to produce behavior- sensory systems (input), the central nervous system (integration), and muscles and glands (output). In this manner, specific stimuli are more likely to elicit certain responses in the appropriate behavioral or social context. In other words, hormones change the *probability* that a particular behavior will occur in the appropriate situation (Nelson, 2011). This is a critical distinction that can affect how we think of hormone-behavior relationships. In most cases, hormones can be considered to affect behavior by influencing any or all of these components.

An example of the influence of hormones on a simple behavior is singing in zebra finches. Only male zebra finches sing. If the testes of adult male finches are removed, then the birds reduce singing, but castrated finches resume singing if the testes are

reimplanted, or if the birds are treated with either testosterone or estradiol. Although we generally consider androgens to be “male” hormones and estrogens to be “female” hormones, it is common for testosterone to be converted to estradiol in nerve cells. Thus, many male-like behaviors are associated with the actions of estrogens! Singing behavior is most frequent when blood testosterone or estrogen concentrations are high. Males sing to attract mates or ward off potential competitors from their territories.

13.1.3.3.2 Behavioral Influence on Sex Hormones

How might behaviors affect hormones? If a male mouse or rhesus monkey loses a fight, blood testosterone levels decrease for several days or even weeks afterward. Comparable results have also been reported in humans. Testosterone concentrations are affected not only in humans involved in physical combat, but also in those involved in simulated battles. For example, testosterone concentrations were elevated in winners and reduced in losers of regional chess tournaments.

People do not have to be directly involved in a contest to have their hormones affected by the outcome of the contest. Male fans of both the Brazilian and Italian teams were recruited to provide saliva samples to be assayed for testosterone before and after the final game of the World Cup soccer match in 1994. At the end of the game, Brazil and Italy were tied for regulation and overtime, but then Brazil won in penalty shots. The Brazilian fans were elated and the Italian fans were crestfallen. When the samples were assayed, 11 of 12 Brazilian fans who were sampled had increased testosterone concentrations, and 9 of 9 Italian fans had decreased testosterone concentrations, compared with pre-game baseline values (Dabbs, 2000).



Figure 13.1.1: The expectation of events can influence one’s hormonal activity. How do you think yours is affected if you anticipate going on a date with a romantic interest soon?

In some cases, hormones can be affected by anticipation of behavior (Figure 13.1.1). For example, testosterone concentrations also influence sexual motivation and behavior in women. In one study, the interaction between sexual intercourse and testosterone was compared with other activities (cuddling or exercise) in women (van Anders, Hamilton, Schmidt, & Watson, 2007). On three separate occasions, women provided a pre-activity, post-activity, and next-morning saliva sample. After analysis, the women’s testosterone was determined to be elevated prior to intercourse as compared to other times. Thus, an anticipatory relationship exists between sexual behavior and testosterone. Testosterone values were higher post-intercourse compared to exercise, suggesting that engaging in sexual behavior may also influence hormone concentrations in women.

13.1.3.4 Anabolic Steroids

The endocrine system can be exploited for illegal or unethical purposes. A prominent example of this is the use of steroid drugs by professional athletes. Commonly used for performance enhancement, anabolic steroids are synthetic versions of the sex hormone testosterone. By boosting natural levels of this hormone, athletes experience increased muscle mass. Synthetic versions of human growth hormone are also used to build muscle mass.

The use of performance-enhancing drugs is banned by all major collegiate and professional sports organizations in the United States because they impart an unfair advantage to athletes who take them. In addition, the drugs can cause significant and dangerous side effects. For example, anabolic steroid use can increase cholesterol levels, raise blood pressure, and damage the liver. Altered testosterone levels (both too low or too high) have been implicated in causing structural damage to the heart, and increasing the risk for cardiac arrhythmias, heart attacks, congestive heart failure, and sudden death. Paradoxically, steroids can

cause shriveled testes and enlarged breast tissue in men. In females, their use can cause analogous effects such as an enlarged clitoris and growth of facial hair. In both sexes, their use can promote increased aggression (commonly known as “roid-rage”), depression, sleep disturbances, severe acne, and infertility.

13.1.4 Sexual Behavior as a Form of Motivation

Sex is an important part of most people's lives. From an evolutionary perspective, the reason is obvious—perpetuation of the species. Sexual behavior in humans, however, involves much more than reproduction. Sexual arousal is the drive state that results in thoughts and behaviors related to sexual activity. It is generated by a large range of internal and external mechanisms that are triggered either after the extended absence of sexual activity or by the immediate presence and possibility of sexual activity (or by cues commonly associated with such possibilities). This section provides an overview of some research that has been conducted on sexual behavior and motivation.

Sexual motivation, often referred to as **libido**, is a person's overall sexual drive or desire for sexual activity. This motivation is determined by biological, psychological, and social factors. In most mammalian species, sex hormones control the ability to engage in sexual behaviors. However, sex hormones do not directly regulate the ability to have sexual intercourse in primates (including humans); rather, they are only one influence on the motivation to engage in sexual behaviors. Social factors, such as work, family, and relationship issues also have an impact, as do internal psychological factors like personality and lifestyle stress. Sex drive may also be affected by medical conditions (including illness or injury), medications, and pregnancy.

13.1.4.1 Physiological Mechanisms of Sexual Motivation and Behavior

Much of what we know about the physiological mechanisms that underlie sexual motivation and behavior comes from animal research. Research on male rats 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 (Everett, 1990; Figure 13.1.2). Similar dissociations of sexual motivation and sexual ability have also been observed in the female rat (Becker, Rudick, & Jenkins, 2001; Jenkins & Becker, 2001).

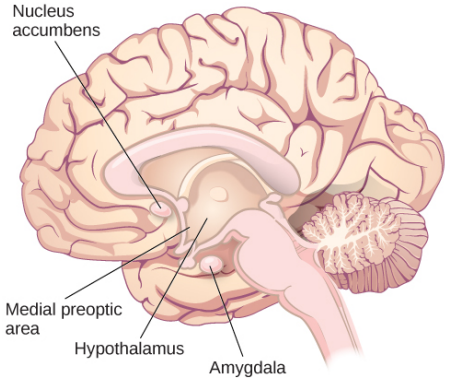


Figure 13.1.2: The medial preoptic area, an area of the hypothalamus, is involved in the ability to engage in sexual behavior, but it does not affect sexual motivation. In contrast, the amygdala and nucleus accumbens are involved in motivation for sexual behavior, but they do not affect the ability to engage in it.

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, but, surprisingly, do not change how hard a male rat is willing to work to gain access to a sexually receptive female (Figure 13.1.3). 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.

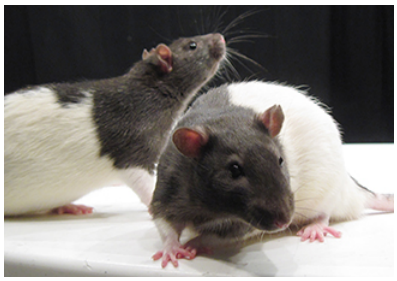


Figure 13.1.3: A male rat that cannot engage in sexual behavior still seeks receptive females, suggesting that the ability to engage in sexual behavior and the motivation to do so are mediated by different systems in the brain.

13.1.4.2 Human Sexual Motivation and Behavior

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). In other words, testosterone maintains libido (sex drive) in both males and females.

Vasopressin is also involved in the male arousal phase, and the increase of vasopressin during erectile response may be directly associated with increased motivation to engage in sexual behavior. The relationship between hormones and female sexual motivation is not as well understood, largely due to the overemphasis on male sexuality in Western research. Estrogen and progesterone typically regulate motivation to engage in sexual behavior for females, with estrogen increasing motivation and progesterone decreasing it. The levels of these hormones rise and fall throughout a woman's menstrual cycle. Research suggests that testosterone, oxytocin, and vasopressin are also implicated in female sexual motivation in similar ways as they are in males, but more research is needed to understand these relationships.

13.1.5 Sex and the Brain

The brain is the organ that translates the nerve impulses from the skin into pleasurable sensations. It controls nerves and muscles used during sexual behavior. The brain regulates the release of hormones, which are believed to be the physiological origin of sexual desire. The cerebral cortex (the outer layer of the brain that allows for thinking and reasoning) is believed to be the origin of sexual thoughts and fantasies. Deep to the cortex is the limbic system, a collection of structures believed to be the origin of emotions and feelings, also important for sexual behavior. The limbic system includes the amygdala, hippocampus, cingulate gyrus, and septal nucleus. The septal nucleus, an area that receives reciprocal connections from many other brain regions (including the hypothalamus and the amygdala), seems to play an important role in sexual pleasure. This region shows rhythmic spiking activity during sexual orgasm, and is also one of the brain regions that rats will most reliably voluntarily self-stimulate (Olds & Milner, 1954). In humans, placing a small amount of acetylcholine into this region, or stimulating it electrically, has been reported to produce a feeling of imminent orgasm (Heath, 1964; Heath, 1972).

13.1.5.1 Erogenous Zones

At first glance- or touch for that matter- the glans of the clitoris and penis are the parts of our anatomies that seem to bring the most pleasure. However, these two organs pale in comparison to our central nervous system's capacity for pleasure. Extensive regions of the brain and brainstem are activated when a person experiences pleasure, including the insula, temporal cortex, limbic system, nucleus accumbens, basal ganglia, superior parietal cortex, dorsolateral prefrontal cortex, and cerebellum (Ortigue et al., 2007; Figure 13.1.4). Neuroimaging techniques show that these regions of the brain are active when patients have spontaneous orgasms involving no direct stimulation of the skin (e.g., Fadul et al., 2005) and when experimental participants self-stimulate erogenous zones (e.g., Komisaruk et al., 2011). Erogenous zones are particularly sensitive areas of skin (which may be different across individuals), and (like all body areas with sensation) are connected (via the nervous system) to the somatosensory cortex in the brain (refer to the section on the central nervous system).



Figure 13.1.4: Some of the many regions of the brain and brainstem activated during pleasure experiences.

A study by Nummenmaa and his colleagues (2016) used a unique method to test the hypothesis that the more sensitive areas of our bodies have greater potential to evoke pleasure. The Nummenmaa research team showed experimental participants images of same- and opposite-sex bodies. They then asked the participants to color the regions of the body that, when touched, they or members of the opposite sex would experience as sexually arousing while masturbating or having sex with a partner. Nummenmaa found the expected “hotspot” erogenous zones around the external sex organs, breasts, and anus, but also reported areas of the skin beyond these hotspots: “[T]actile stimulation of practically all bodily regions trigger sexual arousal….” Moreover, he concluded, “[H]aving sex with a partner…”—beyond the hotspots—“…reflects the role of touching in the maintenance of…pair bonds.” This also underlines the fact that individuals are different, and erogenous zones vary correspondingly.

13.1.5.2 The Role of the Hypothalamus and the Pituitary Gland

One brain structure that is particularly important for sexual functioning is the **hypothalamus** (Figure 13.1.5). This is a small area at the base of the brain consisting of several groups of neuron cell bodies that receive input from the limbic system. One of the reasons for the importance of the hypothalamus is that it controls the pituitary gland, which secretes hormones that control the other glands of the body.

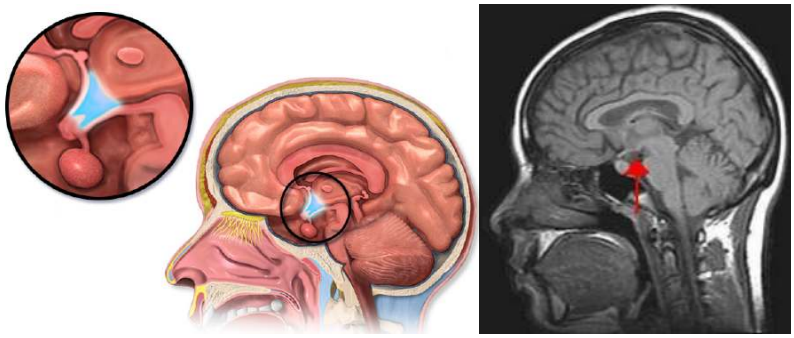


Figure 13.1.5: The hypothalamus controls the pituitary gland. Midsagittal views of the human brain: First, a drawing with the roughly triangular-shaped hypothalamus colored blue, and the small, oval-shaped pituitary gland visible attached below it (circle inset shows a magnified view). In the next image, an arrow points to the location of the hypothalamus on a brain scan.

Several important hormones related to sexual function are secreted by the pituitary gland, which is divided into anterior and posterior sections. The anterior pituitary secretes follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. FSH and LH are responsible for ovulation in females and sperm production in males. Prolactin and oxytocin (which is released by the posterior pituitary) stimulate milk production in lactating females. Oxytocin is sometimes called the "love" hormone and is believed to be involved with maintaining close relationships. It is released with sexual activity during orgasm, causing rhythmic contractions in the uterus and penis. Oxytocin is also released in females during childbirth (causing the contractions of the uterus that push the baby out) and during breast-feeding (as part of the milk let-down reflex).

13.1.6 Parental Behavior

Parental behavior can be considered to be any behavior that contributes directly to the survival of fertilized eggs or offspring that have left the body of the female. There are many patterns of parental care in mammals. The developmental status of the newborn is an important factor driving the type and quality of parental care in a species- **altricial** young are born in an underdeveloped state and require extensive parental care to survive, whereas **precocial** young are born in a more advanced and mature state, already mobile and able to feed themselves. Maternal care is much more common than paternal care.

13.1.6.1 Hormones and Rodent Maternal Behavior

The vast majority of research on the hormonal correlates of mammalian parental behavior has been conducted on rats. Rats bear altricial young, and mothers perform a cluster of stereotyped maternal behaviors, including nest building, crouching over the pups to allow nursing and to provide warmth, pup retrieval, and increased aggression directed at intruders. If you expose nonpregnant female (or male) rats to pups, their most common reaction is to huddle far away from them in fear, since rats avoid new things (neophobia). However, if you expose adult female rats to pups every day, they soon begin to behave maternally.

Of course a new mother needs to act maternally as soon as her offspring arrive- not a week later. Hormones trigger the onset of maternal behavior in rats, and several methods of study (such as hormone removal and replacement therapy) have been used to investigate rat maternal behavior. A fast decline of blood concentrations of progesterone in late pregnancy (after sustained high concentrations of this hormone), in combination with high concentrations of estradiol (and probably prolactin and oxytocin), induces female rats to behave maternally almost immediately in the presence of pups. This pattern of hormones during the delivery of pups overrides the usual fear response of adult rats toward pups, and permits the onset of maternal behavior.

The medial preoptic area (of the hypothalamus) is critical for the expression of rat maternal behavior, and the amygdala appears to inhibit the expression of maternal behavior. The fearful response of adult rats towards pups is apparently mediated by chemosensory information, and lesions of the amygdala (or sensory pathways to the amygdala) allow the expression of maternal behavior. Hormones or sensitization likely act to disinhibit the amygdala, thus permitting the occurrence of maternal behavior. Although correlations have been established, direct evidence of brain structural changes in human mothers remains unspecified (Fleming & Gonzalez, 2009).

13.1.6.2 Maternal Aggression

Laboratory rats are usually docile, but mothers can be quite aggressive toward animals that venture too close to their litter. Progesterone appears to be the primary hormone that induces this maternal aggression in rodents, but species differences exist. The role of maternal aggression in women’s behavior has not been adequately described or tested.

13.1.6.3 Hormones and Human Maternal Behavior

A series of elegant experiments by Alison Fleming and her collaborators studied the endocrine correlates of human mothers' behavior and maternal attitudes, as expressed in self-report questionnaires. Responses such as patting, cuddling, or kissing the baby were called affectionate behaviors; talking, singing, or cooing to the baby were considered vocal behaviors. Both affectionate and vocal behaviors were considered approach behaviors. Basic caregiving activities, such as changing diapers and burping the infants, were also recorded. In these studies, no relationship between hormone concentrations and maternal responsiveness (as measured by attitude questionnaires) was found. For example, most women showed an increasing positive self-image during early pregnancy that dipped during the second half of pregnancy, but recovered after parturition (childbirth). A related dip in feelings of maternal engagement occurred during late pregnancy, but rebounded substantially after birth in most women



Figure 13.1.6: Although cortisol may not directly increase maternal behaviors, the next time your mom gives you a hug you know one hormone to thank.

However, when behavior (rather than questionnaire responses) was compared with hormone concentrations, a different story emerged. Blood plasma concentrations of cortisol were positively associated with approach behaviors. In other words, women who had high concentrations of blood cortisol (in samples obtained immediately before or after nursing) engaged in more physically affectionate behaviors (Figure 13.1.6) and talked more often to their babies than mothers with low cortisol concentrations. Additional analyses from this study revealed that the correlation was even greater for mothers who had reported positive maternal regard (feelings and attitudes) during gestation (pregnancy). Indeed, nearly half of the variation in maternal behavior among women could be accounted for by cortisol concentrations and positive maternal attitudes during pregnancy. Presumably, cortisol does not induce maternal behaviors directly, but it may act indirectly by increasing the mother's general level of arousal, thus increasing her responsiveness to infant-generated cues. New mothers with high cortisol concentrations were also more attracted to their infant's odors, were superior in identifying their infants, and generally found cues from infants highly appealing (Fleming, Steiner, & Corter, 1997).

13.1.7 Summary

Hormones are inextricably linked to the development and maturation of reproductive anatomy (both prenatally and during puberty), as well as the promotion and maintenance of adult reproductive functions. The effects of steroid sex hormones are typically characterized as organizational versus activational. Organizational effects result in permanent changes that usually occur early in development, such as the prenatal development of primary sex characteristics (differences in male and female bodies that are present at birth). Activational effects are usually temporary and occur throughout life, dependent on specific conditions.

The main categories of sex hormones are androgens (more prevalent in biological males, e.g. testosterone), and estrogens (more prevalent in biological females, e.g. estradiol). All individuals have both androgens and estrogens, but the relative proportion of the hormones present varies, usually correlated with biological sex. Testosterone is secreted by the testes in males and in small amounts by the ovaries in females. A small amount of testosterone is also secreted by the adrenal glands in both sexes. Estrogens are secreted by the ovaries in females and by fat cells in both sexes.

The interaction between hormones and behavior is bidirectional: hormones can influence behavior, and behavior can sometimes influence hormone concentrations. Hormones do not cause behavioral changes, but they influence the components that interact to produce behavior- sensory systems, the central nervous system, and muscles and glands. In this manner, specific stimuli are more likely to elicit certain responses in the appropriate behavioral or social context. For behavioral effects on hormones, in animal models, losing a fight results in decreased blood testosterone levels. Comparable results have been reported in humans.

Research on rats suggests that the motivation to engage in sexual behavior is separate from the ability to engage in sexual behavior. The hypothalamus plays an important role in motivated behaviors, including sex. In humans, testosterone maintains libido (sex drive) in both males and females.

Although the glans of the clitoris and penis are known to be associated with pleasure, extensive regions of the brain and brainstem are also activated when a person experiences pleasure. Erogenous zones are particularly sensitive areas of skin, which vary across individuals.

The hypothalamus is important for sexual functioning, particularly because it controls the pituitary gland. Hormones related to sexual function secreted by the pituitary gland include follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin from the anterior pituitary, and oxytocin from the posterior pituitary. FSH and LH are responsible for ovulation in females and

sperm production in males. Prolactin and oxytocin stimulate lactation. Oxytocin causes rhythmic contractions in the uterus and penis (associated with orgasm), as well as uterine contractions during childbirth. Oxytocin is also believed to be involved in maintaining close relationships.

Hormones trigger the onset of maternal behavior in rats. A fast decline of progesterone in late pregnancy, combined with high concentrations of estradiol, induce female rats to behave maternally (overriding the usual fear response of adult rats toward pups). The medial preoptic area is critical for the expression of rat maternal behavior, and the amygdala appears to inhibit the expression of maternal behavior. Progesterone appears to be the primary hormone that induces maternal aggression (in rats) toward animals that venture too close to their litter.

In human studies, no relationship between hormone concentrations and maternal responsiveness (on attitude questionnaires) was found. However, women who had high concentrations of blood cortisol engaged in more physically affectionate behaviors and talked more often to their babies than mothers with low cortisol concentrations. The correlation was even greater for mothers who had reported positive maternal feelings and attitudes during pregnancy.

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13.1.9 Additional Resources

Video: Endocrinology Video (Playlist) - This YouTube playlist contains many helpful videos on the biology of hormones, including reproduction and behavior. This would be a helpful resource for students struggling with hormone synthesis, reproduction, regulation of biological functions, and signaling pathways.

https://www.youtube.com/playlist?list=PLqTetbgey0aemiTfD8QkMsSUq8hQzv-vA

Video: Paul Zak: Trust, morality - and oxytocin- This Ted talk explores the roles of oxytocin in the body. Paul Zak discusses biological functions of oxytocin, like lactation, as well as potential behavioral functions, like empathy.





Video: Sex Differentiation- This video discusses gonadal differentiation, including the role of androgens in the development of male features.



Vid rain Explained- This is a great video explaining the roles of hormones during puberty.





Web: Society for Behavioral Neuroendocrinology - This website contains resources on current news and research in the field of neuroendocrinology.

http://sbn.org/home.aspx

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3. Changes: Text (and images) from above eight sources pieced together with some modifications, transitions and additional content added (particularly the sections: Sex and Hormones, Organizational and Activational Effects of Sex Hormones, and parts of Sex Hormones and Maturation) by Naomi I. Gribneau Bahm, PhD., Psychology Professor at Cosumnes River College, Sacramento, CA.
4. (particularly the Sex and Hormones section, Organizational and Activational Effects of Sex Hormones section, and part of the Sex Hormones and Maturation section)

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13.2: Sexual Development, Anatomy and Physiology

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Describe the process of prenatal sexual differentiation in humans.
2. Identify male and female reproductive structures that originate from homologous embryonic tissues versus those that are formed from separate (Wolffian and Müllerian) duct systems.
3. Identify the functions of the main reproductive structures for both males and females.
4. Understand the basic events occurring in the ovaries and uterus during the human menstrual cycle.
5. Explain the four phases in the human sexual response cycle (Masters and Johnson).

13.2.1 Overview

This section covers development of the male and female reproductive systems (including prenatal sex differentiation, homologous structures and reproductive ducts, and sexual maturation during puberty), and adult sexual anatomy and physiology (including the male reproductive system, the female reproductive system, the menstrual cycle, and the sexual response cycle.

13.2.2 Development of the Reproductive Systems

The **reproductive system** is the human organ system responsible for the production of gametes (sperm or eggs), the meeting of gametes during fertilization, and the carrying of an embryo/fetus. The reproductive system is the only body system that differs substantially between individuals, typically divided into male and female forms (Figure 13.2.1), although there is actually a range of biological sex (see the differences of sexual development section). Many embryonic structures that will develop into the reproductive system start out the same in males and females, but by birth, the reproductive systems have differentiated. This section will describe how male and female reproductive structures typically form during development and the role of several hormones.

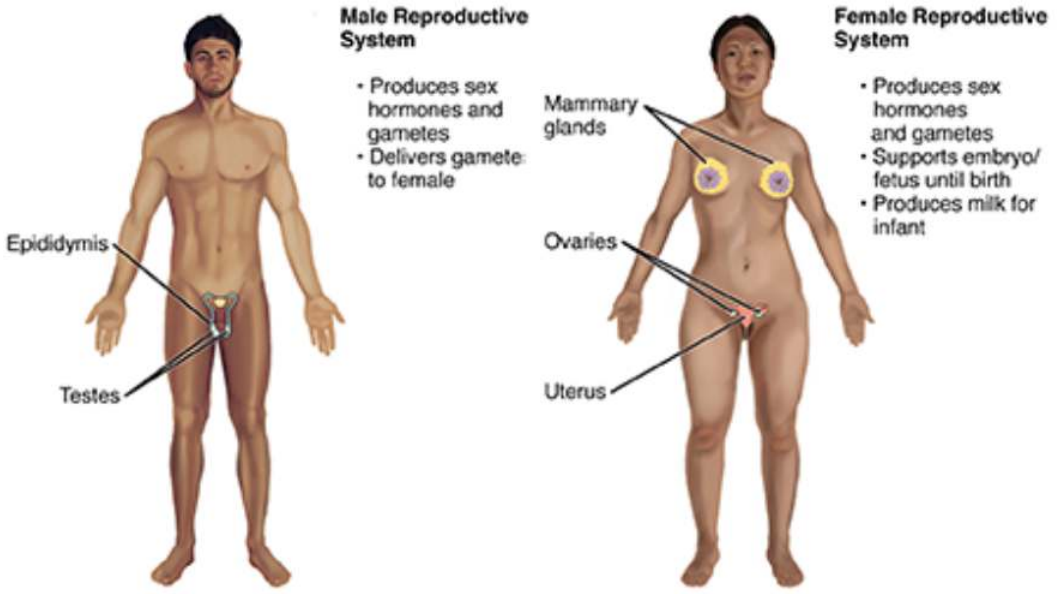


Figure 13.2.1: Reproductive Systems in the Human Male and Female. Both systems produce sex hormones and gametes. The male reproductive system additionally delivers gametes to the female; the epididymis and testes are labeled. The female reproductive system additionally supports an embryo/fetus until birth and produces milk for the infant; the mammary glands, ovaries, and uterus are labeled.

The **gonads** (the testes in males and the ovaries in females) produce gametes (sperm in males and eggs in females). A **gamete** is a haploid cell- a cell that contains one full set of chromosomes, or half the number needed to create a new individual. When two

haploid gametes combine during fertilization, they form a single diploid cell, which now contains two full sets of chromosomes (the necessary number to create a new individual) and is called a zygote (fertilized egg). In mammals, the ovum always contains an X chromosome, which can be fertilized by a sperm bearing either an X or a Y chromosome; this process is called sex determination. XX is the chromosomal sex of a female mammal and XY is the chromosomal sex of a male mammal.

Besides producing gametes, the gonads also produce sex hormones. **Sex hormones**, such as androgens and estrogens, are endocrine hormones that control the development of sex organs before birth, sexual maturation at puberty, and reproduction once sexual maturation has occurred. Other reproductive system organs have various functions, such as maturing gametes, delivering gametes to the site of fertilization, and providing an environment for the development and growth of offspring.

13.2.2.1 Prenatal Sex Differentiation

The process of becoming female or male is called sexual differentiation. Although both the X and the Y chromosomes are called sex chromosomes, only the Y chromosome contains genes that determine sex. A single gene on the Y chromosome, called SRY (for "sex-determining region Y gene"; Figure 13.2.2), triggers male development in the embryo. Without a Y chromosome, the embryo develops a female body plan, so you can think of a female as the default sex of the human species (as is the case for all mammals).

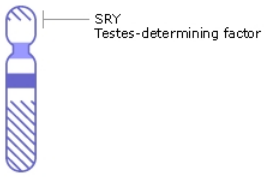


Figure 13.2.2: The SRY gene on the short arm of the Y chromosome causes the undifferentiated gonads of an embryo to develop into testes. Otherwise, the gonads develop into ovaries.

The gonads of the embryo are initially undifferentiated, meaning that they are indeterminate- identical in XX and XY embryos- and able to become either testes or ovaries. Starting around the sixth week after conception in genetically male (XY) embryos, the SRY gene initiates the production of a protein called testes determining factor. Testes determining factor causes the undifferentiated gonads to develop into testes. The testes secrete hormones — including testosterone — that trigger other changes in the developing offspring (now called a fetus), causing it to develop a complete male reproductive system. Without a Y chromosome, an embryo will develop ovaries that will then produce estrogens. Estrogens, in turn, enable the formation of the other organs of a female reproductive system.

13.2.2.2 Homologous Structures and Reproductive Ducts

Undifferentiated embryonic tissues develop into different structures in male and female fetuses. Structures that arise from the same tissues in males and females are called **homologous structures**. The testes and ovaries, for example, are homologous structures that develop from the undifferentiated gonads of the embryo. Likewise, the penis and clitoris are homologous structures that develop from the same embryonic tissues, as are the scrotum and the skin folds of the labia majora. The formation of typical male external anatomy (the penis and scrotum) requires the conversion of testosterone into a more potent androgen called dihydrotestosterone, whereas the formation of typical female external anatomy (the clitoris and the labia) does not require hormones. In this manner, the same embryonic tissue develops into one structure or another in a given individual, or occasionally forms a structure that is intermediate between the typical male or female form.

Not all tissues in the prenatal reproductive tract have the potential to develop into either male or female forms. The internal reproductive structures (for example the uterus, uterine tubes, and part of the vagina in females; and the epididymis, vas deferens, and seminal vesicles in males) form from one of two rudimentary duct systems in the embryo. For full reproductive function in the adult, one set of these ducts must develop properly, and the other must degrade. In males, cells in the testes secrete **Müllerian inhibiting substance**, which causes the **Müllerian duct** (the female duct) to degenerate. At the same time, testosterone secretion stimulates growth of the male tract, the **Wolffian duct**. Without Müllerian inhibiting substance, the Müllerian duct will develop; without testosterone, the Wolffian duct will degrade. Thus, the developing offspring will be female (Figure 13.2.3), following the default female body form.

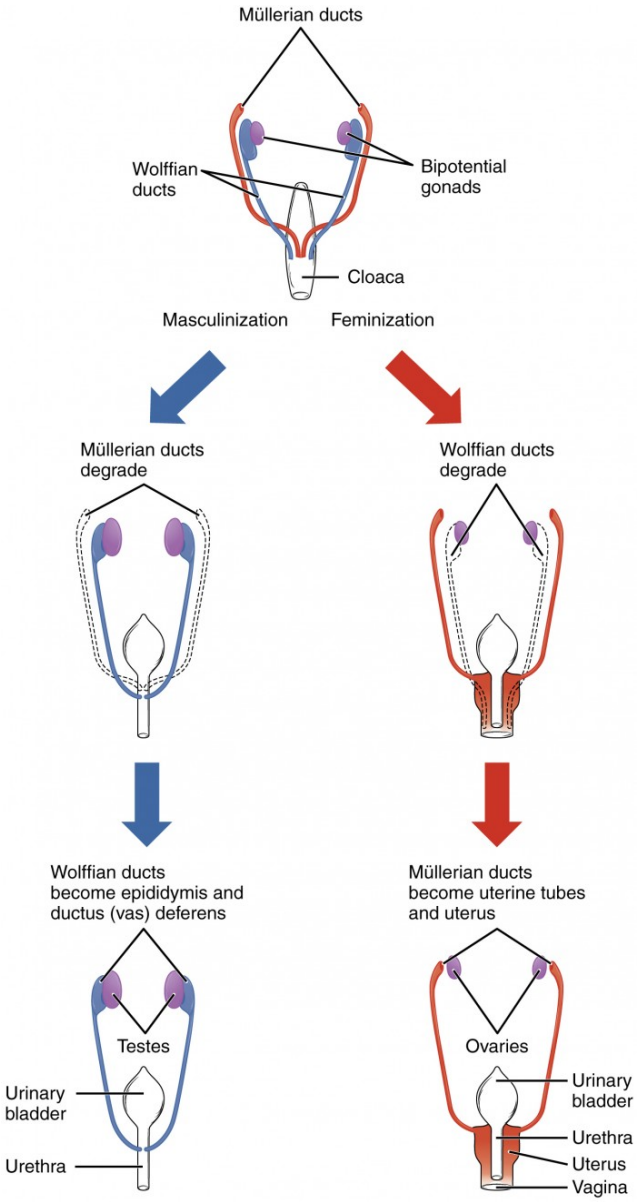


Figure 13.2.3: Differentiation of the male and female reproductive systems occurs during the fetal period of development. Initially, the cloaca, bipotential gonads, and both Wolffian and Mullerian ducts are present. In both sexes, the cloaca becomes the urinary bladder and urethra.With masculinization (shown on the left), the Mullerian ducts degrade and the Wolffian ducts become the epididymis and the ductus (vas) deferens. The bipotential gonads become testes. With feminization (shown on the right), the Wolffian ducts degrade and the Mullerian ducts become the uterine tubes and the uterus. The bipotential gonads become ovaries.

13.2.2.3 Sexual Maturation during Puberty

Puberty is a *period of rapid growth and sexual maturation*. These changes typically begin sometime between the ages of eight and fourteen, and start with an overall physical growth spurt, often most noticeable in the adolescent's increased height. Generally, girls begin puberty at around ten years of age and boys begin approximately two years later. Pubertal changes usually take around three to four years to complete.

Typically, the physical growth spurt is followed by the development of sexual maturity. Changes in the primary sexual characteristics (reproductive organs) in males includes growth of the testes, penis, and scrotum, and in females the growth and maturation of the ovaries, uterus and external genitalia (vulva). Important signals of sexual maturity include **spermarche** *or first ejaculation of semen* in males, and **menarche** *or the first menstrual period* in females. Stress and higher percentage of body fat are correlated with menstruation at younger ages.

Secondary sexual characteristics *are visible physical changes not directly linked to reproduction, but that signal sexual maturity*. For males this includes broader shoulders and a lower voice as the larynx grows. Body hair becomes coarser and darker, and hair growth occurs in the pubic area, under the arms and on the face. For females breast development occurs around age 10, although full development takes several years. Hips broaden and pubic and underarm hair develops and also becomes darker and coarser.

13.2.3 Adult Sexual Anatomy and Physiology

13.2.3.1 The Male Reproductive System

The main structures of the male reproductive system are external to the body (Figure 13.2.4). The two testes (singular, testis) hang between the thighs in a sac of skin called the scrotum. The testes produce both sperm and testosterone. Testosterone production is under the control of luteinizing hormone (LH) from the pituitary gland, which stimulates cells in the testes to secrete testosterone. Both follicle stimulating hormone (FSH) from the pituitary gland and testosterone are needed for normal spermatogenesis to be maintained in the testes. Additionally, testosterone maintains libido (sex drive) and plays a role in erection, allowing sperm to be deposited within the female reproductive tract. Testosterone is necessary for the proper functioning of the prostate gland, and is also important for muscle development and bone growth.

Resting atop each testis is a coiled structure called the epididymis (plural, epididymes). The function of the epididymes is to mature and store sperm. The penis is a tubular organ that contains the urethra and has the ability to stiffen during sexual arousal. Sperm passes out of the body through the urethra during a sexual climax (orgasm). This release of sperm is called ejaculation.

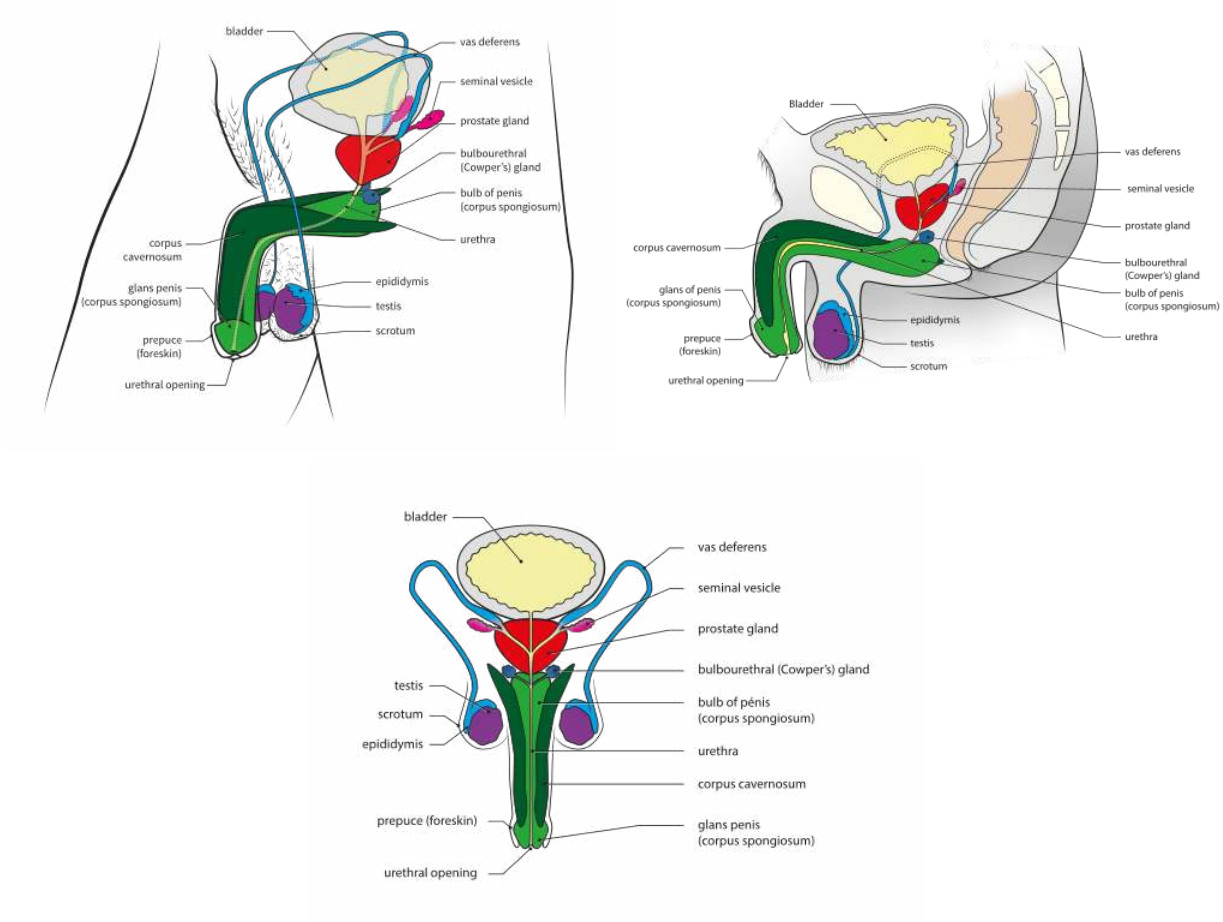


Figure 13.2.4: The main structures of the male reproductive system in 3D view, sagittal view, and frontal view. Note that structures that are homologous to female structures (originating from the same embryonic tissue, such as the testes) are color-coded to match the female reproductive system diagrams in Figure 13.2.5.

In addition to these external organs, there are several ducts and glands that are internal to the body. The ducts, which include the vas deferens (also called the ductus deferens), transport sperm from the epididymis to the urethra. The glands, which include the

prostate gland and seminal vesicles, produce fluids that become part of semen. Semen is the fluid that carries sperm through the urethra and out of the body. It contains substances that control pH and provide sperm with nutrients for energy.

13.2.3.2 The Female Reproductive System

The main structures of the female reproductive system are internal to the body (Figure 13.2.5). They include the paired ovaries, which are small, oval structures that produce eggs and secrete estrogens. The two uterine tubes (also known as Fallopian tubes or oviducts) start near the ovaries and end at the uterus. Their function is to transport eggs from the ovaries to the uterus. If fertilization of an egg occurs, it usually happens while it is traveling through the Fallopian tube. The uterus is a pear-shaped muscular organ that functions to carry a fetus until birth. It can expand greatly to accommodate a growing fetus, and its muscular walls can contract forcefully during labor to push the baby into the vagina. The vagina is a tubular tract connecting the uterus to the outside of the body. The vagina is where sperm are usually deposited during sexual intercourse (via ejaculation). The vagina is also called the birth canal because a baby travels through the vagina to leave the body during birth.

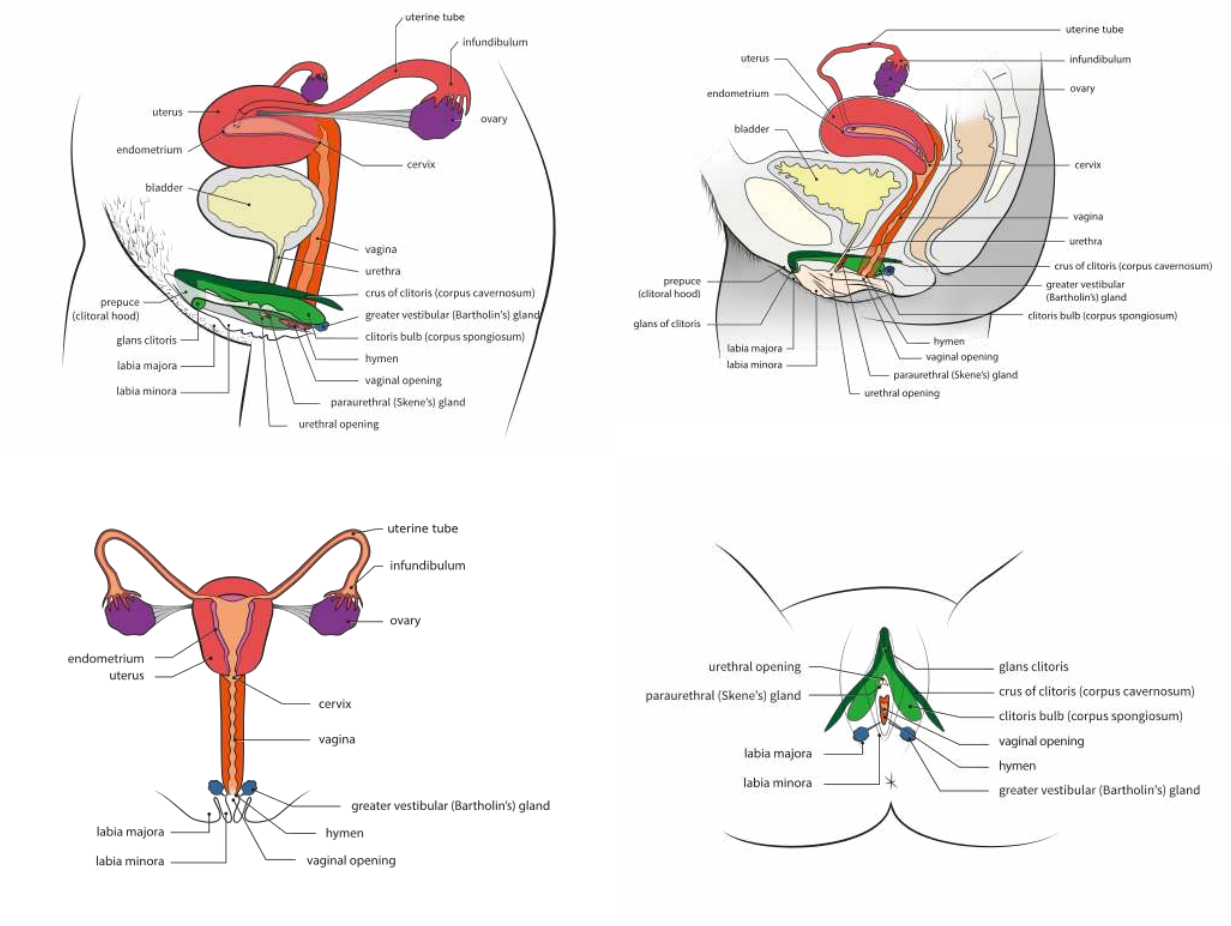


Figure 13.2.5: The main structures of the female reproductive system in 3D view, sagittal view, frontal view, and inferior view (between the legs). Note that structures that are homologous to male structures (originating from the same embryonic tissue, such as the ovaries) are color-coded to match the male reproductive system diagrams in Figure 13.2.4.

The external structures of the female reproductive system are referred to collectively as the vulva. The vulva includes the clitoris, which is homologous to the male penis (the erectile tissues of the penis and clitoris are colored dark green and light green in Figure 13.2.4 and Figure 13.2.5), and the two pairs of labia (singular, labium), which surround and protect the openings of the urethra and vagina.

13.2.3.3 The Menstrual Cycle

The **menstrual cycle** refers to natural changes that occur in the female reproductive system each month during the reproductive years. The cycle is necessary for the production of eggs and the preparation of the uterus for pregnancy. It involves changes in both

the ovaries and the uterus and is controlled by pituitary and ovarian hormones. Day 1 of the cycle is the first day of the menstrual period**,** when bleeding from the uterus begins as the built-up endometrium lining the uterus is shed. The endometrium builds up again during the remainder of the cycle, only to be shed again during the beginning of the next cycle if pregnancy does not occur. In the ovaries, the menstrual cycle includes the development of a follicle, ovulation of a secondary oocyte (the name given to an egg before maturation), and the degeneration of the follicle if pregnancy does not occur. Both uterine and ovarian changes during the menstrual cycle are generally divided into three phases, although the phases are not the same in the two organs.

13.2.3.3.1 Ovarian Cycle

The events of the menstrual cycle that take place in the ovaries make up the ovarian cycle. It consists of changes that occur in the follicles of one of the ovaries. The ovarian cycle is divided into the following three phases: 1) the follicular phase (several follicles begin maturing, but only one is selected to mature completely), 2) ovulation (the mature egg is released), and 3) the luteal phase (progesterone maintains the lining of the uterus for potential implantation of the fertilized egg).

Follicle-stimulating hormone (FSH), secreted by the pituitary gland, rises and causes several follicles to begin to mature. One maturing follicle becomes dominant and starts releasing estrogen. The resulting rising levels of estrogen prevent multiple follicles from fully developing; non-dominant follicles undergo atresia, or degeneration. The continued rise in estrogen triggers a luteinizing hormone (LH) surge from the pituitary gland, which in turn stimulates ovulation. During the luteal phase, progesterone is secreted by the corpus luteum (a structure formed from the remnants of the follicle that released the egg) until the end of the cycle, when the corpus luteum either degenerates (if the egg was not fertilized) or is maintained by the new pregnancy.

13.2.3.3.2 Uterine Cycle

The events of the menstrual cycle that take place in the uterus make up the uterine cycle. This cycle consists of changes that occur mainly in the endometrium, which is the layer of tissue that lines the uterus. The uterine cycle is divided into the following three phases: 1) menstruation (shedding of the unfertilized egg and the endometrium lining that has built up), 2) the proliferative phase (the lining of the uterus grows again), and 3) the secretory phase (endometrium is prepared to receive a fertilized egg).

The ovarian cycle, the uterine cycle, and the changes in hormone levels that occur during the menstrual cycle are illustrated in Figure 13.2.6. Note that the changes in the lining of the endometrium are illustrated in the part showing the uterine cycle phases.

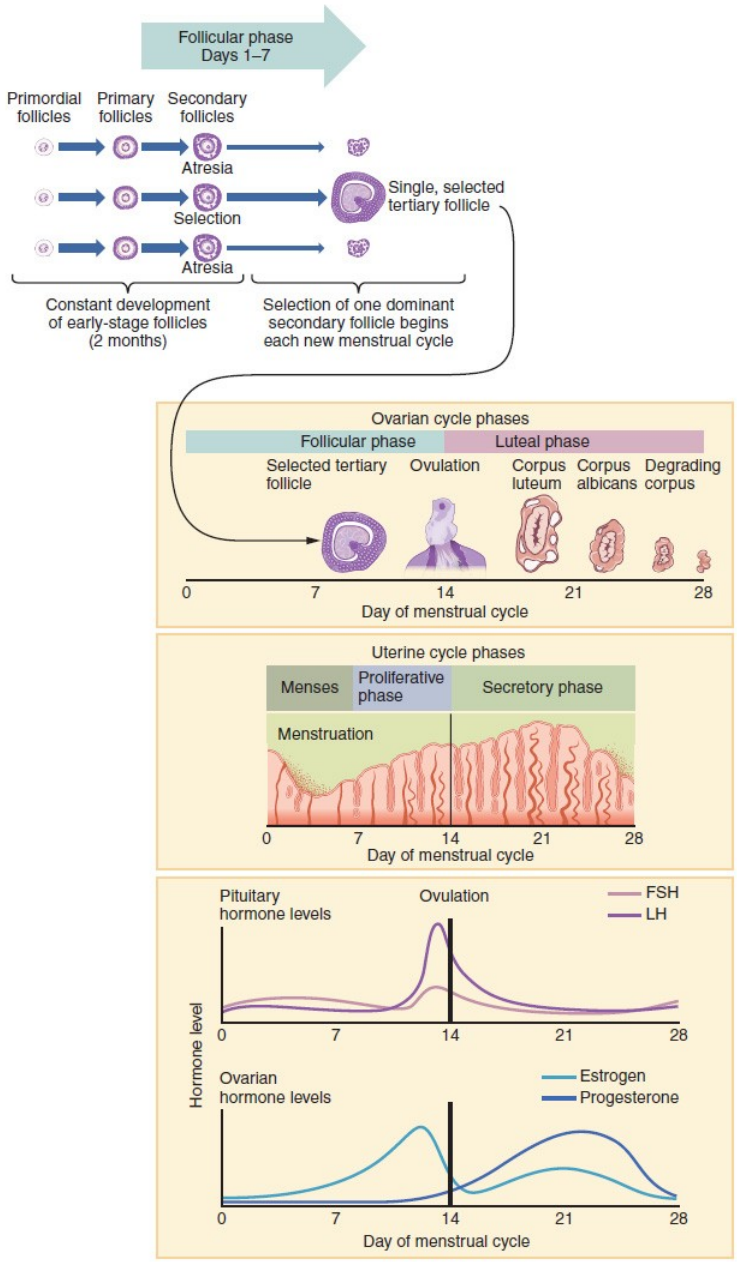


Figure 13.2.6:

The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge.

13.2.3.4 The Sexual Response Cycle

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. Masters and Johnson observed people having intercourse in a variety of positions, as well as people masturbating, manually or with the aid of a device. 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) were recorded. 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 (Masters & Johnson, 1966) into four phases that are fairly similar in men and women:

1. Excitement: Activation of the sympathetic branch of the autonomic nervous system defines the *excitement phase*; heart rate and breathing accelerates, along with increased blood flow to the penis, vaginal walls, clitoris, and nipples. Involuntary muscular movements (**myotonia**), such as facial grimaces, also occur during this phase.
2. Plateau: Blood flow, heart rate, and breathing intensify during the *plateau phase.* During this phase females experience an **orgasmic platform**—the outer third of the vaginal walls tightening—and males often exhibit a release of pre-ejaculatory fluid.
3. Orgasm: The shortest but most pleasurable phase is the *orgasm phase*. After reaching its climax, neuromuscular tension is released and the hormone **oxytocin** floods the bloodstream—facilitating emotional bonding. Although the rhythmic muscular contractions of an orgasm are temporally associated with ejaculation in males, orgasm and ejaculation are actually two separate physiological processes (and can thus occur independently).
4. Resolution: The body returns to a pre-aroused state in the *resolution phase*.

The final phase, resolution, is where the main differences between males and females occur. Males enter a **refractory period** of being unresponsive to sexual stimuli. The length of this period depends on age, frequency of recent sexual behavior, level of intimacy with a partner, and novelty. Because females do not have a refractory period, they have a greater potential—physiologically—of having multiple orgasms. Ironically, females are also more likely to "fake" having orgasms (Opperman et al., 2014). As such, whereas the graph for the male sexual response cycle shows only the most common progression through the four phases including orgasm (with a potential partial second cycle starting after the refractory period ends), the graph for the female sexual response cycle shows three alternative patterns- A. progression through all four stages with multiple orgasms, B. prolonged time in the plateau phase with no orgasm, and C. progression through all four stages with a single orgasm (Figure 13.2.7).

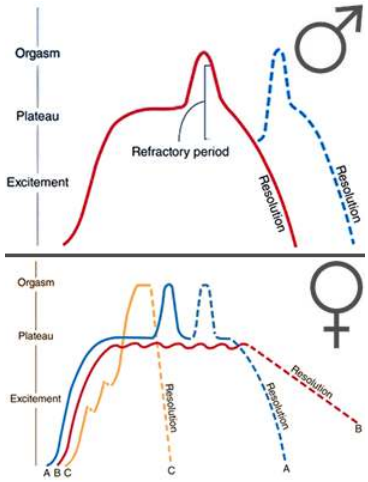


Figure 13.2.7:

Diagram of the common human sexual response cycles as described by Masters and Johnson

Of interest to note, the sexual response cycle is a universal response to sexual stimuli, and occurs regardless of the type of sexual behavior—whether the behavior is masturbation; romantic kissing; or oral, vaginal, or anal sex (Masters & Johnson, 1966). Further, a partner (of any sex/gender) or environmental object is sufficient, but not necessary, for the sexual response cycle to occur.

Feature: Human Biology in the News

Lung, heart, kidney, and other organ transplants have become relatively commonplace, so when they occur, they are unlikely to make the news. However, when America's first penis transplant took place, it was considered very newsworthy.

In 2016, Massachusetts General Hospital in Boston announced that a team of its surgeons had performed the first penis transplant in the United States. The patient who received the donated penis was a 64-year-old cancer patient. During the 15-hour procedure, the intricate network of nerves and blood vessels of the donor penis were connected with those of the penis recipient. The surgery went well, but doctors reported it would be a few weeks until they would know if normal urination would be possible, and even longer before they would know if sexual functioning would be possible. At the time that news of the surgery was reported in the media, the patient had not shown any signs of rejecting the donated organ. The surgeons also reported they were hopeful that such transplants would become relatively common, and that patient populations would expand to include wounded warriors and transgender males seeking to transition.

> The 2016 Massachusetts operation was not the first penis transplant ever undertaken. The world's first successful penis transplant was actually performed in 2014 in Cape Town, South Africa. A young man who had lost his penis from complications of a botched circumcision at age 18 was given a donor penis three years later. That surgery lasted nine hours and was highly successful. The young man made a full recovery and regained both urinary and sexual functions in the transplanted organ.
>
> In 2005, a man in China also received a donated penis in a technically successful operation. However, the patient asked doctors to reverse the procedure just two weeks later, because of psychological problems associated with the transplanted organ for both himself and his wife.

13.2.4 Summary

The reproductive system is responsible for the production of gametes (sperm or eggs), the meeting of gametes during fertilization, and the carrying of an embryo/fetus. The gonads (the testes in males and the ovaries in females) produce gametes and sex hormones. Sex hormones (androgens and estrogens) control the development of sex organs before birth, sexual maturation at puberty, and reproduction once sexual maturation has occurred.

Sexual differentiation is the process of becoming male or female. A gene on the Y chromosome called SRY is critical for stimulating testis development and subsequently the development of male reproductive structures. Without a Y chromosome, the embryo develops a female body plan.

Undifferentiated embryonic tissues develop into different homologous structures in male and female fetuses, such as the testes and ovaries, or the penis and clitoris. However, the tissue that forms the internal reproductive structures stems from ducts that will develop into only male (Wolffian) or only female (Müllerian) structures. To be able to reproduce as an adult, one of these systems must develop properly and the other must degrade.

Further development of the reproductive systems occurs at puberty. The increase in sex steroid hormones leads to maturation of the gonads and other reproductive organs. Important signals of sexual maturity include spermarche (first ejaculation of semen) in males, and menarche (first menstrual period) in females. Increases in sex steroid hormones also lead to the development of secondary sex characteristics such as breast development in girls and facial hair and larynx growth in boys.

The main male reproductive structures are external to the body: the penis and the paired testes. The penis contains the urethra and is able to stiffen during sexual arousal. Sperm passes out of the body through the urethra during orgasm, called ejaculation. The testes produce sperm and testosterone, and are located in the scrotum. Luteinizing hormone (LH) stimulates cells in the testes to secrete testosterone. Both follicle stimulating hormone (FSH) and testosterone are needed for spermatogenesis. Additionally, testosterone maintains libido (sex drive), plays a role in erection, is necessary for prostate gland function, and is important for muscle development and bone growth. Internal ducts and glands include the vas deferens (which transports sperm from the epididymis to the urethra), the prostate gland and the seminal vesicles (which produce fluids that become part of semen).

The external structures of the female reproductive system are referred to as the vulva: the clitoris and the two pairs of labia surrounding and protecting the openings of the urethra and vagina. The main female reproductive structures are internal to the body and include the paired ovaries (which produce eggs and secrete estrogens), the two Fallopian tubes (which transport eggs from the ovaries to the uterus), the uterus (a muscular organ that carries a fetus until birth), and the vagina. The vagina is a tubular tract connecting the uterus to the outside of the body. Sperm are usually deposited in the vagina during sexual intercourse (via ejaculation), and a baby travels through the vagina (also called the birth canal) to leave the body.

The menstrual cycle in females is necessary for the production of eggs and the preparation of the uterus for pregnancy. It involves changes in both the ovaries and the uterus and is controlled by pituitary and ovarian hormones. The ovarian cycle is divided into the follicular phase (several follicles begin maturing, but only one is selected to mature completely), ovulation (the mature egg is released), and the luteal phase (progesterone maintains the lining of the uterus for potential implantation of the fertilized egg). The uterine cycle is divided into menstruation (shedding of the unfertilized egg and the endometrium lining that has built up), the proliferative phase (the lining of the uterus grows again), and the secretory phase (endometrium is prepared to receive a fertilized egg).

Masters and Johnson (1966) divided the sexual response cycle into four phases that are fairly similar in men and women: excitement (heart rate and breathing accelerates, increased blood flow to the penis, vaginal walls, clitoris, and nipples), plateau (blood flow, heart rate, and breathing intensify; females experience an orgasmic platform—the outer third of the vaginal walls tightening—and males often exhibit a release of pre-ejaculatory fluid), orgasm (shortest but most pleasurable phase), and resolution

(the body returns to a pre-aroused state). The main differences between males and females occur during resolution. Males enter a refractory period of being unresponsive to sexual stimuli. Females do not have a refractory period, so they have a greater potential for having multiple orgasms.

13.2.5 References

Note: These are no references added to the content of this page. Refer to the text attributions to locate citations for articles from outside sources used.

13.2.6 Additional Resources

13.2.7 Attributions

Figures:

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13.3: Differences of Sexual Development

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Identify the basic characteristics of the most common sex chromosome abnormalities (Turner Syndrome and Klinefelter Syndrome).
2. Understand the term intersex and the various conditions it encompasses.
3. Explain the role of hormones in the development of anomalous sexual differentiation for XX individuals with congenital adrenal hyperplasia (CAH) and XY individuals with androgen insensitivity syndrome (AIS).
4. Explain how David Reimer's case challenged Dr. John Money's theory of psychosexual neutrality.

13.3.1 Overview

This section discusses some of the many ways in which sexual development can differ from typical XX/male and XY/female formats. Note that while the scientific literature on this topic typically labels these conditions "Disorders of Sexual Development (DSD)", we prefer to refer to them as "Differences of Sexual Development". Chromosomal abnormalities (such as Triple X syndrome, Turner syndrome, and Klinefelter syndrome), intersex conditions, anomalous female differentiation (such as congenital adrenal hyperplasia) and anomalous male sexual differentiation (such as 5α-reductase deficiency and androgen insensitivity syndrome) demonstrate some of the diverse variations of biological sex found in humans. The case of David Reimer illustrates that raising a typically-developed biological male (who lost his penis in infancy due to a circumcision accident) as a girl can fail catastrophically.

13.3.2 Chromosomal Abnormalities

13.3.2.1 Aneuploidy

As discussed in the chapter on genetics, a typical human individual has 22 pairs of autosomes ("self" chromosomes) and one pair of sex chromosomes (either XX for females or XY for males), resulting in a total of 46 chromosomes (Figure 13.3.1).

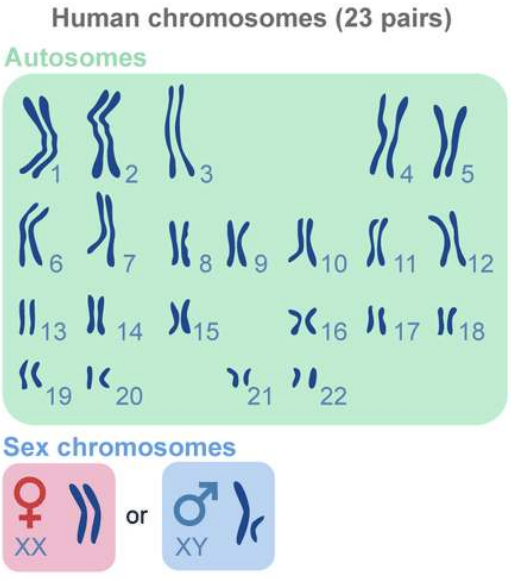


Figure 13.3.1: Humans have 23 pairs of chromosomes. Pairs 1-22 are autosomes. Females have two X chromosomes, and males have an X and a Y chromosome.

Sometimes errors occur during the formation of the gametes (eggs in females and sperm in males), resulting in missing chromosomes or extra chromosomes. When an individual inherits too many or two few chromosomes, it is called a **chromosomal**

abnormality. (Or, more specifically, **aneuploidy**- the presence of an abnormal number of chromosomes in a cell.) The most common cause of chromosomal abnormalities is older age of the mother. As a female ages, the immature eggs in her ovaries (which have been present since before birth, unlike the sperm cells in males) are more likely to suffer damage due to longer term exposure to environmental factors. Consequently, some gametes do not divide evenly when they are forming, and some eggs have more (or less) than 23 chromosomes. Often when the error includes one of the autosomes, the resulting zygote (fertilized egg) is not viable. In fact, it is believed that close to half of all zygotes have an abnormal number of chromosomes. Most of these zygotes fail to develop and are spontaneously aborted by the body of the mother (often without her knowledge that conception ever occurred).

One of the few chromosomal abnormalities that more commonly survives (to birth and decades beyond) is Down syndrome (trisomy 21- three copies of chromosome number 21). In addition to some degree of intellectual disability and characteristic facial features, affected individuals often have heart defects and other health problems. The overall occurrence of Down Syndrome is one in every 691 births, but it increases to one in every 300 births for women aged 35 and older.

Interestingly, chromosomal errors involving the sex chromosomes (the 23rd pair), called **sex chromosome aneuploidy**, are less lethal. The exception is having only a single Y chromosome- there are many important genes on the X chromosome, so a zygote with only one Y chromosome (and no X chromosome) will not survive. At least 1 in every 1,000 conceptions results in a variation of chromosomal sex beyond the typical XX or XY sets. Some of these variations include XXX (Figure 13.3.2), XYY, XXY, or even a single X (Dreger, 1998).



Figure 13.3.2: 9 year old girl with Triple X Syndrome.

Some individuals with atypical sex chromosomes may have unusual physical characteristics, such as being taller than average, having a thick neck, or being sterile (unable to reproduce); but in many cases, these individuals have no cognitive, physical, or sexual issues (Wisniewski et al., 2000). These sex-linked chromosomal disorders are briefly described in Table 13.3.1. It is even possible to have four or more sex chromosomes (XXXX, XXYY, XXXYY, etc.).

Table 13.3.1: Sex-Linked Chromosomal Disorders

Disorder	Sex Appearance & Fertility	Characteristics
Turner Syndrome (XO)	Female, but immature (infertile)	Affects cognitive functioning and sexual maturation; short stature may be noted.
Klinefelter Syndrome (XXY)	Male, may have some breast development (often infertile)	The Y chromosome stimulates the growth of male genitalia, but the additional X chromosome inhibits this development (may have low levels of testosterone).
Supermale Syndrome (XYY)	Male (usually normal fertility)	Few symptoms, which may include being taller than average, acne, and an increased risk of learning problems. Generally otherwise normal.
Triple X Syndrome (XXX)	Female (usually normal fertility)	May result in being taller than average, having learning difficulties, decreased muscle tone, seizures, and kidney problems.

The more common of these sex chromosome disorders are Turner Syndrome and Klinefelter Syndrome. **Turner Syndrome** occurs when one of the X chromosomes is missing or damaged and the resulting zygote has XO sex chromosomes. This occurs in 1 of every 2,500 live female births (Carroll, 2007) and affects the individual's cognitive functioning and sexual maturation. The external genitalia appear normal, but breasts and ovaries do not develop fully and the woman does not menstruate. Turner's syndrome also results in short stature and other physical characteristics, such as a webbed neck, shield-shaped thorax, and cardiac defects. Figure 13.3.3 illustrates the symptoms of Turner's syndrome and Figure 13.3.4 shows pictures of 18 individuals of Asian descent with Turner's syndrome.

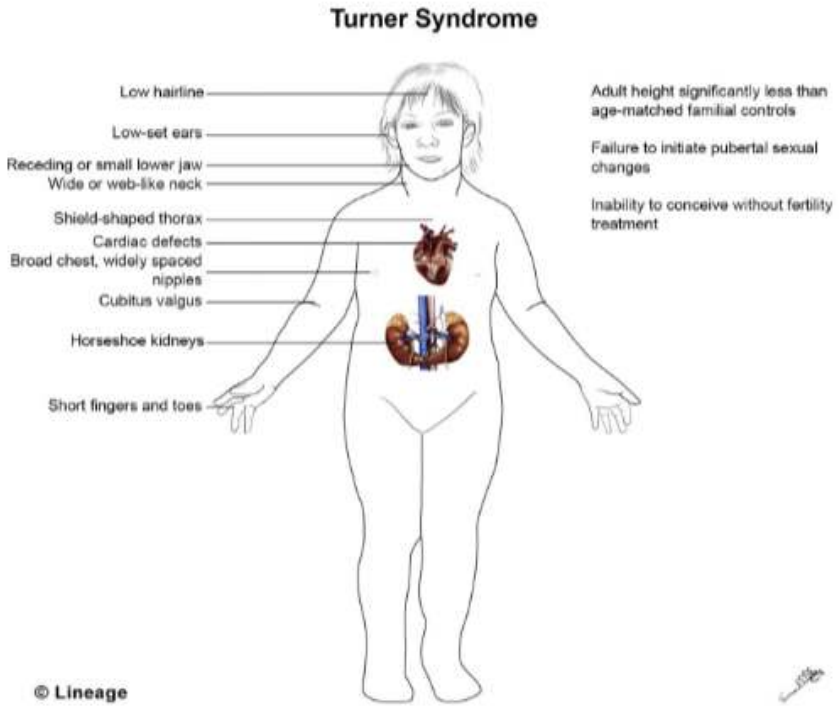


Figure 13.3.3: Symptoms of Turner's syndrome.



Figure 13.3.4: Eighteen Asian girls and women with Turner's syndrome.

Klinefelter Syndrome (XXY) *results when an extra X chromosome is present in the cells of a male* and occurs in 1 out of 700 live male births. The Y chromosome stimulates the growth of male genitalia, but the additional X chromosome inhibits this development. An individual with Klinefelter Syndrome often has some breast development, wide hips, infertility (this is the most common cause of infertility in males), small testicular size, and low levels of testosterone (National Institutes of Health, 2019).

Figure 13.3.5 illustrates the symptoms of Klinefelter's syndrome on the left and a 29 year old male with Klinefelter`s syndrome who is undergoing testosterone treatment on the right. Regular testosterone injections can promote strength and facial hair growth, build a more muscular body type, increase sexual desire, and enlarge the testes.

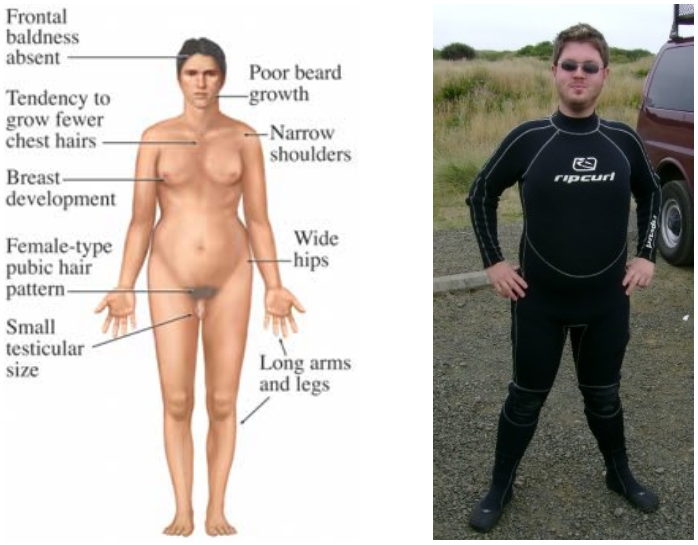


Figure 13.3.5: Symptoms of Klinefelter's syndrome [left] and 29 year old male undergoing testosterone treatment [right].

13.3.2.2 Other Chromosomal Alterations

As mentioned in Section 13.2, the SRY gene on the Y chromosome is the gene that directs development of the testes (typically leading to male reproductive structure development). Occasionally during sperm formation the SRY gene can cross over from the Y chromosome to the X chromosome. (Gene cross over regularly occurs between the 22 autosomes during the formation of gametes, but usually does *not* occur between the X and Y chromosomes, since they do not have the same genes.) If a sperm carrying a Y chromosome that has lost its SRY gene fertilizes an egg, although chromosomally genetically male (XY), the resulting embryo will not form testes and consequently will not develop male reproductive structures. (For mammals, female development is the "default" in the absence of hormones.) Likewise, if a sperm carrying an X chromosome that has an SRY gene attached to it fertilizes an egg, although chromosomally genetically female (XX), the resulting embryo will develop testes (which will then produce testosterone) and reproductive structures will develop in a male pattern. The individual will be infertile, however, since other genes on the Y chromosome are necessary for viable sperm production. This is another way in which abnormalities on the X or Y chromosomes (rather than having entire chromosomes that are extra or missing) produce variations in human sex characteristics.

13.3.3 Variations in Reproductive Structures

13.3.3.1 Intersex Conditions

In cases where hormones are not produced (or responded to) following the two most common patterns, a fetus may develop biological characteristics in between typical male and typical female structures. These people are considered to have intersex conditions. According to the Intersex Society of North America, intersex is a general term used for a variety of conditions in which a person is born with a reproductive or sexual anatomy that doesn’t fit the typical definitions of male or female. For example, a person might be born appearing to be male on the outside, but having mostly female-typical anatomy on the inside. Or a person may be born with genitals that seem to be intermediate between the usual male and female types—for example, a girl may be born with a notably large clitoris, or lacking a vaginal opening, or a boy may be born with a micropenis, or with a scrotum that is divided so that it has formed more like labia. Some people have mosaic genetics, meaning that two separate sets of chromosomes merged into one individual early in embryonic development. Any given body cell will contain one set or the other, and if all cells have either XX chromosomes or XY chromosomes, the condition may never even be detected. However, if some of their cells have XX chromosomes and some of them have XY chromosomes, separate areas of the body may have developed differently as a result. For example, a person may have an ovary on one side of the body and a testis on the other side. This is the true meaning of the word "hermaphrodite"- having both male and female gonadal tissue in the same body. (It is also possible to have a mixture of ovarian and testicular tissue in the gonads.) The intersex conditions discussed below are sometimes called "pseudohermaphrodites"- having something similar to both male and female anatomical structures in the same body (Figure 13.3.6).



Figure 13.3.6: Wax figure of human intersex genitalia from the Panoptikum House of Wax, Hamburg.

Though intersex is commonly thought of as an inborn condition, intersex anatomy isn't always apparent at birth. Some intersex traits are not recognizable until puberty or later in life (interACT 2021), or never even realized at all. Sometimes a person isn't found to have intersex anatomy until they reach the age of puberty, or find themselves to be infertile as an adult, or die of old age and are autopsied. Some people live and die with intersex anatomy without anyone (including themselves) ever knowing. Which variations of sexual anatomy count as intersex? In practice, different people have different answers to that question. That's not surprising, because intersex isn't a discrete category. Nature presents us with a spectrum of sexual anatomy. Breasts, penises, clitorises, scrotums, labia, gonads—all of these vary in size and shape and morphology. However, in human cultures, sex categories generally get simplified into male or female, sometimes with "intersex", "third sex" or "two spirit" included as an "other" option.

So nature doesn't determine where the category of "male" ends and the category of "intersex" begins, or where the category of "intersex" ends and the category of "female" begins. Humans decide. Humans (typically doctors today, at least in Western cultures) decide how small a penis has to be, or how unusual a combination of parts has to be, before it counts as intersex. Humans decide whether a person with XXY chromosomes or XY chromosomes and androgen insensitivity will count as intersex. Doctors' opinions about what should count as intersex vary substantially. Some think you have to have "ambiguous genitalia" to count as intersex, even if your inside is mostly of one sex and your outside is mostly of another. Some think your brain has to be exposed to an unusual mix of hormones prenatally to count as intersex—so that even if you're born with atypical genitalia, you're not intersex unless your brain experienced atypical development. And some think you have to have both ovarian and testicular tissue (be a true hermaphrodite- very rare!) to count as intersex. Intersex and transgender (having a gender identity that does not match your assigned birth sex) are not interchangeable terms; many transgender people have no intersex traits, and many intersex people do not consider themselves transgender.

According to the Intersex Society of North America, it is up to the individual to decide if they "count" as intersex. However, since some forms of intersex signal underlying metabolic concerns, a person who thinks they might be intersex should seek a diagnosis and find out if they need professional healthcare. Everyone, regardless of their sexual anatomy, should be free of shame, secrecy, and unwanted genital surgeries, even if someone else believes they have non-standard sexual anatomy. It used to be standard practice to surgically alter any newborn who didn't quite fit to the typical "male" or "female" body pattern, which often meant attempting to make the child look more like a typical girl (Figure 13.3.7). Although that is much easier surgically, gender identity confusion, loss of sexual sensation, and possibly unsatisfactory future sexual relationships are unfortunate possible outcomes. Current recommendations are to simply leave the child alone and see where development takes them, being prepared for any possible combinations of gender expression and sexual orientation. If desired, the individual can choose genital reconstruction surgery for themselves when they are old enough to understand and consent to the procedure.

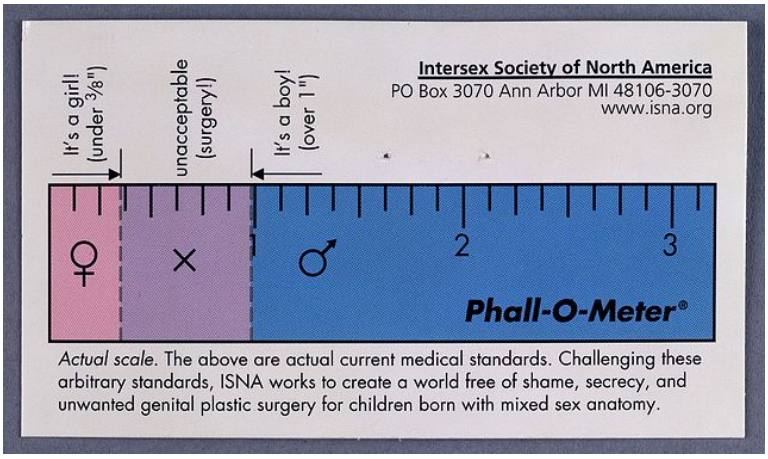


Figure 13.3.7: Phall-O-Meter, a ruler used to determine when to perform genital surgery on a newborn baby.

13.3.3.2 Anomalous Female Sexual Differentiation

By studying individuals who do not neatly fall into the dichotic boxes of female or male and for whom the process of sexual differentiation is atypical, behavioral endocrinologists glean hints about the process of typical sexual differentiation. Prenatal exposure to androgens is the most common cause of anomalous sexual differentiation among females. The source of androgen may be internal (e.g., secreted by the adrenal glands- endocrine glands located on top of the kidneys) or external (e.g., exposure to environmental estrogens). One case of prenatal exposure to internal androgens is congenital adrenal hyperplasia (CAH). CAH develops when an enzyme needed to produce cortisol is defective or missing, resulting in abnormal hormonal feedback which leads to excessive production of androgens by the adrenal cortex. In a female (XX) fetus, the elevated androgen levels caused by CAH result in varying degrees of masculinization of the external genitalia. As a result, the baby's sex may appear ambiguous or may even be mistaken as male. CAH is the most common cause of intersex conditions.

Although the effects of CAH on anatomical development are more noticeable in biological females, males can also inherit CAH. If a male (XY) fetus has CAH, his prenatal body development is similar to other males. However, he is likely to show precocious (early) sexual development as a result of the excessive androgens, such as enlargement of the penis and facial hair as a toddler (Jones & Lopez, 2006).

13.3.3.3 Anomalous Male Sexual Differentiation

Female mammals are considered the “neutral” sex; additional physiological steps are required for male differentiation, and more steps bring more possibilities for errors in differentiation. One example of male anomalous sexual differentiation (seen in Dominican Republic populations) is Guevedoces syndrome ("eggs at twelve") or 5α-reductase deficiency. Individuals with 5α-reductase deficiency are genetic males (XY) with testes that produce testosterone and cells that respond to androgens. However, because they lack the enzyme 5α-reductase, which converts testosterone to dihydrotestosterone, they are born with ambiguous genitalia and are raised as females. As mentioned in Section 13.2, dihydrotestosterone is required for typical prenatal development of the penis and scrotum. The high levels of testosterone occurring during puberty result in recognizable masculinization of the body. The "girls" become boys in dress and behavior and generally have heterosexual orientations (Jones & Lopez, 2006). In other words, these individuals readily transition to a masculine gender identity and are attracted to women.

Another example of male anomalous sexual differentiation is androgen insensitivity syndrome (AIS). Individuals with AIS lack receptors for androgens and develop as females. Androgen insensitivity syndrome is an example of an endocrine disorder where an endocrine gland secretes a typical amount of hormone, but target cells do not respond normally to it. Individuals with AIS are genetically male and have an X and a Y chromosome, but they develop and are raised as females. This is due to a mutation in the androgen receptor gene which is located on the X chromosome. The androgen hormone testosterone normally causes the testes to descend and typical male characteristics to develop.

People with AIS have the external sex characteristics of females; they are typically raised as females and have a female gender identity. Affected individuals have male gonads (testes) that are undescended, which means they are located in the pelvis or abdomen (instead of inside a scrotum hanging between the legs). However, these individuals have neither female nor male internal reproductive structures. During prenatal development, the testes produced Mullerian inhibiting substance, which caused the duct system that would form female internal sex organs to degenerate. Thus, these individuals do not have a uterus and do not menstruate. Without ovaries, Fallopian tubes, or a uterus, they are infertile and thus unable to conceive a child. Since the Wolffian

ducts (that form male internal sex organs) require testosterone to develop, they also degenerate prenatally. The testes did (and do) produce testosterone, but since the body cells lack receptors for androgens, male development does not occur.

13.3.4 Conclusion: Variations in Biological Sex

"Although male and female are the most typical biologically ordained poles of sexual identity, a vast number of gradations can be produced by normally occurring variations in the underlying hormonal control mechanisms that guide gender differentiation" (Panksepp, 2004, page 234). In humans, intersex individuals make up about two percent—more than 150 million people—of the world's population (Blackless et al., 2000). There are dozens of conditions that can lead to intersex anatomical variations, such as Androgen Insensitivity Syndrome and Turner's Syndrome (Lee et al., 2006). The term "syndrome" can be misleading; although intersex individuals may have physical limitations (e.g., about a third of Turner's individuals have heart defects; Matura et al., 2007), they otherwise lead relatively normal intellectual, personal, and social lives. In any case, intersex individuals demonstrate the diverse variations of biological sex.

13.3.5 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 "daughter" wasn't really behaving as most girls did, and by the time Brenda was nearing adolescence, it was painfully obvious to the family that Brenda was really having a hard time identifying as a female. In addition, Brenda was becoming increasingly reluctant to continue the visits with Dr. Money to the point that Brenda threatened suicide if she ever saw him again.

At that point, Janet and Ronald disclosed the true nature of Brenda's early childhood to their children. While initially shocked, Brenda reported that things made more sense now, and ultimately, decided to identify as a male, choosing the name David Reimer (after the biblical story of David and Goliath, the small boy who defeated a giant). Brian did not take the news as well and distanced himself from his twin brother.

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 Brian to go public with their experiences in an 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). In 2017, California became the first US State to add a non-binary option to birth certificates and several other states have followed in recent years.

13.3.6 Summary

Although the scientific literature regarding sexual development that differs from typical XX/male and XY/female formats refers to these conditions as "Disorders of Sexual Development (DSD)", we use "Differences of Sexual Development" in this chapter. It is called a chromosomal abnormality (or aneuploidy) when an individual inherits too many or two few chromosomes, typically as a result of an error during gamete (egg or sperm) formation in one (or both) of the parents. The most common aneuploidies of the sex chromosomes (X and Y) include Triple X syndrome (XXX), Supermale syndrome (XYY), Klinefelter syndrome (XXY), and Turner syndrome (XO). (A zygote that inherits only one Y chromosome and no X chromosome is spontaneously aborted.) While individuals with Klinefelter syndrome and Turner syndrome usually have visible anatomical differences and are often infertile, individuals with Triple X syndrome and Supermale syndrome may have no noticeable symptoms and usually have normal fertility. Another chromosomal alteration that affects sexual development is the transfer of the SRY gene from the Y chromosome to the X chromosome. A zygote with a Y chromosome that has lost its SRY gene will develop in the "default" female pattern (since the gonads will not develop as testes without an SRY gene), and a zygote with an X chromosome that has the SRY gene attached to it will develop in a male pattern, but will not be fertile.

When an individual develops biological characteristics that are in between typical male and typical female structures during prenatal development, they are said to have an intersex condition. There are many anatomical and physiological variations which fit under this umbrella term, and there is no current consensus on what "counts" as intersex and what does not. The Intersex Society of North America states that it is up to the individual to decide if they "count" as intersex, and that everyone, regardless of their sexual anatomy, should be free of shame, secrecy, and unwanted genital surgeries. While immediate surgery to try to create a more typical (usually female) appearance used to be common practice, current recommendations are to simply leave the intersex child alone and see where development takes them, being prepared for any possible combinations of gender expression and sexual orientation. Although intersex individuals may have physical limitations, they otherwise lead relatively normal intellectual, personal, and social lives.

Prenatal exposure to androgens is the most common cause of anomalous sexual differentiation among females. Congenital adrenal hyperplasia (CAH) develops when excessive production of androgens by the adrenal cortex occurs due to a missing enzyme. In a female (XX) fetus, the elevated androgen levels result in varying degrees of masculinization of the external genitalia. As a result, the baby's sex may appear ambiguous or may even be mistaken as male. CAH is the most common cause of intersex conditions.

Androgen insensitivity syndrome (AIS) and 5α-reductase deficiency are the most common causes of anomalous male (XY) sexual differentiation. People with AIS have the external sex characteristics of females and they are typically raised as females and have a female gender identity. However, they are infertile because they do not have female internal structures and their gonads are testes rather than ovaries. Although their testes produce testosterone, their body cells lack testosterone receptors and thus do not respond accordingly. Individuals with 5α-reductase deficiency are born with ambiguous genitalia and are raised as females. During puberty, high levels of testosterone result in recognizable masculinization of the body, and these individuals usually transition to male gender identities and are generally attracted to women.

David Reimer was one of a pair of identical twin boys born in Canada in August 1965 (birth name Bruce). As a result of a tragic circumcision accident in infancy, his penis was destroyed, and he was raised as "Brenda" under the advice of Dr. John Money, who erroneously believed that gender identity was exclusively determined by experiences during childhood development. By early adolescence, it was clear that Brenda was having difficulties identifying as a girl, and the truth was revealed to Brenda and "her" twin brother Brian by their parents. Brenda returned to a masculine gender identity, choosing the name David, and initially his life was going well. In the early 2000s, after discovering that Dr. Money was still touting the "experiment" as a success, the Reimer family went public with their story. Ultimately a number of unfortunate events (including the death of Brian due to a drug overdose) led to David's suicide in 2004. The truth of this story (which had originally been used to support decisions to reassign the gender of intersex children at birth) made the scientific and medical communities more cautious in dealing with cases that involve intersex children and how to deal with their unique circumstances.

13.3.7 References

Note: These references are specifically those added to the content of this page by Naomi Bahm and do not include citations from the outside sources used. Refer to the text attributions to locate citations for articles from other sources.

Jones, R.E. & Lopez, K.H. (2006) *Human Reproductive Biology, 3rd edition*. Academic Press.

Panksepp, J. (2004). *Affective neuroscience: The foundations of human and animal emotions*; *Chapter 12: The varieties of love and lust: Neural control of sexuality*. Oxford University Press.

13.3.8 Additional Resources

Intersex- Video link from Wakim & Grewal textbook: https://youtu.be/jhHGCvMlrb0

Websites for specific conditions:

- XO: https://rarediseases.org/rare-diseas...rner-syndrome/
- XXY: https://rarediseases.org/rare-diseas...lter-syndrome/
- XXX: https://rarediseases.org/rare-diseases/trisomy-x/
- XYY:
  - https://rarediseases.org/rare-diseases/xyy-syndrome/
  - http://www.pathguy.com/xyy.html
  - https://healthjade.net/xyy-syndrome/
  - https://www.rarechromo.org/media/inf...XYY%20FTNW.pdf
- AIS: https://rarediseases.org/gard-rare-d...vity-syndrome/
- CAH: https://rarediseases.org/rare-diseas...l-hyperplasia/
- Guevodoces:
  - https://rarediseases.org/gard-rare-d...se-deficiency/
  - https://www.bbc.com/news/magazine-34290981

Intersex Society of North America: https://isna.org/

13.3.9 Attributions

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13.4: Gender

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Distinguish between sex, gender, and sexual orientation
2. Describe gender variations recognized in some cultures

13.4.1 Overview

This section begins by explaining the difference between sex, gender, and sexual orientation. The terms cisgender and transgender are introduced, and gender variations across cultures are explored. Finally, the role of hormones in transgender treatment and the scientific and societal understanding of gender variations is addressed.

13.4.2 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 often birth-date. Additionally, applications usually ask for your sex or gender. The terms “sex” and “gender” are commonly used interchangeably. However, these terms are distinct from one another. Sex describes means of biological reproduction. Sex includes sexual organs, such as ovaries- defining biological reproduction as a female- or testes- defining biological reproduction as a male. As detailed in the section on differences of sexual development, biological sex is not as easily defined or determined as you might expect.

By contrast, the term gender describes psychological (gender identity) and sociological (gender role) representations of biological sex. 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 (or lack thereof) to others. Within the context of sexual orientation, sexual attraction refers to a person’s capacity to arouse the sexual interest of another, or, conversely, the sexual interest one person feels toward another.

We live in an era when sex, gender, and sexual orientation are controversial religious and political issues. Some nations have laws against homosexuality, while others have laws protecting same-sex marriages. At a time when there seems to be little agreement among religious and political groups, it makes sense to wonder, “What is normal?” and, “Who decides?”

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 and the orientation of sexual behavior occur naturally throughout the animal kingdom. More than 65,000 animal species have intersex individuals (Figure 13.4.1), born with either an absence or some combination of male and female reproductive organs, sex hormones, or sex chromosomes (Jarne & Auld, 2006). More than 500 animal species engage in homosexual or bisexual behaviors (Lehrer, 2006), such as the Mallard ducks shown in Figure 13.4.2.



Figure 13.4.1: A rare intersexed two-spotted bumble bee.

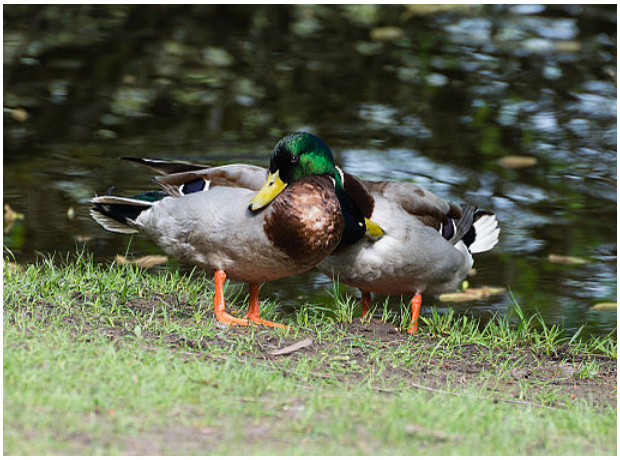


Figure 13.4.2: A male Mallard duck couple.

13.4.3 Gender

At an early age, we begin learning cultural norms for what is considered masculine and feminine. For example, American children may associate long hair or dresses with femininity. Later in life, as adults, we often conform to these norms by behaving in gender-specific ways: as men, we build houses; as women, we bake cookies (Marshall, 1989; Money et al., 1955; Weinraub et al., 1984).

Because cultures change over time, so too do ideas about gender. For example, European and American cultures today associate pink with femininity and blue with masculinity. However, less than a century ago, these same cultures were swaddling baby boys in pink, because of its masculine associations with "blood and war," and dressing little girls in blue, because of its feminine associations with the Virgin Mary (Kimmel, 1996).

13.4.3.1 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 (biological) sexes- biological males with masculine gender identities and biological females with feminine gender identities. In contrast, transgender individuals' gender identities do not correspond with their birth (biological) sexes. The Latin prefix "cis" 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 or gender role expression (TSER, 2022). As mentioned in the section on intersex conditions (people whose sex characteristics or anatomy differ from typical development), intersex and transgender are not interchangeable terms; many transgender people have no intersex traits, and many intersex people do not consider themselves transgender. Because gender is so deeply ingrained culturally, rates of transgender individuals vary widely around the world (Table 13.4.1).

Nation	Transgender people per 100,000
Sweden	.17
Poland	.26
Ireland	1.4
Japan	1.4
India	167
Thailand	333
United States	476
Malaysia	1,333

Table 13.4.1: Nations vary in the number of transgender people found 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).

13.4.3.2 Cultural Recognition of Gender Variations

Some cultures formally recognize the presence of people who do not conform to an expectation of biological sex matching gender identity. For example, "[some Native American tribes] believed that in addition to the prevailing variants of *man within man* and *woman within woman*, nature sometimes created a *man's mind within the body of a woman* and a *woman's mind within the body of a man*" (Panksepp, 2004, page 232). Transgender women are referred to as *fa'afafine* in the Samoan population (prevalence of five percent, Tan, 2016); *muxes* in Oaxaca, Mexico (as many as six percent of biological males, Stephen, 2002); *kathoey* (Figure 13.4.3) in Thailand; and *hijras* (Figure 13.4.3) in Pakistan, India, Nepal, and Bangladesh. Hijiras are recognized by their governments as a third gender (Pasquesoone, 2014).



Figure 13.4.3: Hjira dancer in Nepal and kathoey performers at a cabaret in Pattaya, Thailand.

Although incidence rates of transgender individuals differ significantly between cultures, transgender women (TGW)- whose birth sex was male- are by far the most frequent type of transgender individuals worldwide. Of the 18 countries studied by Meier and Labuski (2013), 16 of them had higher rates of TGW than transgender men (TGM)- whose birth sex was female- and the 18 country TGW to TGM ratio was 3 to 1.

However, the ratio of TGW to TGM individuals may be changing. A 2015 meta-analysis found that the overall incidence of transgender was 4.6 per 100,000 individuals, comprised of 6.8 TGW and 2.6 TGM, numbers that corroborate earlier reports of significantly higher rates of TGW than TGM individuals. A time analysis of the studies included revealed that the overall prevalence of transgender individuals had increased over the past 50 years (Arcelus et al., 2015). Echoing this trend, Leinung and Joseph (2020) reported an increase in individuals seeking hormone therapy in the past 25 years, and also indicated that the number of people requesting hormone therapy specifically for TGM transitions had increased steadily since 1990, resulting in equivalent numbers of TGW and TGM individuals being treated by 2017. It is unclear whether or how much this change reflects greater acceptance, destigmatization, and decreasing barriers to care specifically for TGM individuals (as the authors suggest), or if it may also represent a true increase in the number of TGM individuals in contemporary populations.

13.4.3.3 Role of Sex Hormones in Transgender Treatment

Feminizing or masculinizing hormone therapy is the administration of exogenous endocrine agents to induce changes in physical appearance. 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 (TGM, sometimes called female-to-male [FTM] individuals) or breast development in transgender women (TGW, sometimes called male-to-female [MTF] 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. Transgender women are prescribed estrogen and anti-testosterone medication (such as cyproterone acetate and spironolactone). Transgender men are prescribed testosterone.

13.4.3.4 Scientific and Societal Understanding of Gender Variations

Hormones that masculinize the brain in chromosomally male (XY) individuals are distinct from those that lead to the development of a typically male body form. "Due to this branching of control factors for brain and body organization, it is quite possible for a male-type body to contain a female-type brain, and for a female-type body to contain a male-type brain" (Panksepp, 2004, page 225). These developmental deviations could influence an individual's ultimate sexual orientation and/or gender identity. An example of conflicting brain and body organization comes from a study which found that the bed nucleus of the stria terminalis (BNST, an area located near the hypothalamus that is known to be important for sexual behavior) was "female-like" in size (smaller than cisgender males and similar to cisgender females) in the brains of six male-to-female transsexuals. This difference was not correlated with either adult hormone levels or sexual orientation (Zhou et al., 1995). Given that studies requiring post-mortem brain tissue to examine tiny brain areas are very difficult to conduct, this type of information is scarce.

Nonetheless, our scientific knowledge and general understanding of 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 a majority of Millennials (birth years 1981-1996) 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 (birth years 1997-2012) 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. Despite these changes, those who exist outside of traditional gender norms face difficult challenges. Even people who vary slightly from traditional norms can be the target of discrimination and sometimes even violence.

13.4.4 Summary

Although often used interchangeably, the terms sex and gender refer to distinct concepts, and sexual orientation is a third aspect of an individual's characteristics. Sex refers to the structures relevant for biological reproduction (such as ovaries in females and testes in males), whereas gender refers to an individual's sense of being masculine, feminine, neither or both. Gender identity is the psychological representation of biological sex, and gender role is the sociological representation. Sexual orientation describes a person's sexual attraction (or lack thereof) to others. Variations in each of these (sex, gender, and sexual orientation) is considered normal by international scientific and medical communities.

Children begin to learn cultural norms for masculine and feminine behaviors very early, but cultures vary widely and even the same culture changes over time- thus, ideas about gender also change. Cisgender individuals’ gender identities correspond with their birth (biological) sexes, while transgender individuals’ gender identities do not correspond with their birth (biological) sexes. Intersex (people whose sex characteristics or anatomy differ from typical development) and transgender are not interchangeable terms; many transgender people have no intersex traits, and many intersex people do not consider themselves transgender. Rates of transgender individuals vary widely around the world. Some cultures formally recognize the presence of people who do not conform to an expectation of biological sex matching gender identity, such as some Native American tribes. Transgender women specifically are referred to as *fa'afafine* in Samoa; *muxes in* Oaxaca, Mexico; *kathoey* in Thailand; and *hijras* in Pakistan, India, Nepal, and Bangladesh.

Worldwide, transgender women (whose birth sex was male) have been by far the most frequent type of transgender individuals, with a ratio of about three transgender women to one transgender man. However, recent trends (at least in people requesting hormone therapy) have progressively changed since the 1990s, such that by 2017, an equivalent number of transgender women and transgender men were being treated. Hormone therapy is used to induce changes in physical appearance. It 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, and breast development in transgender women. Hormone therapy is often the first (and sometimes only) medical gender affirmation intervention accessed by transgender individuals.

During prenatal development, hormones that masculinize the brain are distinct from those that lead to the development of a typically male body form. Developmental deviations can occur (such that the body is masculinized but the brain is not, for example), and could in turn influence an individual's ultimate sexual orientation and/or gender identity. Our scientific knowledge and general understanding of gender identity continue to evolve. Recent studies indicate that a majority of Millennials (birth years 1981-1996) regard gender as a spectrum instead of a strict male/female binary, and that 12% identify as transgender or gender non-conforming. Nonetheless, individuals who exist outside of traditional gender norms face difficult challenges, and may be the target of discrimination and even violence.

13.4.5 References

Note: These references are specifically those added to the content of this page by Naomi Bahm and do not include citations from the outside sources used. Refer to the text attributions to locate citations for articles from other sources.

Arcelus, J., Bouman, W.P., Van Den Noortgate, W., Claes, L., Witcomb, G., & Fernández Aranda, F. (2015) Systematic review and meta-analysis of prevalence studies in transsexualism. *European Psychiatry, 30*, 807–815.

Dimock, M. (2019). Defining generations: Where Millennials end and Generation Z begins. Pew Research Center (January 17), https://pewrsr.ch/2szqtJz

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Panksepp, J. (2004). *Affective neuroscience: The foundations of human and animal emotions*; *Chapter 12: The varieties of love and lust: Neural control of sexuality*. Oxford University Press.

TSER- Trans Student Educational Resources (2022). Definitions. https://transstudent.org/about/definitions/ (accessed 5/12/2022)

Zhou, J.-N., Hofman, M., Gooren, L.J.G., & Swaab, D.F. (1995). A sex difference in the human brain and its relation to transsexuality. *Nature*, *378*, 68-70.

13.4.6 Additional Resources

Trans Student Educational Resources: https://transstudent.org/

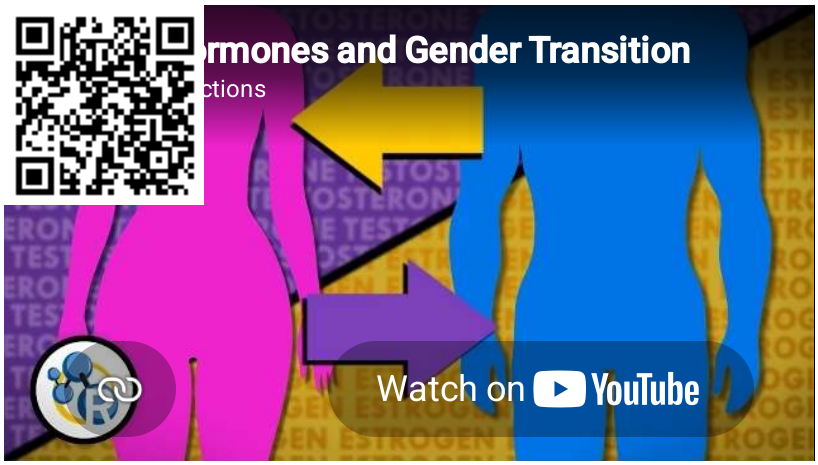
Guide to non-binary birth certificates and US State IDs: https://www.usbirthcertificates.com/articles/gender-neutral-birth-certificates-states

APA's non-binary (gender identity) fact sheet: https://www.apadivisions.org/divisio...fact-sheet.pdf

Educational graphics for understanding sex, gender, sexual orientation, and more: https://www.itspronouncedmetrosexual.com/2018/10/the-genderbread-person-v4/

Free e-book "A Guide to Gender: The Social Justice Advocate's Handbook" by Sam Killermann: https://impetus.gumroad.com/l/g2g2

People's sense of gender identity does not always match their anatomy. Some people do not identify as either male or female, and instead, they identify as non-binary, or genderqueer. Others may identify as a gender that is the opposite of what is typically associated with their chromosomes or reproductive organs. These people are called transgender, and they may choose to transition to the opposite gender, a process that may or may not involve physical modifications. Watch the video below to learn about the use of hormones in gender transitioning.



Muxes, a documentary about Mexican children identified as male at birth, but who choose at a young age to be raised as female.



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    2. Birth year ranges for Millennials and Generation Z from: https://www.pewresearch.org/fact-tan...tion-z-begins/ (accessed 5/12/22; see Dimock, 2019 in references)

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13.5: Sexual Orientation

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Understand Kinsey's continuum of sexual orientation and the range of sexual orientation labels used now
2. Explain the evidence for at least two nonsocial causes of sexual orientation

13.5.1 Overview

This section discusses sexual orientation, a person's emotional and sexual attraction to other individuals of a particular sex or gender. Kinsey's continuum of sexual orientation (a range from exclusively heterosexual through equally bisexual to exclusively homosexual) is introduced, as well as some additional terms that are in contemporary use (polysexual, pansexual, and asexual). The development and origins of sexual orientation are addressed, including research exploring genetics, prenatal hormone exposure, the fraternal-birth-order effect, and childhood development. Regardless of the root cause(s) for a person's sexual orientation (and/or gender identity), it is not a conscious choice and cannot be easily changed.

13.5.2 Sexual Orientation

A person's **sexual orientation** is their emotional and sexual attraction to a particular sex or gender, including a continuing pattern of romantic or sexual attraction (or a combination of these) 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, 2009)- sexual orientations are relatively stable over one's lifespan, and are influenced by genetics (Frankowski, 2004). Sexual orientation is distinct and independent from both biological sex and gender, as discussed in Section 13.4.

While some argue that sexual attraction is primarily driven by reproduction (e.g., Geary, 1998), empirical studies point to pleasure as the primary force behind our sex drive. For example, in a survey of college students who were asked, "Why do people have sex?" respondents gave more than 230 unique responses, most of which were related to pleasure rather than reproduction (Meston & Buss, 2007). Here's a thought-experiment to further demonstrate how reproduction has relatively little to do with driving sexual attraction: Add the number of times you've had and/or hope to have sex during your lifetime. With this number in mind, consider how many times the goal was (or will be) for reproduction versus how many it was (or will be) for pleasure. Which number is greater?



Figure 13.5.1: 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).

13.5.2.1 A Continuum of Sexual Orientation

Instead of thinking of sexual orientation as being two dichotomous categories- homosexual (attracted to the same sex, Figure 13.5.1) and heterosexual (attracted to the opposite sex)- sexuality researcher Alfred Kinsey and colleagues argued that it is a continuum (Kinsey, Pomeroy, & Martin, 1948). They measured sexual orientation using a seven-point scale called the Heterosexual-Homosexual Rating Scale (Figure 13.5.2), in which zero is exclusively heterosexual, three is bisexual (with equal attractions to the same and opposite sexes), and six is exclusively homosexual. Research done over several decades has supported this idea that sexual orientation ranges along a continuum, from exclusive attraction to the opposite sex/gender to exclusive attraction to the same sex/gender (Carroll, 2016).

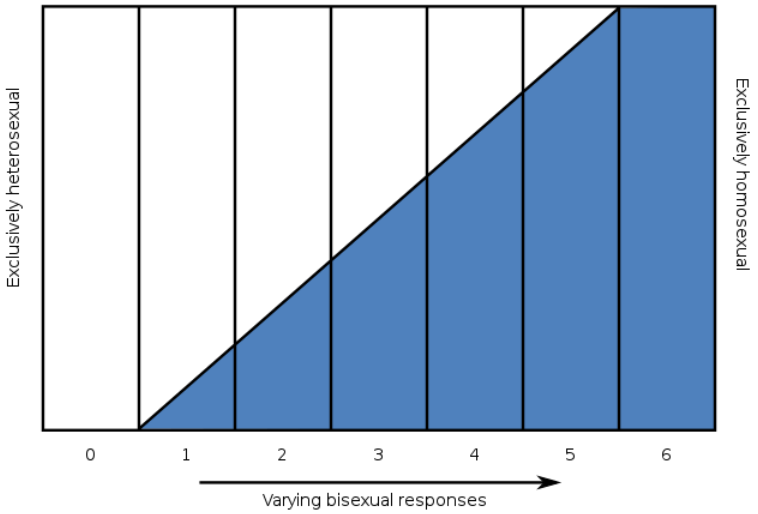


Figure 13.5.2: The Kinsey scale, a tool which enables an individual to select a response on a scale between heterosexual and homosexual. 0= exclusively heterosexual, 1= predominantly heterosexual, only incidentally homosexual, 2= predominantly heterosexual, more than incidentally homosexual, 3= equally heterosexual and homosexual, 4= predominantly homosexual, more than incidentally heterosexual, 5= predominantly homosexual, only incidentally heterosexual, and 6= exclusively homosexual.

The commonly stated notion that “10% of people are homosexual” originates (erroneously) from Kinsey’s 1948 study, which found that 10% of men reported being exclusively homosexual for at least three years during adulthood. In addition to the likelihood that Kinsey’s sample overestimated the actual occurrence of homosexuality in the population, only 4% of the male respondents in his study reported being homosexual their entire lifetime. This figure is much closer to the 3.5% prevalence of non-heterosexual (gay/lesbian/bisexual) orientation found in more recent and representative studies of US and other Western populations (Bailey et al., 2016). However, it is important to note that how a respondent is asked to report their sexual orientation produces very different results. Researchers using the Kinsey Scale have found 18% to 39% of Europeans and Americans identifying as somewhere between heterosexual and homosexual (Lucas et al., 2017; YouGov.com, 2015). These percentages drop dramatically to only 0.5% to 1.9% non-heterosexual when researchers force individuals to respond using only two categories (Copen, Chandra, & Febo-Vazquez, 2016; Gates, 2011).

Although the percentage of US adults identifying as LGBT (lesbian/gay/bisexual/transgender) remained relatively stable through the early 2010s (and still remains stable in older-aged cohorts), there is evidence that younger people are more likely to identify as LGBT than previous generations, which is in turn increasing the overall prevalence in the population. Gates (2017, page 1221) reports that “the percentage of older age cohorts identifying as LGBT has remained stable or declined despite large increases among Millennials, who are now three times more likely than Baby Boomers to identify as LGBT (7.3% vs 2.4%).” (Millennials are people born during the years 1981 through 1996 and Baby Boomers are people born during the years 1946 through 1964 (Dimock, 2019).)

Indeed, even beyond a continuum from heterosexual to homosexual, sexual orientation is as diverse as gender identity. Some examples of sexual orientation include **heterosexuality** (attraction to the opposite sex/gender), **homosexuality** (attraction to the same sex/gender, also referred to as **same-sex attraction**- some people find the term homosexuality offensive since it was previously classified as a mental illness), **bisexuality** (attraction to two sexes/genders), **polysexuality** (attraction to multiple sexes/genders), **pansexuality** (attraction to all sexes/genders), and **asexuality** (no sexual attraction to any sex/gender).

13.5.2.2 Development and Origins of Sexual Orientation

According to current scientific understanding, individuals are usually aware of their sexual orientation between middle childhood and early adolescence. However, this is not always the case, and some do not become aware of their sexual orientation until much later in life. It is not necessary to participate in sexual activity to be aware of these emotional, romantic, and physical attractions; people can be celibate (not participating in any type of sexual activity) and still recognize their sexual orientation. Some researchers argue that sexual orientation is not static and inborn, but is instead fluid and changeable throughout the lifespan. Regardless of when sexual orientation is recognized or how it is expressed, it is clearly not a conscious "choice" for either heterosexual or non-heterosexual individuals.

There is no scientific consensus regarding the exact reasons why an individual holds a particular sexual orientation. Research has examined possible biological, developmental, social, and cultural influences on sexual orientation, but there is no conclusive evidence that links sexual orientation to one specific factor (APA, 2016). In an extensive review of evidence for the causal mechanisms of human sexual orientation, Bailey et al. (2016, page 46) state that "no causal theory of sexual orientation has yet gained widespread support", further pointing out that the most probable scientific hypotheses are difficult to test. The most commonly suggested social causes of homosexuality, "sexual recruitment by homosexual adults, patterns of disordered parenting, or the influence of homosexual parents", generally have only weak support and are compromised by many confounding factors (Bailey et al., 2016, page 46). They conclude that "there is considerably more evidence supporting nonsocial causes of sexual orientation than social causes". Some of the prominent nonsocial causes that have been examined include genetics, prenatal hormone exposure, the fraternal-birth-order effect, and behavior differences during childhood development.

13.5.2.2.1 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 calculated and compared between people who share the same genetics (monozygotic twins, 99%), some of the same genetics (dizygotic twins, 50%, and siblings, 50%), and non-related people (randomly selected from the population). Researchers find that 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 are most similar for monozygotic twins, this indicates that "nature" (genetics) influences the expression of 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 hotly debated issue, an appreciation of the genetic aspects of attraction can be an important piece of this dialogue.

13.5.2.2.2 Prenatal Hormone Exposure

Excess or deficient exposure to hormones during prenatal development has also been theorized as an explanation for non-heterosexual orientation. One-third of females exposed to abnormal amounts of prenatal androgens due to congenital adrenal hyperplasia (CAH, see the section on differences of sexual development) identify as bisexual or lesbian (Cohen-Bendahan, van de Beek, & Berenbaum, 2005). In contrast, too little exposure to prenatal androgens may affect male sexual orientation (Carlson, 2011).

13.5.2.2.3 Fraternal-Birth-Order Effect

The "fraternal-birth-order effect" is the well-documented (and cross-culturally robust) finding that homosexual males tend to have more older brothers than heterosexual males (Bailey et al., 2016). Interestingly, this effect is particular to right-handed homosexual males (Blanchard et al., 2006; Bogaert, 2007). This effect is also specific to biological brothers (Figure 13.5.3), meaning that the number of sons that have been gestated by the man's mother is the important factor, whether or not the man was raised with those brothers. "The effect is almost certainly causal, with each additional older brother causing an increase in the chances of a man’s 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). 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 prevent the normal functioning of subsequent sons' Y chromosomes (Bailey et al., 2016; O'Hanlan et al., 2018).



Figure 13.5.3: Four of 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 (of six- the eldest died in infancy, https://en.Wikipedia.org/wiki/Marx_Brothers) and called himself "straight but curved around the edges" (http://everydayheterosexism.blogspot.com/2012/11/the-marx-brothers.html).

13.5.2.2.4 Childhood Development

Two other forms of evidence supporting non-social causes of sexual orientation, particularly for males, are related to childhood development and behavior: gender nonconformity and outcomes from attempts to alter gender identity. Children who display gender nonconformity by not following the roles that society expects (Figure 13.5.4) are more likely to be homosexual as adults. This is a robust finding across cultures, but applies much more strongly to boys than girls. Additionally, "when infant boys are surgically and socially “changed” into girls, their eventual sexual orientation is unchanged (i.e., they remain sexually attracted to females)" (Bailey et al., 2016, page 46). This "natural experiment" is most commonly the result of irreparable damage to the penis, as was the case with David Reimer (see the section on differences of sexual development).



Figure 13.5.4: A two-year-old boy plays nursing his doll. Gender nonconformity in childhood is associated with homosexuality in adulthood.

13.5.3 In Closing: Gender and Sexual Orientation

Although gender (discussed in Section 13.4) and sexual orientation are distinct, some research addresses both concepts concurrently. A review of biological origins for both sexual orientation and gender identity concludes that "multidisciplinary evidence reveals that ... sexual orientation and gender identity are conferred ... during the first half of pregnancy" and that "multiple layers of evidence confirm that sexual orientation and gender identity are as biological, innate and immutable as the other traits conferred during that critical time in gestation" (O'Hanlan et al., 2018). In other words, you cannot change an individual's sexual

orientation and/or gender identity any more easily than you can change whether or not they developed a standard human body form with two arms and legs, two eyes and ears, a nose, mouth and typical internal organs.

13.5.4 Summary

Sexual orientation is an individual's emotional and sexual attraction to a particular sex or gender, including their sense of identity based on those attractions and related behaviors. A person may exhibit sexual fluidity (with attractions and behaviors changing due to circumstances), but sexual orientations tend to be relatively stable over the lifespan. Some argue that sexual attraction is primarily driven by reproduction, but empirical studies suggest that pleasure is the primary force behind our sex drive, and that reproduction has relatively little to do with it.

Arguing that dividing people into homosexual and heterosexual did not capture the breadth of human sexual orientation, Kinsey created a continuum with a seven-point scale called the Heterosexual-Homosexual Rating Scale. Zero is exclusively heterosexual, three is bisexual (with equal attractions to the same and opposite sexes), and six is exclusively homosexual. Subsequent research has supported this idea that sexual orientation ranges along a continuum. Representative studies of US and other Western populations report a 3.5% prevalence of non-heterosexual (gay/lesbian/bisexual) orientation. However, how a respondent is asked to report their sexual orientation produces very different results: using the Kinsey Scale, 18% to 39% of Europeans and Americans identify as somewhere between heterosexual and homosexual, whereas only 0.5% to 1.9% of respondents identify as non-heterosexual when researchers force individuals to respond using only two categories. While the percentage of US adults identifying as LGBT (lesbian/gay/bisexual/transgender) remains stable in older-aged cohorts, younger people are more likely to identify as LGBT than previous generations. Examples of terms currently used to identify sexual orientation include heterosexuality (attraction to the opposite sex/gender), homosexuality or same-sex attraction (attraction to the same sex/gender), bisexuality (attraction to two sexes/genders), polysexuality (attraction to multiple sexes/genders), pansexuality (attraction to all sexes/genders), and asexuality (no sexual attraction to any sex/gender).

Individuals are usually 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 clearly 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 causes (such as having homosexual parents, recruitment by homosexual adults, and experiencing disordered parenting) have only weak support and many confounding factors. Nonsocial causes (such as genetics, prenatal hormone exposure, the fraternal-birth-order effect, and behavior differences during childhood development) have much more supporting evidence.

Genetic influence on sexual orientation is explored using twin studies. Concordance for sexual orientation is highest for monozygotic twins; and concordance rates for dizygotic twins, siblings, and randomly-selected pairs do not differ. Since concordance rates are most similar for monozygotic twins, this indicates that "nature" (genetics) influences the expression of sexual orientation. However, since monozygotic twins are not 100% concordant, "nurture" (the environment and individual experiences) also plays a role. During prenatal development, excess exposure to androgens for females and deficient exposure to androgens for males has also been theorized as explaining non-heterosexual orientation. Homosexual males tend to have more older brothers than heterosexual males, termed the "fraternal-birth-order effect. One proposed mechanism for this is that the mother creates antibodies against proteins on her developing son's Y chromosome, and that those antibodies may prevent the normal functioning of subsequent sons' Y chromosomes.

Childhood gender nonconformity and outcomes from attempts to alter gender identity also support non-social causes of sexual orientation (particularly for males). Boys who do not follow expected societal roles are more likely to be homosexual as adults. Additionally, when boys are “changed” into girls during childhood (often as a result of irreparable damage to the penis), they remain sexually attracted to women in adulthood. Both sexual orientation and gender identity are determined, at least in part, during prenatal development, and as such are not easily altered.

13.5.5 References

Note: These references are specifically those added to the content of this page by Naomi Bahm and do not include citations from the outside sources used. Refer to the text attributions to locate citations for articles from other sources.

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13.5.6 Additional Resources

Educational graphics for understanding sex, gender, sexual orientation, and more: https://www.itspronouncedmetrosexual.com/2018/10/the-genderbread-person-v4/

How do queer couples have babies? Learn more here:



13.5.7 Attributions

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2. Birth year ranges for Millennials and Baby Boomers from: https://www.pewresearch.org/fact-tan...tion-z-begins/ (accessed 5/12/22; see Dimock, 2019 in references)

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13.6: Sex Differences and Evolutionary Interpretations

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the ASCCC OERI (oeri@asccc.org).

Learning Objectives

1. Explain sex differences that have been reported in the brain, sensory systems and cognitive functions, and the limitations of these findings
2. Describe how hormones may influence sex differences in behavior, such as childhood toy preferences and aggressive behaviors
3. Identify the core premises of sexual strategies theory

13.6.1 Overview

After noting that the dichotomy does not truly reflect the variations seen in both biological sex and gender identity, this section discusses sex differences that have been reported between human males and females. Sex differences in the brain, sex differences in sensory systems and cognition, and sex differences in behavior are covered, with the last topic including a review of hormonal influences on sex differences in behavior followed by discussions of childhood toy preferences and aggressive behaviors. Finally, evolutionary interpretations of reproductive behavior is addressed, including sexual strategies theory and error management theory (as it relates to reproductive behaviors).

13.6.2 Sex Differences

13.6.2.1 Preliminary Note

Earlier sections have emphasized the lack of a strict dichotomy between males and females, both in terms of biological sex and gender identity. Nonetheless, most research splits people into two categories- most commonly based on their biological sex assigned at birth- and often also assumes that the biological sex reported correlates with gender identity. While this is useful to a degree, hopefully future research will take a more nuanced approach to all three aspects of an individual's "sexual" self- sex, gender, and sexual orientation! You will note below that when we compare men and women on psychological traits and characteristics, there is actually only a slight difference (typically no more than 5%) between the two, and only at the group level. Think of it this way- adult men in the U.S. are about 9% taller than adult women, on average (McDowell et al., 2008), and about 15% larger in body mass (Larsen, 2003). Yet everyone can think of examples of men who are shorter and/or smaller than many women, and women who are taller and/or larger than many men- and this physical difference is at least twice the size of any of the differences found in psychological domains!

Also, as you will learn in the section on sex differences in the brain, while differences between male and female brains have been reported at a group level, there is no way to reliably classify an individual brain as either male or female, due to both the large overlap between males and females and the fact that each brain has its own unique mosaic of both "male" and "female" traits in differing (and unpredictable) ways.

13.6.2.2 Introduction to Sex Differences

Hens and roosters are different (Figure 13.6.1). Cows and bulls are different. Men and women are different. Even girls and boys are different. Humans, like many animals, are sexually dimorphic (*di*, “two”; *morph*, “type”) in the size and shape of their bodies, their physiology, and for our purposes, their behavior.



Figure 13.6.1: Sex differences in appearance are often more pronounced in nonhuman animals than in humans. Male birds particularly, for example roosters, tend to have physical features that differ from the females and also differ significantly in size.

Interestingly, the physical differences in size and appearance (for many individuals, we can readily determine biological sex from visible traits) between human males and females is related to some of the differences we see in human reproductive behaviors. In the animal kingdom, many animals whose mating strategy is to form monogamous pairs have virtually indistinguishable males and females, whereas polygamous species (where one male typically mates with many females, and some males completely miss out on mating) are conspicuously different, often in both physical features and in size. While apparent in some bird species, such as the obviously different polygamous rooster and hen mentioned above (versus monogamous swans, with nearly identical males and females), these differences are particularly evident in (non-human) primate species (and many other mammals). Examples in primate species include the similarly-appearing monogamous gibbons (Jaffe, 2019, page 210-211), versus the polygamous gorillas (Jaffe, 2019, page 209), where adult males are much larger than females and gain the characteristic "silverback" coloring as they mature (Figure 13.6.2). A difference of around ten percent- precisely where the human species falls on this size-difference continuum- is the dividing line between "monogamous" and "polygamous"; in other words, species that have less than ten-percent difference in physical appearance and size between males and females are usually monogamous and species that have greater than ten-percent difference tend to be polygamous. For humans, "...the sexes differ more in human beings than in monogamous mammals, but much less than in extremely polygamous mammals..." (Daly & Wilson, 1996, page 13). Thus, it is not really surprising, from an evolutionary standpoint, that some humans adopt a monogamous strategy for mating and reproduction, and others follow a polygamous strategy.

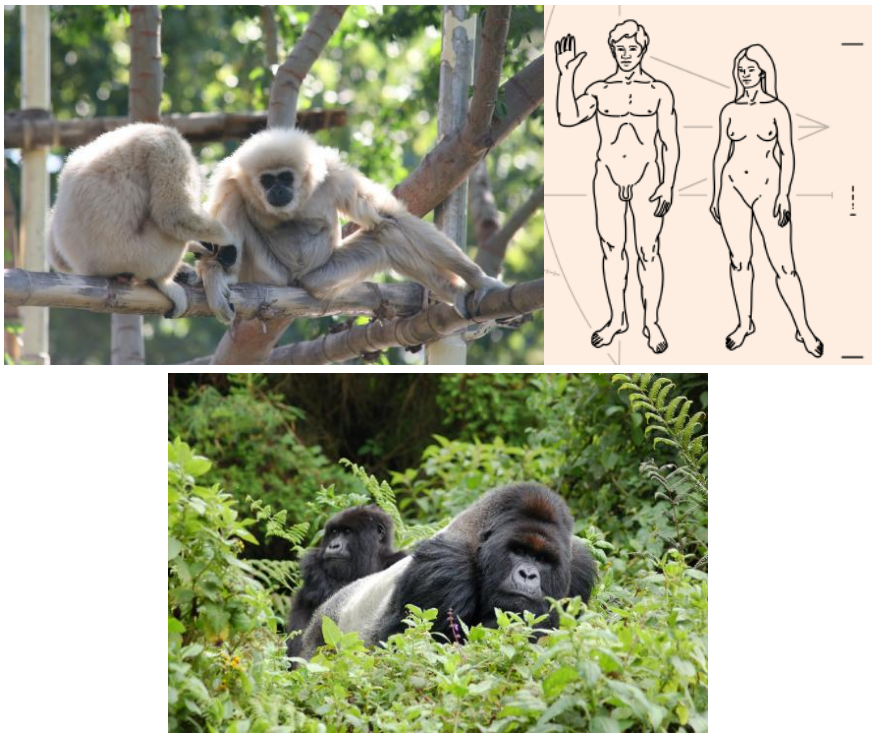


Figure 13.6.2: In humans (middle picture), males and females differ more than monogamous species, like White-handed Gibbons (left picture), but much less than polygamous species, like Mountain Gorillas (right picture).

Returning to human behavior, the behavior of boys and girls differs in many ways. Girls generally excel in verbal abilities relative to boys; boys are nearly twice as likely as girls to suffer from dyslexia (reading difficulties) and stuttering, and nearly four times more likely to suffer from autism. Boys are generally better than girls at tasks that require visuospatial abilities. Girls engage in nurturing behaviors more frequently than boys. More than 90% of all anorexia nervosa cases involve young women. Young men are twice as likely as young women to suffer from schizophrenia. Boys are much more physically aggressive and generally engage in more rough-and-tumble play than girls (Berenbaum, Martin, Hanish, Briggs, & Fabes, 2008). Many behavioral sex differences, such as the difference in physical aggressiveness, persist throughout adulthood. For example, there are many more men than women serving prison sentences for violent behavior. Below, this section addresses sex differences in the brain, in sensory systems and cognition, and in behavior, where sex differences in toy preferences and the previously mentioned aggressive behavior are discussed in greater detail.

13.6.2.3 Sex Differences in the Brain

Sex differences in overall human brain size have been reported for years (although the true significance of this finding is debatable). More recently, sex differences in specific brain structures have been discovered. For example, in rats, the sexually dimorphic nucleus (SDN-POA) of the preoptic area of the hypothalamus is much larger in males than females. This is a result of the organizing effects of gonadal steroid hormones upon brain and behavior, which is relatively constrained to the early stages of development. In rats, exposure to testosterone (which is converted to estradiol) or estradiol causes masculinization of the brain. (The same mechanism of a "female" hormone masculinizing the fetal brain is not present in primates, and thus presumably not in humans. Alpha-fetoprotein binds to estradiol in female rats to prevent masculinization of their brains.) Figure 13.6.3 depicts cross-sections through the brains of rats that show a male (A, left), a female (B, center), and a female treated with testosterone as a newborn (C, right). Note that the SDN-POA (the dark cell bodies) of the male are substantially larger than those of the untreated female but are equal in size to those of the testosterone-treated female. The extent that these sex differences in brain structure account for sex differences in behavior remain unspecified in mammals.

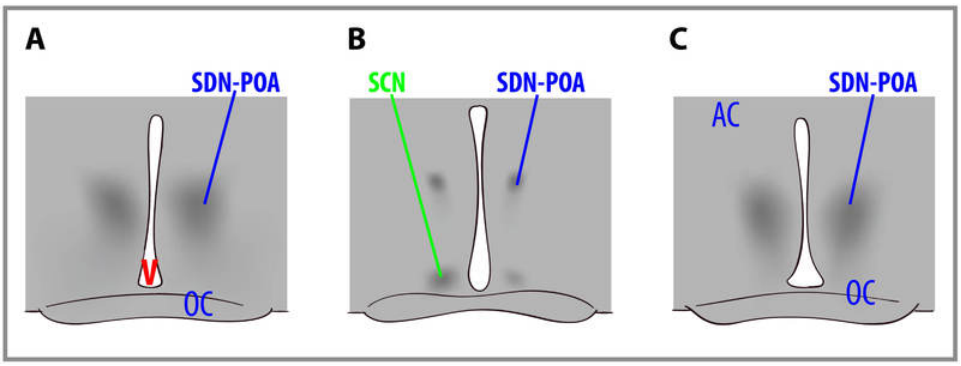


Figure 13.6.3: The sexually dimorphic nucleus of the preoptic area (SDN-POA). Rat brain cross-sections from a A) male (left), B) female (center), and C) female treated with testosterone as a newborn (right). OC = optic chiasm; SCN = suprachiasmatic nucleus; V = third ventricle.

In an area similar to the rat's SDN-POA, Simon LeVay (1991) reported a comparable difference in the human hypothalamus-INAH-3, the third interstitial nucleus of the anterior hypothalamus. Specifically, heterosexual men had INAH-3 nuclei that were more than twice as large (by volume) as homosexual men, whose INAH-3 nuclei volumes were similar to those of women. Although LeVay was able to replicate the result, attempts by another researcher lead to only a trend-level difference between heterosexual and homosexual men in the volume of INAH-3 (Byne 2000 & 2001, as cited by Bailey et al., 2016). Regardless of the true status of the possible differences in the human male's INAH-3 nucleus (it could be intermediate between the two researchers' findings, for example), "it would be unlikely that the INAH-3 size would be a key factor regulating sexual orientation. This is because there would be too many exceptions—homosexual men with a large INAH-3 and heterosexual men with a small INAH-3—to believe that INAH-3 size is crucial" (Bailey et al., 2016, page 72). The INAH-3 is a tiny structure- about the size of a grain of sand- and studying it requires post-mortem tissue. As such, it is unlikely that it will be studied further in the near future (Bailey et al., 2016).

For larger brain features, which can be studied in living people using imaging techniques, many brain differences between adult men and women have been reported, both in cortical regions and subcortical structures. An example of this includes magnetic resonance imaging (MRI) data suggesting that women have larger volumes of frontal and medial paralimbic cortices and men have larger volumes in the frontomedial cortex, amygdala and hypothalamus (Goldstein et al., 2001). However, closer scrutiny sometimes renders these sex differences unimportant. For example, the corpus callosum was widely believed to differ between males and females- the purported increased size in women was touted to result in greater connectivity between the right and left hemispheres of the brain- but has been found to not differ at all when men and women were matched for brain size (Luders et al., 2014). Another study underlining the importance of taking brain size into consideration was a twin study that found that a weak correlation between sex differences in the brain and behavioral sex differences turned out to be mainly driven by brain size. The authors warned that caution should therefore be used when inferring causality (van Eijk et al., 2021).

Additionally, Joel et al. (2015) conducted an extensive study of over 1400 MRIs of human brains and found that when taking the entire brain into account (and not just looking at one specific area versus another, where sex differences have been reported at a group level), it is impossible to categorize brains into male and female forms. Instead, there was extensive overlap of “male” and “female” features in human brains and it was very rare to have internal consistency (only “male” or only “female” features) in a specific brain. Thus, while we can often categorize biological sex by looking at anatomical structures- there are often distinct differences between male and female bodies, and a given body usually has only male or only female structures- we cannot determine if a specific brain came from a male or female body, nor can we predict by knowing the sex/gender of a particular individual what form their brain has taken. The authors state that “each brain is a unique mosaic of features, some of which may be more common in females compared with males, others may be more common in males compared with females, and still others may be common in both males and females” (Joel et al., 2015, page 15472). Additionally, their findings support the notion that masculinization and feminization of brain areas are two separate processes that progress independently, allowing variations of differentiation in a “male” or “female” pattern to occur within the same brain.

13.6.2.4 Sex Differences in Sensory Systems and Cognition

Sex differences in a number of sensory and cognitive functions have also been reported. Females are generally more sensitive to auditory information, whereas males are more sensitive to visual information. Females are also typically more sensitive than males to taste and olfactory input. Women display less lateralization of cognitive functions than men. On average, females generally excel

in verbal, perceptual, and fine motor skills, whereas males outperform females on quantitative and visuospatial tasks, including map reading and direction finding. Interestingly, women with Turner syndrome (whose ovaries are not functional) often have impaired spatial memory.

Although reliable sex differences can be documented, these differences in ability are slight. It is important to note that there is more variation *within* each sex than *between* the sexes for most cognitive abilities (Figure 13.6.4).

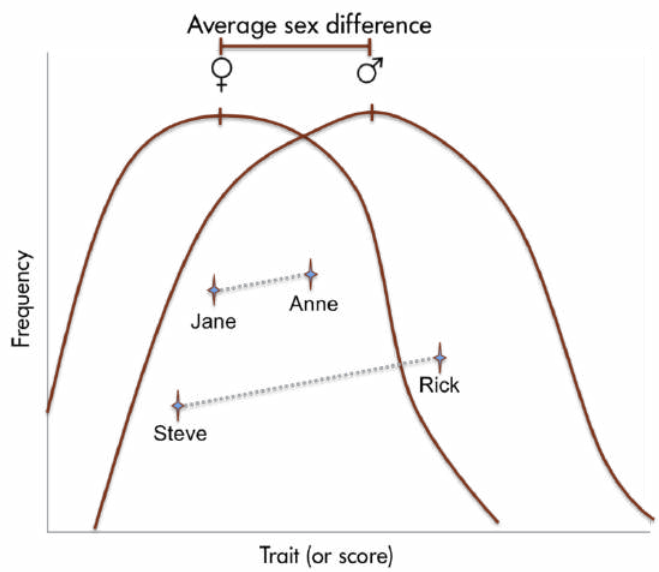


Figure 13.6.4: The average sex differences in human performance often reflect significant overlap between the sexes There are often greater differences in performance between individuals of the same sex (for example, between Steve and Rick in the figure) than between individuals of the opposite sex (for example, between Steve and Jane in the figure).

To emphasize the importance of recognizing the vast variation of personality traits and behavioral expressions found within all humans, regardless of their sex/gender, consider the following study results. Joel et al. (2015) conducted an analysis of the personality traits, attitudes, interests, and behaviors of more than 5,500 individuals. Their findings mirrored their MRI findings (great overlap between males and females and little internal consistency within the same individual). They report: “In accordance with the brain data, our analyses of gender-related data revealed extensive overlap between females and males in personality traits, attitudes, interests, and behaviors. Moreover, we found that substantial variability of gender characteristics is highly prevalent, whereas internal consistency is extremely rare, even for highly gender-stereotyped activities... Thus, most humans possess a mosaic of personality traits, attitudes, interests and behaviors, some more common in males compared with females, others more common in females compared with males, and still others common in both males and females” (Joel et al., 2015, page 15472). It is reasonable to conclude that overall, human males and females are more similar than they are different, both with regards to brain features and psychological traits.

13.6.2.5 Sex Differences in Behavior

13.6.2.5.1 Review of Hormonal Influences on Sex Differences in Behavior

The hormonal differences between men and women may account for adult sex differences that develop during puberty, but what accounts for behavioral sex differences among children *prior* to puberty and activation of their gonads? As discussed in section 13.2, the presence (or absence) of androgens determine whether the fetus develops a male or female body form. Androgens from the fetal testes steer the development of the body, central nervous system, and subsequent behavior in a male direction. In contrast, fetal ovaries do not secrete high concentrations of hormones, so the body, central nervous system, and later, behavior, follow a female pathway.

As discussed in section 13.1, gonadal steroid hormones have organizational (or programming) effects upon brain and behavior (Phoenix, Goy, Gerall, & Young, 1959). These organizing effects are relatively constrained to the early stages of development. In rats, early steroid hormone treatment causes relatively irreversible and permanent masculinization of later adult behavior (mating and aggressive). In contrast, activational effects of hormones (provided in adulthood to influence behaviors) are temporary and reversible. Thus, typical male behavior requires exposure to androgens during gestation (in humans) or immediately after birth (in rats) to somewhat masculinize the brain and also requires androgens during or after puberty to activate these neural circuits. Typical

female behavior requires a lack of exposure to androgens early in life which leads to feminization of the brain and also requires estrogens to activate these neural circuits in adulthood. But this simple dichotomy, which works well with animals with very distinct sexual dimorphism in behavior, has many caveats when applied to people.

13.6.2.5.2 Childhood Toy Preferences

If you walk through any major toy store, then you will likely observe a couple of aisles filled with pink boxes and the complete absence of pink packaging of toys in adjacent aisles. Remarkably, you will also see a strong self-segregation of boys and girls in these aisles. It is rare to see boys in the “pink” aisles and vice versa. The toy manufacturers are often accused of making toys that are gender biased, but it seems more likely that boys and girls enjoy playing with specific types and colors of toys. Indeed, toy manufacturers would immediately double their sales if they could sell toys to both sexes. Boys generally prefer toys such as trucks and balls and girls generally prefer toys such as dolls. Although it is doubtful that there are genes that encode preferences for toy cars and trucks on the Y chromosome, it is possible that hormones might shape the development of a child’s brain to prefer certain types of toys or styles of play behavior. It is also reasonable to believe that children learn which types of toys and which styles of play are appropriate to their gender (Figure 13.6.5). How can we separate the contribution of learning from underlying physiological mechanisms to understand sex differences in human behaviors? To untangle these issues, animal models are often used. Unlike the situation in humans, where sex differences are usually only a matter of degree (often slight), in some animals, members of only one sex may display a particular behavior. For example, often only male songbirds sing. Studies of such strongly sex-biased behaviors are particularly valuable for understanding the interaction among behavior, hormones, and the nervous system.



Figure 13.6.5: If you think back to the toys you played with and clothing you wore in your youth, do you think they were more a result of your hormonal activity or the choices that society and your parents made for you?

A study of vervet monkeys calls into question the primacy of learning in the establishment of toy preferences (Alexander & Hines, 2002). Female vervet monkeys preferred girl-typical toys, such as dolls or cooking pots, whereas male vervet monkeys preferred boy-typical toys, such as cars or balls. There were no sex differences in preference for gender-neutral toys, such as picture books or stuffed animals. Presumably, monkeys have no prior concept of “boy” or “girl” toys. Young rhesus monkeys also show similar toy preferences.

What then underlies the sex difference in toy preference? It is possible that certain attributes of toys (or objects) appeal to either boys or girls. Toys that appeal to boys or male vervet or rhesus monkeys, in this case, a ball or toy car, are objects that can be moved actively through space, toys that can be incorporated into active, rough and tumble play. The appeal of toys that girls or female vervet monkeys prefer appears to be based on color. Pink and red (the colors of the doll and pot) may provoke attention to infants.

Society may reinforce such stereotypical responses to gender-typical toys. The sex differences in toy preferences emerge by 12 or 24 months of age and seem fixed by 36 months of age, but are sex differences in toy preference present during the first year of life? It is difficult to ask pre-verbal infants what they prefer, but in studies where the investigators examined the amount of time that babies looked at different toys, eye-tracking data indicate that infants as young as three months showed sex differences in toy

preferences; girls preferred dolls, whereas boys preferred trucks. Another result that suggests, but does not prove, that hormones are involved in toy preferences is the observation that girls diagnosed with congenital adrenal hyperplasia (CAH), whose adrenal glands produce varying amounts of androgens early in life, played with masculine toys more often than girls without CAH. Further, a dose-response relationship between the extent of the disorder (i.e., degree of fetal androgen exposure) and degree of masculinization of play behavior was observed. Are the sex differences in toy preferences or play activity, for example, the inevitable consequences of the differential hormonal environments of boys and girls, or are these differences imposed by cultural practices and beliefs? Are these differences the result of receiving gender-specific toys from an early age, or are these differences some combination of hormonal and cultural factors? Again, these are difficult questions to unravel in people.

13.6.2.5.3 Aggressive Behaviors

Note that in this section "aggressive behavior" is referring specifically to the expression of physical aggression (arguably the only type of aggression that can be studied in animals as well as humans). When aggression is defined more broadly to include relational aggression (such as non-physical bullying, gossiping, and humiliation), human males and females show much more similar overall levels of aggression (Swearer Napolitano, 2008).

The possibility for aggressive behavior exists whenever the interests of two or more individuals are in conflict (Nelson, 2006). Conflicts are most likely to arise over limited resources such as territories, food, and mates. A social interaction decides which animal gains access to the contested resource. In many cases, a submissive posture or gesture on the part of one animal avoids the necessity of actual combat over a resource. Animals may also participate in threat displays or ritualized combat in which dominance is determined but no physical damage is inflicted.

There is overwhelming circumstantial evidence that androgens mediate aggressive behavior across many species. First, seasonal variations in blood plasma concentrations of testosterone and seasonal variations in aggression coincide. For instance, the incidence of aggressive behavior peaks for male deer in autumn, when they are secreting high levels of testosterone. Second, aggressive behaviors increase at the time of 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, in any given species, males are generally more aggressive than females. This is certainly true of deer; relative to stags, female deer rarely display aggressive behavior, and their rare aggressive acts are qualitatively different from the aggressive behavior of males. Finally, castration (removal of the testes) typically reduces aggression in males, and testosterone replacement therapy restores aggression to pre-castration levels. There are some interesting exceptions to these general observations that are outside the scope of this section.

As mentioned, males are generally more aggressive than females. Certainly, human males are much more physically aggressive than females. Many more men than women are convicted of violent crimes in North America. The sex differences in human aggressiveness appear very early. At every age throughout the school years, many more boys than girls initiate physical assaults. Almost everyone will acknowledge the existence of this sex difference, but assigning a cause to behavioral sex differences in humans always elicits much debate. It is possible that boys are more aggressive than girls because androgens promote aggressive behavior and boys have higher blood concentrations of androgens than girls. It is possible that boys and girls differ in their aggressiveness because the brains of boys are exposed to androgens prenatally and the “wiring” of their brains is thus organized in a way that facilitates the expression of aggression (Figure 13.6.6). It is also possible that boys are encouraged and girls are discouraged by family, peers, or others from acting in an aggressive manner. These three hypotheses are not mutually exclusive, but it is extremely difficult to discriminate among them to account for sex differences in human aggressiveness.

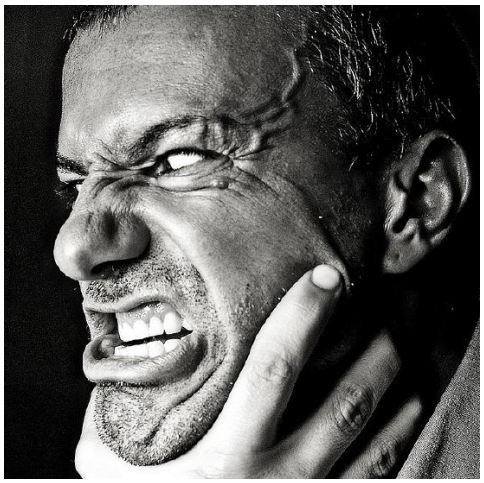


Figure 13.6.6: Researchers have electrically stimulated particular regions in people's brains, and these individuals have burst into aggressive, violent behavior, helping demonstrate that such responses are hardwired into us.

What kinds of studies would be necessary to assess these hypotheses? It is usually difficult to separate out the influences of environment and physiology on the development of behavior in humans. For example, boys and girls differ in their rough-and-tumble play at a very young age, which suggests an early physiological influence on aggression. This pattern of more physical play behavior is seen in a number of other species including nonhuman primates, rats, and dogs. Is the difference in the frequency of rough-and-tumble play between boys and girls due to biological factors associated with being male or female, or is it due to cultural expectations and learning? Parents interact with their male and female offspring differently; they usually play more roughly with male infants than with females, which suggests that the sex difference in aggressiveness is partially learned. This difference in parental interaction style is evident by the first week of life. If there is a combination of biological and cultural influences mediating the frequency of rough-and-tumble play, then what proportion of the variation between the sexes is due to biological factors and what proportion is due to social influences? Importantly, is it appropriate to talk about "normal" sex differences when these traits virtually always arrange themselves along a continuum rather than in discrete categories? Because of these complexities in the factors influencing human behavior, the study of hormonal effects on sex-differentiated behavior has been pursued in nonhuman animals, where it is easier to hold environmental influences relatively constant.

With the appropriate animal model, we can address the questions posed above: Is the sex difference in aggression due to higher adult blood concentrations of androgens in males than in females, or are males more aggressive than females because their brains are organized differently by perinatal hormones? Are males usually more aggressive than females because of an interaction of early and current blood androgen concentrations? If male mice are castrated prior to their sixth day of life, then treated with testosterone in adulthood, they show low levels of aggression. Similarly, female mice ovariectomized prior to their sixth day but given androgens in adulthood do not express male-like levels of aggression. Treatment of perinatally gonadectomized males or females with testosterone prior to their sixth day life and also in adulthood results in a level of aggression similar to that observed in typical male mice. Thus, in mice, the proclivity for males to act more aggressively than females is organized perinatally by androgens but also requires the presence of androgens after puberty in order to be fully expressed. In other words, aggression in male mice is both organized and activated by androgens. Testosterone exposure in adulthood without prior organization of the brain by steroid hormones does not evoke typical male levels of aggression. The hormonal control of aggressive behavior in mice is thus similar to the hormonal mediation of heterosexual male mating behavior in other rodent species. Aggressive behavior is similarly both organized and activated by androgens in many species, including rats, hamsters, voles, dogs, and possibly some primate species.

13.6.3 Evolutionary Interpretations of Reproductive Behavior

Evolutionary psychology connects evolutionary principles with modern psychology and focuses primarily on psychological adaptations: changes in the way we think in order to improve our survival. (See Chapter 3 for more information on evolution.) This section describes one of the major evolutionary psychological theories that is relevant to reproductive behaviors- sexual strategies theory- which describes the psychology of human mating strategies and the ways in which women and men differ in those strategies. Additionally, an example from another evolutionary psychological theory- error management theory- that is relevant to human mating is provided.

13.6.3.1 Sexual Strategies Theory

Sexual strategies theory is based on sexual selection theory- the evolution of characteristics due to mating advantage rather than survival advantage, such as traits that make an individual more attractive to the opposite sex, and competition between members of the same sex. It proposes that humans have evolved a list of different mating strategies, both short-term and long-term, that vary depending on culture, social context, parental influence, and personal mate value (desirability in the “mating market”). Initially the focus was on the differences between men and women in mating preferences and strategies (Buss & Schmitt, 1993), starting by looking at the minimum parental investment needed to produce a child. For women, even the minimum investment is significant: after becoming pregnant, they have to carry that child for nine months inside of them (Figure 13.6.7). For men, on the other hand, the minimum investment to produce the same child is considerably smaller—simply the act of sex.



Figure 13.6.7: Because women bear responsibility for pregnancy, they may use different mating strategies than men do.

These differences in parental investment have an enormous impact on sexual strategies. For a woman, the risks associated with making a poor mating choice is high. She might get pregnant by a man who will not help to support her and her children, or who might have poor-quality genes. And because the stakes are higher for a woman, *wise* mating decisions for her are much more valuable. While this discussion is not intended in any way to endorse "bad behavior", for men, biologically speaking, the need to focus on making wise mating decisions isn’t as important. That is, unlike women, men 1) don’t biologically have the child growing inside of them for nine months, and 2) do not have as high a cultural expectation to raise the child. This logic leads to a powerful set of predictions: In short-term mating, women will likely be choosier than men (because the costs of getting pregnant are so high), while men, on average, will likely engage in more casual sexual activities (because this cost is greatly lessened). Due to this, men will sometimes deceive women about their long-term intentions for the benefit of short-term sex, and men are more likely than women to lower their mating standards for short-term mating situations.

An extensive body of empirical evidence supports these and related predictions (Buss & Schmitt, 2011). Men express a desire for a larger number of sex partners than women do. They let less time elapse before seeking sex. They are more willing to consent to sex with strangers and are less likely to require emotional involvement with their sex partners. They have more frequent sexual fantasies and fantasize about a larger variety of sex partners. They are more likely to regret missed sexual opportunities. And they lower their standards in short-term mating, showing a willingness to mate with a larger variety of women as long as the costs and risks are low.

However, it is also important to note that in situations where both the man and woman are interested in long-term mating, both sexes tend to invest substantially in the relationship and in their children. In these cases, the theory predicts that both sexes will be extremely choosy when pursuing a long-term mating strategy. Much empirical research supports this prediction, as well. In fact, the qualities women and men generally look for when choosing long-term mates are very similar: both want mates who are intelligent, kind, understanding, healthy, dependable, honest, loyal, loving, and adaptable.

Nonetheless, women and men do differ in their preferences for a few key qualities in long-term mating, because of somewhat distinct adaptive problems. Modern women have inherited the evolutionary trait to desire mates who possess resources, have qualities linked with acquiring resources (e.g., ambition, wealth, industriousness), and are willing to share those resources with them. On the other hand, men more strongly desire youth and health in women, as both are cues to fertility. These male and female

differences are universal in humans. They were first documented in 37 different cultures, from Australia to Zambia (Buss, 1989), and have been replicated by dozens of researchers in dozens of additional cultures (for summaries, see Buss, 2012).

As we know, though, just because we have these mating preferences (e.g., men with resources; fertile women), people don't always get what they want. There are countless other factors which influence who people ultimately select as their mate. For example, the sex ratio (the percentage of men to women in the mating pool), cultural practices (such as arranged marriages, which inhibit individuals' freedom to act on their preferred mating strategies), the strategies of others (e.g., if everyone else is pursuing short-term sex, it's more difficult to pursue a long-term mating strategy), and many others all influence who we select as our mates.

Sexual strategies theory—anchored in sexual selection theory— predicts specific similarities and differences in men and women's mating preferences and strategies. Whether we seek short-term or long-term relationships, many personality, social, cultural, and ecological factors will all influence who our partners will be.

13.6.3.2 Error Management Theory

How we think, make decisions, and evaluate uncertain situations (error management theory) has also been used to predict adaptive biases in the domain of mating. Consider something as simple as a smile. In one case, a smile from a potential mate could be a sign of sexual or romantic interest. On the other hand, it may just signal friendliness. Because of the costs to men of missing out on chances for reproduction, error management theory predicts that men have a *sexual overperception bias*: they often misread sexual interest from a woman, when really it's just a friendly smile or touch. In the mating domain, the sexual overperception bias is one of the best-documented phenomena. It's been shown in studies in which men and women rated the sexual interest between people in photographs and videotaped interactions. As well, it's been shown in the laboratory with participants engaging in actual "speed dating," where the men interpret sexual interest from the women more often than the women actually intended it (Perilloux, Easton, & Buss, 2012). In short, error management theory predicts that men, more than women, will over-infer sexual interest based on minimal cues, and empirical research confirms this adaptive mating bias.

13.6.4 Summary

Humans, like many animals, are sexually dimorphic in the size and shape of their bodies, their physiology, and for our purposes, their behavior. Girls generally excel in verbal abilities, whereas boys generally have better visuospatial abilities. Boys are more likely to suffer from dyslexia, stuttering, autism, and schizophrenia, while most anorexia nervosa cases involve young women. Girls engage in nurturing behaviors more frequently, and boys generally engage in more rough-and-tumble play. One behavioral sex difference that persists into adulthood is the higher levels of physical aggression exhibited by boys and men.

In rats, the sexually dimorphic nucleus of the preoptic area in the hypothalamus (SDN-POA) is much larger in males than females. A female rat treated with testosterone as a newborn develops an SDN-POA similar in size to a typical male rat. In humans, a similar brain area, the third interstitial nucleus of the anterior hypothalamus (INAH-3), was found to be larger in heterosexual men than homosexual men (whose INAH-3 was similar in size to those of women). However, replication outside of the initial lab did not reach statistical significance. Brain imaging studies have reported various differences in cortical regions and subcortical structures, but closer scrutiny sometimes renders these sex differences unimportant, and caution should be used when inferring causality. A study of over 1400 MRIs of human brains found that when taking the entire brain into account, it is impossible to categorize brains into male and female forms. There was extensive overlap of "male" and "female" features in human brains and it was very rare to have internal consistency in a specific brain. These findings also support the notion that masculinization and feminization of brain areas are two separate processes that progress independently, allowing for considerable variation across individuals.

Sex differences in a number of sensory and cognitive functions have also been reported, but these differences in ability are slight. Furthermore, there is more variation *within* each sex than *between* the sexes for most cognitive abilities. An analysis of personality traits, attitudes, interests, and behaviors of more than 5,500 individuals mirrored the MRI findings (great overlap between males and females and little internal consistency within the same individual). It is reasonable to conclude that overall, human males and females are more similar than they are different, both with regards to brain features and psychological traits.

Boys generally prefer toys such as trucks and balls and girls generally prefer toys such as dolls. It is possible that hormones shape the development of a child's brain to prefer certain types of toys or styles of play behavior, but children also learn which types of toys and which styles of play are appropriate to their gender. Studies of vervet monkeys and rhesus monkeys find that females prefer girl-typical toys, and males prefer boy-typical toys, with no sex differences in preference for gender-neutral toys. While society likely reinforces stereotypical responses to gender-typical toys in human children, sex differences in toy preferences emerge

by 12 or 24 months of age and seem fixed by 36 months of age. Studies using eye-tracking indicate that infants as young as three months show stereotypical sex differences in toy preferences. Additionally, in a dose-response relationship, girls diagnosed with congenital adrenal hyperplasia (CAH) played with masculine toys more often than girls without CAH, suggesting that prenatal hormones may affect later toy preferences.

Aggressive behavior may occur when two (or more) individuals are in conflict, typically over limited resources such as territories, food, and mates. Evidence strongly suggests that androgens mediate aggressive behavior across many species. Seasonal variations in testosterone levels and variations in aggression coincide; aggressive behaviors increase at puberty (when the testes become active and androgens rise); in any given species, males are generally more aggressive than females; and castration (removal of the testes) typically reduces aggression in males, while testosterone replacement therapy restores aggression. Human males are much more physically aggressive than females, and these sex differences appear very early. It is possible that boys are more aggressive than girls because androgens promote aggressive behavior, it could be due to exposure to androgens prenatally, or boys may be encouraged to act in aggressive ways. These three hypotheses are not mutually exclusive, but it is extremely difficult to discriminate among them to account for sex differences in human aggressiveness. In many animal species (mice, rats, hamsters, voles, dogs, and possibly some primates), aggressive behavior is both organized and activated by androgens.

Sexual strategies theory describes the psychology of human mating strategies and the ways in which women and men differ in those strategies. Because differences in parental investment are so large between males and females- men have little necessary investment and consequently don't need to make wise choices, whereas mating decisions for women are much more important (since a minimum of none months carrying the child is required)- women are predicted to be choosier than men in short-term mating. Thus, men will sometimes deceive women for the benefit of short-term sex, and men are more likely than women to lower their mating standards for short-term mating situations. However, when choosing long-term mates, the qualities women and men seek are very similar: mates who are intelligent, kind, understanding, healthy, dependable, honest, loyal, loving, and adaptable. There are nonetheless some universal differences in mate preference- women desire mates who possess resources (and are willing to share them), and men more strongly desire youth and health in women (as both are cues to fertility).

13.6.5 References

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13.6.6 Additional Resources

Web: Main international scientific organization for the study of evolution and human behavior, HBES

http://www.hbes.com/

Web: Books and Interviews with David Buss

https://labs.la.utexas.edu/buss/books/

Web: Publications by Buss and colleagues

https://labs.la.utexas.edu/buss/publications/

Journal article: Founders of Evolutionary Psychology

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CHAPTER OVERVIEW

14: Emotion and Stress

14.1: The Neurological Bases of Emotions

14.2: Theories of Emotion- Fight or Flight and More

14.3: Social Neuroscience

14.4: Stress and health

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14.1: The Neurological Bases of Emotions

Learning Objectives

- Identify what general and specific brain parts are involved in emotions.
- Analyze the anatomical and chemical bases of basic emotions.
- Analyze the biopsychological methods of studying emotions.
- Evaluate the functions of emotions.

14.1.1 Overview

There is a strong connection between brain/body and emotions/affective states. Human and animal research findings have shown brain networks and several neurotransmitter systems involved in basic emotion/affective systems. This chapter will introduce foundation theories of emotion and the field of "Affective Neuroscience." The neuroanatomy and neurochemistry of the most common emotional states will be examined, along with an exploration of their functions.

14.1.2 **Affective Neuroscience: What is it?**

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, the emotions. Affective neuroscience uses unbiased, observable measures that provide credible evidence to other sciences and laypersons on the importance of emotions. It also leads to biologically based treatments for affective disorders (e.g., depression).



Figure 14.1.1: Although we all experience emotions all the time, they are very difficult to describe and study. Fortunately, technological advances are making this easier. (Image: Waag Society, https://goo.gl/F0KdnB, CC BY-NC-SA 2.0, goo.gl/iF4hmM)

The human brain and its responses, including emotions, are complex and flexible. In comparison, nonhuman animals possess simpler nervous systems and more basic emotional responses. Invasive neuroscience techniques, such as electrode implantation, lesioning, and hormone administration, can be more easily used in animals than 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. Thus, animal research provides useful models for understanding affective processes in humans. Affective circuits found in other species, particularly social mammals such as rats, dogs, and monkeys, function similarly to human affective networks, although nonhuman animals' brains are more basic.

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.

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, Chapman, & Anderson, 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.

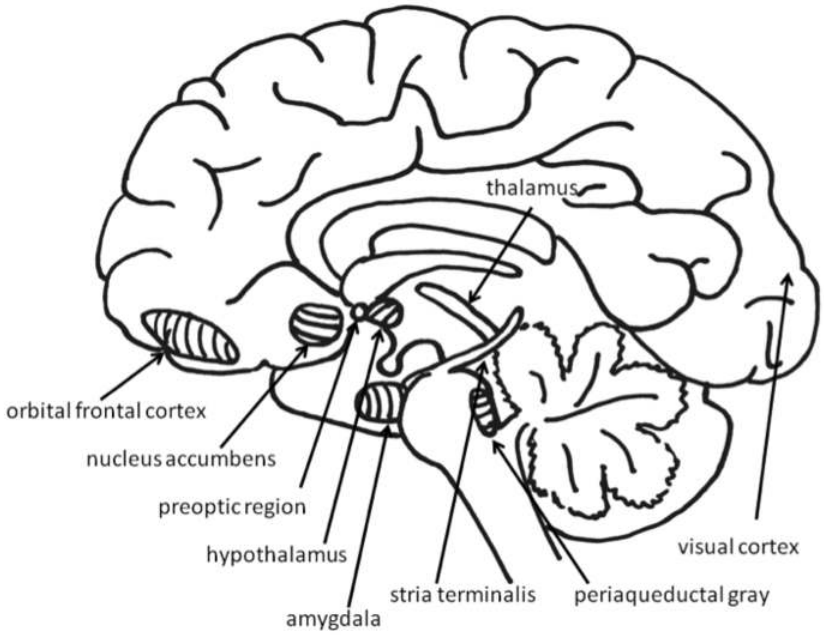


Figure 14.1.2: Structures in the brain - orbital frontal cortex, nucleus accumbens, preoptic region, hypothalamus, amygdala, stria terminalis, PAG, visual cortex and thalamus play a role in emotion. From Affective Neuroscience By Eddie Harmon-Jones and Cindy Harmon-Jones, University of New South Wales, Noba Project, licensed CC BY-NC-SA 4.0

14.1.3 Basic Emotions

14.1.3.1 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 "behavioural 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. The 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 because they are dopamine agonists (Panksepp & Biven, 2012).



Figure 14.1.3: Just looking at an image of appealing food should increase the activity in your left frontal cortex. Yum! (Wikimedia Commons, Public Domain)

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. Researchers first noted that persons who had 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 (that is those emotions that involve a movement toward the stimulus such as with happiness and also with anger) 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, Mueller, Pizzagalli, Hennig, & Stemmler, 2013).

14.1.3.2 "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 he or she likes that reward. This is because the neural structures involved in the enjoyment of rewards are different from the structures involved in the desire for the 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, de Wit, & Eikelboom, 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 (endogenously produced substances that have effects similar to marijuana). 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.

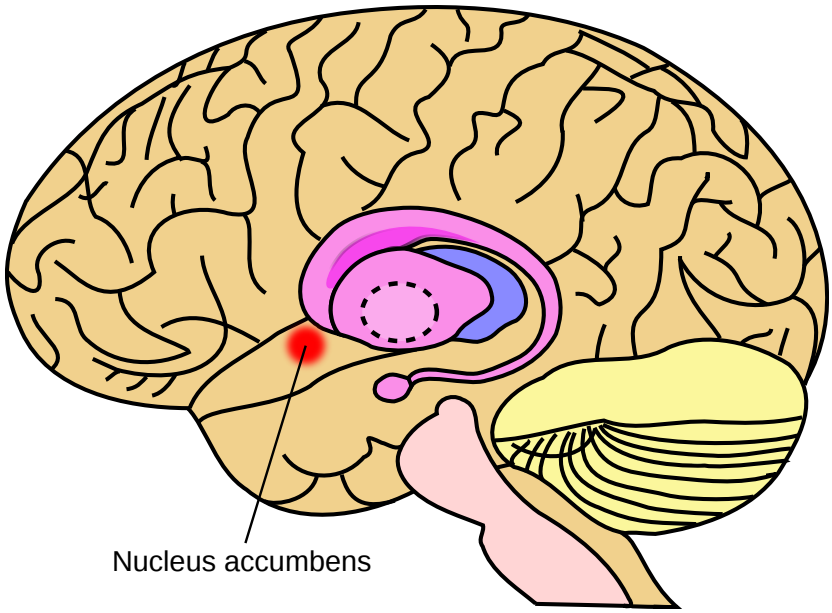


Figure 14.1.4: The experience of pleasure also involves the orbitofrontal cortex. Neurons in this region and the nucleus accumbens particularly shown here in red fire when monkeys taste, or merely see pictures of, desirable foods. In humans, this region is activated by pleasant stimuli including money, pleasant smells, and attractive faces (Gottfried, O'Doherty & Dolan, 2002; O'Doherty, Deichmann, Critchley, & Dolan, 2002; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; O'Doherty, Winston, Critchley, Perrett, Burt, & Dolan, 2003). (File:BrainCaudatePutamen.svg: User:Leevanjackson Derivative work: User:SUM1, CC BY-SA 4.0, via Wikimedia Commons)

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, O'Doherty & Dolan, 2002; O'Doherty, Deichmann, Critchley, & Dolan, 2002; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; O'Doherty, Winston, Critchley, Perrett, Burt, & Dolan, 2003).

14.1.3.3 **Fear: The Neural System of Freezing and Fleeing**



Figure 14.1.5: 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 ourselves are even consciously aware of them. (Wikimedia Commons, CC BY-SA 4.0)

Fear is an unpleasant emotion that motivates avoidance of potentially harmful situations. Slight stimulation of the fear-related areas in the brain 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 a variety of signals from neurotransmitters, neurohormones, and several differentneuropeptides. **Benzodiazepines** are a common anti-anxiety drug that inhibit activation in these areas (Panksepp & Biven, 2012). As is discussed in a later section, stress plays a role in releasing these chemicals activating the fight/flight/freeze response. Benzodiazepines are able to lower anxiety or anticipation of a fearful situation by inhibiting the activity of these areas by activating the **GABA** system.

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, Farb, & Ruggiero, 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).

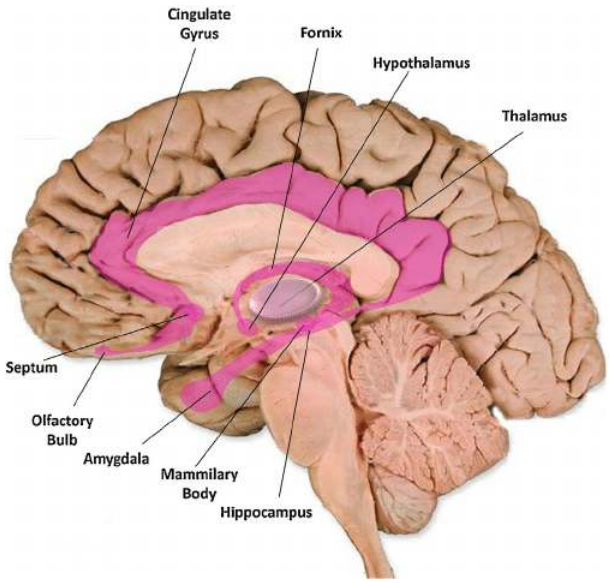


Figure 14.1.6: The limbic system (highlighted here in pink), which includes the hypothalamus, thalamus, amygdala, and the hippocampus, is involved in mediating emotional response and memory. (Limbic system by SoniaM2020 licensed CC BY-SA 4.0)

14.1.3.4 Love: The Neural Systems of Care and Attachment



Figure 14.1.7: 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.” [Image: Go-tea 郭天, https://goo.gl/KLFxJP, CC BY 2.0, goo.gl/zHmGV2]

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) (see Figure) and the bed nucleus of the **stria terminalis**(Panksepp, 1998).

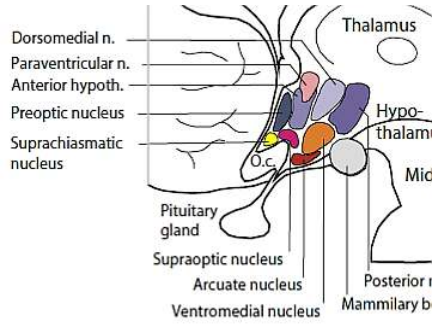


Figure 14.1.8: Figure showing key hypothalamic nuclei including the preoptic nucleus in dark blue anterior to the anterior hypothalamus, behind the frontal cortex and above the SCN and supraoptic nucleus. Sanador2.0, CC BY-SA 3.0, via Wikimedia Commons

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). Refer to the previous chapter and sex and gender for more details on these mechanisms.

14.1.3.5 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, Normansell, Herman, Bishop, & Crepeau, 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 effectively 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.

14.1.4 Knowledge Emotions

Paul Silvia (University of North Carolina, Greensboro) suggested that when people think of emotions they usually think of the obvious ones, such as happiness, fear, anger, and sadness. He instead looks at the knowledge emotions, a family of emotional states that foster learning, exploring, and reflecting. **Surprise, interest, confusion, and awe** come from events that are unexpected, complicated, and mentally challenging, and they motivate learning in its broadest sense, be it learning over the course of seconds (finding the source of a loud crash, as in surprise) or over a lifetime (engaging with hobbies, pastimes, and intellectual pursuits, as in interest). Of course there are several causes, consequences, and individual differences. As a group, the knowledge emotions motivate people to engage with new and puzzling things rather than avoid them. Over time, engaging with new things, ideas, and people broadens someone's experiences and cultivates expertise. The knowledge emotions thus don't gear up the body like fear, anger, and happiness do, but they do gear up the mind—a critical task for humans, who must learn essentially everything that they know.

So while emotions are something we think of in terms of feelings and the fight or flight response, or even as longer lasting sadness or love, Silvia's ideas point out the less noticed strong connection between emotion and cognition. It is clear that emotions can and do provide a strong basis for how and what we think about.

14.1.5 Plasticity: Experiences Can Alter the Brain

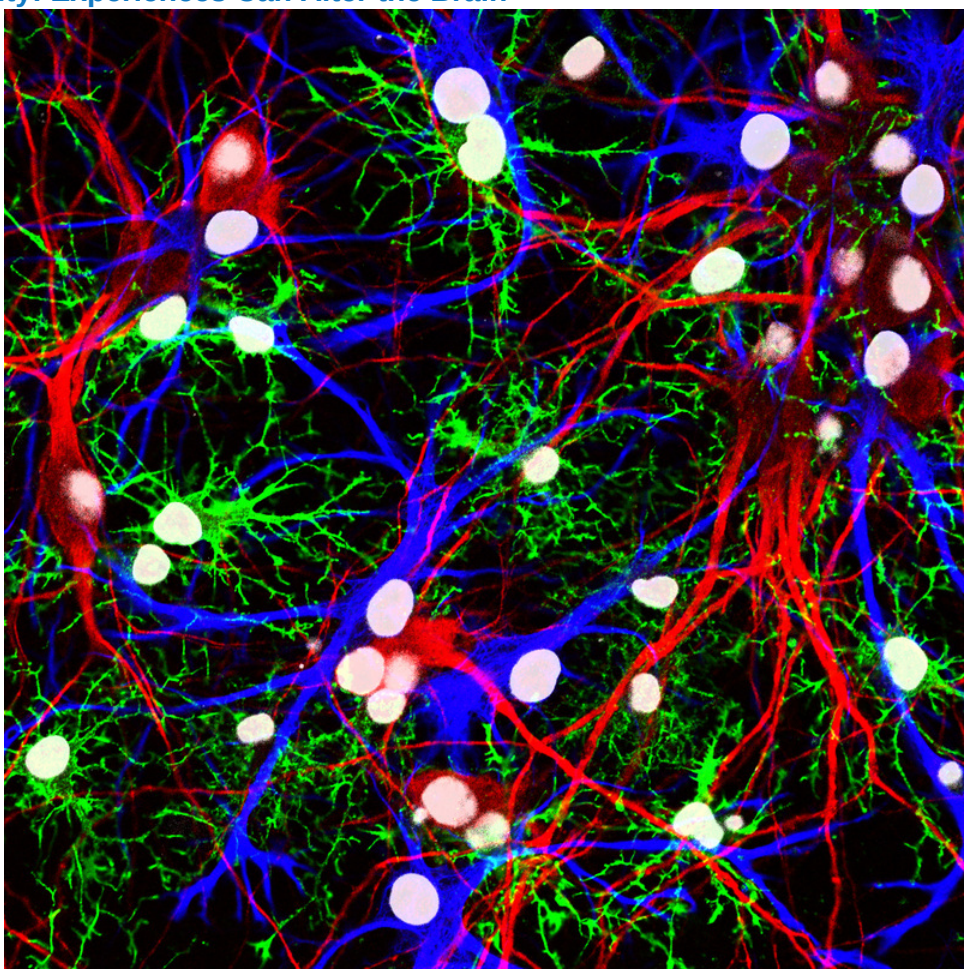


Figure 14.1.9: Neural plasticity can be summed up in the phrase: "Neurons that fire together, wire together." Or in other words, when certain emotions are paired with certain contexts, we learn to associate the two together. Here we see the networks of neurons that are connected to each other. [Image: NICHD NIH, https://goo.gl/T3PUlg, CC BY 2.0, goo.gl/BRvSA7]

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, Daw, Dayan, Singer, & Dolan, 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). Consider how this might be generalized to human experiences that are stressful versus those that are generally comforting and comfortable.

14.1.6 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 brainstem 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).

14.1.7 Summary

Research in affective neuroscience has contributed to knowledge regarding emotional, motivational, and behavioral processes. The study of the basic emotional systems of nonhuman animals provides information about the organization and development of more complex human emotions. Although much still remains to be discovered, current findings in affective neuroscience have already influenced our understanding of drug use and abuse, psychological disorders such as panic disorder, and complex human emotions such as desire and enjoyment, grief and love.

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14.1.9 Attributions

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14.2: Theories of Emotion- Fight or Flight and More

Learning Objectives

- Compare different theories about the generation of emotions.
- Describe the anatomical and chemical bases of anger and fear.
- Analyze how epigenetic research has enhanced our understanding of the nature-nurture debate surrounding anger and fear.

14.2.1 Overview

An important function of emotions in humans, and other animals that live in groups of any kind, is to communicate with other members of one's own species. The emotions that are particularly important to communicate to other members are those related to fear, and those related to anger. When we think of the physiological arousal associated with emotions, we often talk about the "fight or flight" response. These correspond nicely with the two major negative emotions - anger and fear. Multiple animal paradigm studies and human neuroscientific research, including studies with psychopathological conditions, have served to examine the nature of these emotions. Some of these theories and findings will be discussed.

14.2.2 Foundation Theories of Emotion

14.2.2.1 James-Lang and Cannon-Bard Theories

One of the older theories about the origin of emotion is based on the most common sense interpretation of cause and effect. For example, imagine some noticeable emotional stimulus, such as encountering a hungry lion on the sidewalk. The logical cause and effect explanation suggests that seeing the lion prompts the emotion of fear, which then causes the sympathetic nervous system “fight-or-flight” response (elevated heart rate and blood pressure, increased respiration, and cellular mobilization of energy). In the 1880s, psychologist William James and physician Carl Lange independently developed a new theory about the origin of emotion.

According to the **James-Lange theory** of emotion, and contrary to a common sense understanding of the origin of emotion, the **body’s physiological changes *precede* the onset of an emotional response**. For example, imagine encountering that same hungry lion on the sidewalk. The James-Lange theory tells us that the perception of the threat of being eaten causes the sympathetic nervous system response, and that these physiological changes trigger the onset of fear. Soon after, in the 1920s and 30s, two physiologists named Walter Cannon and his doctoral student Philip Bard criticized the James-Lange theory. In one experiment, they surgically removed the entire sympathetic nervous system from cats, destroying the nerves that regulate vascular dilation, the activity of liver enzymes, and the reaction that causes the hair standing on end. These cats were then put before a threatening aggressor. If the James-Lange theory was true, then the physiological changes should precede the emotive response. However, the cats exhibited the fear / aggression response (such as posturing, hissing, and clawing) even without an intact sympathetic nervous system. Relatedly, patients with spinal cord injuries have a similar lack of autonomic inputs to the brain, but their capacity for emotional responding is still intact.

In a second criticism, Cannon and Bard proposed that the physiological changes seen in sympathetic nervous system activity may arise for a variety of reasons, not always for emotionally salient reasons. For example, intense exercise causes strong cardiorespiratory changes; however, we do not necessarily feel a strong emotional state after this physiological perturbation. Likewise, exogenous administration of epinephrine, onset of fever, or being in cold temperatures may also trigger some physiological changes without causing a strong emotional response. Based on their evidence opposing the James-Lange theory, Cannon and Bard developed an alternative explanation for the origin of emotions. According to the **Cannon-Bard theory** of emotion, the perception of an emotionally charged stimulus prompts **simultaneous but independent activation of both the autonomic nervous system and the emotional response**.

14.2.2.2 Reinforcement Sensitivity Theory - Behavioral Activation vs. Behavioral Inhibition

The **reinforcement sensitivity theory (RST)**, postulated by Gray (1982, 1987), theorizes that there are two primary mechanisms that regulate and control emotions and behaviors. The **behavioral inhibition system (BIS)** reacts to punishment, non-reward, and novelty stimuli. The BIS decreases behavioral responses to avoid negative consequences. Activation of the BIS is associated with negative subjective emotions, such as anxiety, fear, sadness, and frustration. Conversely, the **behavioral activation system (BAS)** responds to reward and non-punishment stimuli. Once activated, the BAS triggers approach behaviors and is associated with the experience of positive emotions, such as excitement, happiness, and hope.

This theory has undergone many updates and revisions over the years including the addition of a third system focused on the fight-flight-freeze response and the neural mechanisms that underlie it. In addition, some evidence exists for the hemispheric specialization or **lateralization** of BAS and BIS emotional states. In general, the left hemisphere is more active during BAS emotions and behaviors, while the right is related more to BIS states (Balconi and Mazza, 2009).

14.2.3 Theories of Emotional Distinctions

Can emotions be better described as ***qualitatively*** distinct, for example, as discrete "basic emotions" or "natural kinds" (Ekman et al., 1983; Izard, 1992; Panksepp, 2005) or as ***quantitatively*** distinct, for example, as points along multiple dimensions like **arousal and valence** (Russell and Barrett, 1999; Barrett and Wager, 2006)? Recent years have seen a protracted debate in the literature about how to most accurately capture the nature of emotion (Barrett et al., 2007; Izard, 2007; Panksepp, 2007; Tracy and Randles, 2011), with proposed models of emotion including not only basic emotion and dimensional models, but also those that focus upon goal-relevant appraisals of emotional stimuli (Moors et al., 2013), emotions as coping responses (Roseman, 2013), and emotions as survival circuits (LeDoux, 2012). An extended conversation about the strengths and weaknesses of these various views will not be reviewed in full here, rather, the focus will be on the basic consideration of whether different emotions (e.g., fear, anger) are best viewed as qualitatively or quantitatively distinct.

14.2.3.1 Qualitative Ideas



Figure 14.2.1: Individual emotions as they develop - first we only have basic emotions (fear, anger, disgust, contempt, joy, sadness and interest). Then self conscious (guilt, pride, embarrassment, shame, triumph) ones devleop. And then finally more cognitively complex (envy, gratitude, disappointment, regret, hope, schadenfreude, empathy, compassion) ones appear.(Copyright; Individual emotions by U3161650, CC BY-SA 4.0, via Wikimedia Commons)

Models that posit emotions to be **qualitatively distinct**, such as "**basic emotion**" models, holds that a limited number of emotions like fear, anger, and positive excitement emerge from dissociable neurophysiological processes (Ekman et al., 1983; Izard, 1992; Panksepp, 2005; Lench et al., 2011). In Figure 14.2.1 we see one representation of this idea that initially we have basic emotions including fear, anger, disgust, contempt, joy, sadness and interest, which then grow to include self conscious emotions (guilt, pride, embarrassment, shame, triumph) and finally cognitively complex emotions (envy, gratitude, disappointment, regret, hope, schadenfreude, empathy, compassion). These neurophysiological processes are generally linked to activity in the evolutionarily ancient subcortical structures of the midbrain, striatum, and limbic system most commonly linked to emotion (Panksepp, 2005; Vytal and Hamann, 2010). So, for example, the generation of positive excitement is linked to activation in a striatal circuit centered on dopaminergic neurons in the nucleus accumbens (Ikemoto and Panksepp, 1999), whereas the generation of fear is associated with activity in a circuit involving the periaqueductal gray, anterior and medial hypothalamus, and amygdala (LeDoux, 2000). These neuroanatomical distinctions are in line with the Reinforcement Sensitivity Theory discussed above. Also, finer gradations of experience result when basic emotions are modulated or elaborated by higher-level cognitive processes controlled by the cerebral cortex, but the emergence of qualitatively distinct emotions is not dependent on these cortically-controlled processes (Panksepp, 2005).

14.2.3.2 Quantitative Ideas

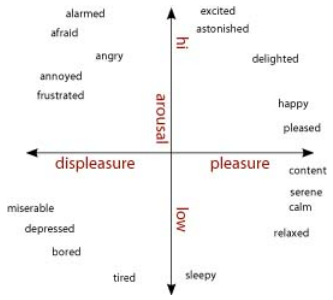


Figure 14.2.2: Model showing two orthogonal dimensions of valence (on the horizonal axis) and arousal (on the vertical axis) with examples of emotions and where they might fall on the graph. For example, delight falls in the top right quadrant because it indicates high arousal and high pleasure while boredom falls in the diagonally opposite quadrant, and relaxed in the bottom right (Copyright; Psychologist Russell's model of arousal and valence by http://imagine-it.org/gamessurvey/, licensed CC BY 3.0, via Wikimedia Commons)

Models that posit emotions to be **quantitatively distinct** hold that emotions like fear, anger, and happiness are best described as **points on one or more core dimensions**. Core dimensions typically proposed to distinguish among emotions are physiological arousal or activation (low—high) and valence (bad—good) (Bradley et al., 2001). [Some have proposed a withdrawal—approach dimension as a substitute or supplement to the valence axis (Wager et al., 2003; Christie and Friedman, 2004; van Honk and Schutter, 2006)]. As shown in figure 14.2.2, arranged orthogonally, these dimensions form a circumplex upon which emotions can be plotted and quantitatively compared (Barrett and Russell, 1999; Russell and Barrett, 1999; Colibazzi et al., 2010). Positive excitement is plotted as high in arousal and positive in valence, and sadness is low in arousal and negative in valence. Fear is typically plotted as high arousal and strongly negative, as is anger (Russell and Barrett, 1999). Further distinctions among emotions are thought to reflect differences in cognitive construals of the events surrounding the basic changes in arousal and valence. Thus, whether an individual experiences anger or fear (which are similar in terms of arousal or valence) may be shaped by interpretations of neurophysiological changes in valence and arousal in light of the eliciting stimulus and the individual's idiosyncratic stores of semantic knowledge, memories, and behavioral responses that shape the subjectively experienced state (Russell, 2003). Under this view, distinctions among experienced emotional states are highly dependent on these cognitively complex processes, which are subserved by a distributed network of regions of the cerebral cortex (Lindquist et al., 2012).

These models generate distinct predictions to the question of whether a disorder or lesion could result in a single emotion being disabled without affecting the experience of other emotions. The discrete emotions view would argue that a disorder or lesion that resulted in dysfunction in the specific structures subserving a particular emotion could affect the experience of one emotion while leaving others intact. In contrast, the dimensional view would require either that other emotions that are dimensionally similar to the affected emotion also be affected, or that deficits in a particular emotion would reflect dysfunction in cortically-driven higher-level cognitive processes.

14.2.3.3 Psychopathy Supports the Qualitative Model

The case of psychopathy lends clear support to notion that fear is qualitatively distinct from other emotions. In psychopathy, the bulk of the clinical and empirical evidence points toward the conclusion that fear responding is uniquely disabled, with other high-arousal (positive excitement, anger) and negatively valenced (anger, disgust) emotions remaining intact. The dimensional view cannot easily explain why in psychopaths the high arousal, negatively valenced state of anger is easily (perhaps too easily) generated, whereas the high arousal, negatively valenced state of fear is not. The problem cannot lie in a failure to fully engage neurocognitive systems underlying either the arousal or valence dimension, because psychopaths experience other high-arousal emotions (positive excitement) as well as other negatively valenced emotions (disgust). It also cannot result from some difficulty arising at the interaction of these axes, because anger and fear are highly similar in terms of both dimensions. Models that substitute a withdrawal—approach axis for a negative—positive axis are no more successful; the two most strongly withdrawal-linked emotions are disgust and fear, and there is no evidence for disgust-based impairments in psychopathy. Individuals with psychopathy also fail to recognize and therefore have no empathic response to others' fear.

On the whole, the empirical data support the idea that the amygdala, along with its efferent projections, is an essential structure for the generation of conditioned fear responses, which account for the majority of experienced fear (Davis, 1992, 1997). Extensive early evidence demonstrated that the amygdala plays a crucial role in the creation of conditioned fear in rodents. For example, lesions to the amygdala prevent rats from developing a conditioned fear response, like freezing in response to a stimulus that predicts shock (Blanchard and Blanchard, 1972). Later studies clarified the roles of the various subnuclei of the amygdala, demonstrating that the lateral nucleus is primarily involved in the acquisition of the fear response whereas the central nucleus is

involved in both the acquisition and the expression of conditioned fear responses (Davis, 1992; Wilensky et al., 2006). The amygdala's many efferent projections coordinate autonomic and behavioral responses to fear eliciting stimuli. Projections from the central nucleus of the amygdala to the lateral hypothalamus are involved in activating autonomic sympathetic nervous system responses, and projections to the ventrolateral periaqueductal gray direct the expression of behavior responses, such as defensive freezing (Davis, 1992; LeDoux, 2012). The amygdala's central role in coordinated fear responding can be demonstrated by electrical stimulation studies showing that complex patterns of behavioral and autonomic changes associated with fear responses result from stimulation of the relevant regions of the amygdala (Davis, 1992). Heavy reliance on animal models is justified in the study of fear responding and the amygdala given how strongly conserved the amygdala nuclei involved in responding to conditioned threats are across species ranging from reptiles to birds to rodents to primates (LeDoux, 2012).

14.2.4 Research Suggesting Connections Between Anger and Fear

Neumann et al. (2010) hypothesize that aggressive behaviors, that are of two basic types - reactive and proactive, are mediated by anxiety-based neurological bases. Based on animal models, they suggest the following: "Male aggression is necessary for the acquisition and maintenance of nutrition, territory, and mating partners. Species-specific rules have to be strictly obeyed to guarantee effective and harmless communication. Thus, adaptive offensive aggression is comprised primarily of harmless threat behaviors allowing the opponent to escape or to switch to submissive behaviors in order to avoid direct physical confrontation. In rodents, such signs of offensive aggression include piloerection (intimidation of the opponent by larger appearance) and lateral threat (arched back and exposure of the flank). In case of an offensive attack, less vulnerable body parts of the opponent, such as those covered with muscles and a thick layer of skin, are targeted to avoid serious injuries (Blanchard and Blanchard, 1977 ; Blanchard et al., 2003). While offensive aggression is usually expressed during a fight for territory or exclusive mating, defensive aggression is mainly displayed in life-threatening situations and is linked to increased fear (Blanchard and Blanchard, 1981). As opposed to offensive aggression, defensive aggression is less or not signaled in advance, and attack targets include more vulnerable body parts (such as the head, belly, and genitals) (Blanchard and Blanchard, 1977 ; Blanchard et al., 2003)." The resident-intruder animal paradigms have been used to measure these ideas (see Figure 14.2.3).



Figure 14.2.3: Resident mouse with aggressive behavior and intruder mouse. Image by DataBase Center for Life Science (DBCLS) licensed CC-BY 4.0 via Wikimedia commons.

They also claim: "Anxiety may be interpreted as an emotional anticipation of an aversive situation and is reflected by species-specific behavioural fear responses to stressful and threatening stimuli characteristic for individual trait anxiety. Fear is not seen as basal state (as is anxiety), but as a complex behavioural response, such as startle or freezing. Further, in addition to factors which determine innate (trait) anxiety, several environmental or pharmacological factors may interact with the genetic background and determine the individual level of state anxiety and the final behavioural phenotype. Emotionality, often used as synonym for anxiety as well as fearfulness, may be seen in a broader sense, comprising both trait and state anxiety and stimulus-related fear. Emotionality is one of the major components underlying the ability of an organism to assess stressful stimuli and scenarios, and to adequately cope with them." (Neumann et al., 2010)

Neumann et al. (2010) show that several clinical and laboratory studies with humans and rodents have shown that there are complicated mechanisms by which anxiety and aggression are co-regulated. There are several neurochemicals found to be involved in complex ways as follows:

Glucocorticoids: The regulation of the HPA (Hypothalamic-Pituitary-Adrenal) axis seems very much connected to the experience of anxiety and aggression. However, the direction is not straightforward in that both high and low glucocorticoids are related to high aggression.

Vasopressin: Vasopressin is produced in the hypothalamus, and testosterone is produced in the gonads, and both modulate aggression as well as anxiety in males. Vasopressin is also involved in reducing anxiety as well as pair-bonding.

Testosterone: Along with aggression, testosterone rises in puberty, castration reduces both (through reduction in Vasopressin also). There are some environmental factors that have a moderating effect, but in general, testosterone is clearly related to modulating aggression in males.

Serotonin: Lower serotonin seems linked to greater aggression and violence in female rhesus. Genetic factors and early life stressors tend to mediate these effects.

GABA: When anxiety levels are increased, aggression increased depending on genetic predispositions to it, and activity also increased in "brain regions including the central amygdala, BST (Bed nucleus of the stria terminalis), lateral septum, and PVN (paraventricular nucleus) that are associated with stress-, fear- and aggression-related behaviour."

"The striking evidence for an overlap in neuroendocrine and neurochemical systems regulating aggression as well as anxiety suggests a strong correlation between these two behaviours. Thus, aggression and anxiety are not always co-regulated, but, under some circumstances, these behaviours may come under the control of the same genes and neuroactive substances including sexual steroids, neuropeptides and neuroamines within specific brain circuitries. Such a view is in agreement with clinical findings. On the one hand, excessive and violent behaviours are seen in humans exposed to adverse early life experiences and in patients with depression- and anxiety-related disorders, or PTSD. On the other hand, rather conflicting data exist on the effects of anxiolytic drugs on anti-social and aggressive behaviours. In future studies that focus on the neurobiological mechanisms of (co-)regulation of aggression and anxiety, epigenetic modifications need to be considered in addition to the neuronal and neuroendocrine parameters discussed above." (Neumann et al, 2010).

14.2.5 Nature vs. Nurture

Both genetic factors and experiences play a role in aggressive behaviors. The genetic regulation of serotonin release appears to play a role in aggression in many mammals including humans. For example, Peeters et al.'s (2020) study concluded that the short version of the serotonin transporter gene (S-allele of the 5-HTTLPR) seems to be linked to greater reactive aggression, and those individuals with higher avoidance tendencies toward angry facial expressions. Because of the chief role of Monoamine Oxidase enzymes (MAOs) in the metabolism of key neurotransmitters involved in aggressive behavior, most notably serotonin, it is not surprising that a substantial body of research has linked aggression with the MAO system. Many results inspired both the scientific community and media outlets to refer to *MAO-A* as the *warrior* or *criminal* gene. Although initial pharmacological studies supported a role for MAO inhibititors (MAOIs) in the reduction of aggression, data from these studies were hard to interpret because of the side effects of MAOIs, and because of their impact on a myriad of unrelated behaviors.

Substantive evidence supporting the role of the *MAO* genes in aggression comes from studies in knockout (KO) mice. Selective knockout models for the *MAO-A* gene, for instance, exhibited increased aggressiveness compared to their wild-type counterparts. Genetic studies in humans provide evidence that *MAO-A* is linked to aggression but only when other environmental factors are also present during development (e.g., abuse, stressors). Other lines of research have demonstrated that the gene product of *MAO-A* (rather than the gene per se) influences violent traits. For instance, cortical and subcortical MAO-A activity in vivo -measured with positron emission tomography (PET)- was negatively associated with trait aggression (attribution: Mentis, Dardiotis, Katsouni & Chrousos, 2021).

Over the last two decades, the study of the relationship between *nature* and *nurture* in shaping human behavior has encountered a renewed interest. Behavioral genetics showed that distinct polymorphisms of genes that code for proteins that control neurotransmitter metabolic and synaptic function are associated with individual vulnerability to aversive experiences, such as stressful and traumatic life events, and may result in an increased risk of developing psychopathologies associated with violence. On the other hand, recent studies indicate that experiencing aversive events modulates gene expression by introducing stable changes to DNA without modifying its sequence, a mechanism known as “epigenetics”. See the earlier chapter on genetics for a

discussion of epigenetics. For example, experiencing adversities during periods of maximal sensitivity to the environment, such as prenatal life, infancy and early adolescence, may introduce lasting epigenetic marks in genes that affect maturational processes in brain, thus favoring the emergence of dysfunctional behaviors, including exaggerate aggression in adulthood.

Adverse environmental influences during critical periods of development have been correlated with epigenetic markers that affect a variety of neurochemical systems. As seen in many studies, low cortisol release is correlated with low self control and higher aggression. Production of oxytocin is related to higher social functioning and attachment formation. Oxytocin secretion is stimulated by early maternal care, whereas adverse experiences in prenatal and early infancy development are related to lower oxytocin receptor methylation (a process involved in epigenetics).

As indicated previously, serotonin is related to regulation of aggression. Genes responsible for controlling the reuptake of serotonin from the synaptic cleft are affected by early stressors (including trauma as well as conditions generated by poverty like poor medical care, housing quality and exposure to violent neighborhoods) that alter brain anatomy and function such as cortical thickness and amygdala reactivity. (See Figure 14.2.4 for the multiple ways in which stress and traumas lead to epigenetic modifications in the oxytocin, serotonin and HPA axis systems that affect aggressive behavior: reactive and proactive aggression, hostility, delinquency externalizing problems, violence, conduct disorders, physical and verbal aggression and callous unemotional traits.)

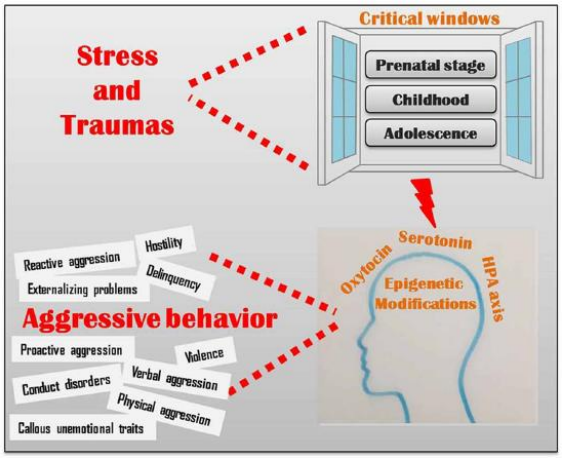


Figure 14.2.4: The epigenetic control of biological pathways, including the neuroendocrine, serotonergic and oxytocinergic pathways, significantly mediates the behavioral responses to the environment (Copyright; Genes and Aggressive Behavior: Epigenetic Mechanisms Underlying Individual Susceptibility to Aversive Environments by Sara Palumbo, Veronica Mariotti, Caterina Ioffreda & Silvia Pellegrini in Frontiers in Behavioral Neuroscience (2018) licensed CC BY 4.0)

Palumbo, Mariotti, Ioffreda and Pellegrini (2018) conclude that epigenetics is shedding a new light on the fine interaction between *nature* and *nurture*, by providing a novel tool to understand the molecular events that underlie the relationship among genes, brain, environment and behavior. Altogether, the results of the studies that we briefly discussed in the present article, clearly indicate that, when it comes to (human) behavior, *nature* and *nurture* are not to be regarded as two distinct and separate factors, contrary to the alternating predominance of either one that has been proposed in different historic phases (Levitt, 2013; Moore, 2016). Indeed, distinct genetic backgrounds differentially modulate the individual susceptibility to the environment and at the same time various environmental conditions differentially affect gene expression, in an intimate and fascinating manner that scientists have now begun to disentangle. The findings from this research pave the way to a novel approach to the understanding of human behavior, with important implications also for social sciences, including philosophy, ethics and law.

14.2.6 Summary

Various models of emotion have been debated in the field of Psychology almost from it's beginnings. The James/Lang, Cannon/Bard, Reinforcement Sensitivity, and Qualitative/Quantitative models each play a role in the explanation of the variety of emotions and associated physiological responses that humans experience. The example of anger and fear highlight the qualitatively distinct basic emotions. While these are primarily negative, they serve very important survival functions. They appear to have clear genetic and biological bases and suggest that similar conclusions can be made for other basic emotions given the necessary research support.

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14.2.8 Attributions

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14.3: Social Neuroscience

Learning Objectives

- Analyze the neural and physiological bases of social behavior including brain areas that are associated with social tasks.
- Evaluate how social behaviors and phenomena affect biological systems.

14.3.1 Overview

The current section provides an overview of the new field of social neuroscience, which combines the use of neuroscience methods and theories to understand how other people influence our thoughts, feelings, and behavior. The module reviews research measuring neural and hormonal responses to understand how we make judgments about other people and react to stress. Through these examples, it illustrates how social neuroscience addresses three different questions: (1) how our understanding of social behavior can be expanded when we consider neural and physiological responses, (2) what the actual biological systems are that implement social behavior (e.g., what specific brain areas are associated with specific social tasks), and (3) how biological systems are impacted by social processes.

Psychology has a long tradition of using our brains and body to better understand how we think and act. For example, in 1939 Heinrich Kluver and Paul Bucy removed (i.e. lesioned) the temporal lobes in some rhesus monkeys and observed the effect on behavior. Included in these **lesions** was a subcortical area of the brain called the **amygdala**. After surgery, the monkeys experienced profound behavioral changes, including loss of fear. These results provided initial evidence that the amygdala plays a role in emotional responses, a finding that has since been confirmed by subsequent studies (Phelps & LeDoux, 2005; Whalen & Phelps, 2009).

14.3.2 What Is Social Neuroscience?

Social neuroscience similarly uses the brain and body to understand how we think and act, with a focus on how we think about and act toward other people. More specifically, we can think of social neuroscience as an interdisciplinary field that uses a range of neuroscience measures to understand how other people influence our thoughts, feelings, and behavior. As such, social neuroscience studies the same topics as social psychology, but does so from a multilevel perspective that includes the study of the brain and body. Figure 14.3.1 shows the scope of social neuroscience with respect to the older fields of social psychology and neuroscience. Although the field is relatively new – the term first appeared in 1992 (Cacioppo & Berntson, 1992) – it has grown rapidly, thanks to technological advances making measures of the brain and body cheaper and more powerful than ever before, and to the recognition that neural and physiological information are critical to understanding how we interact with other people.

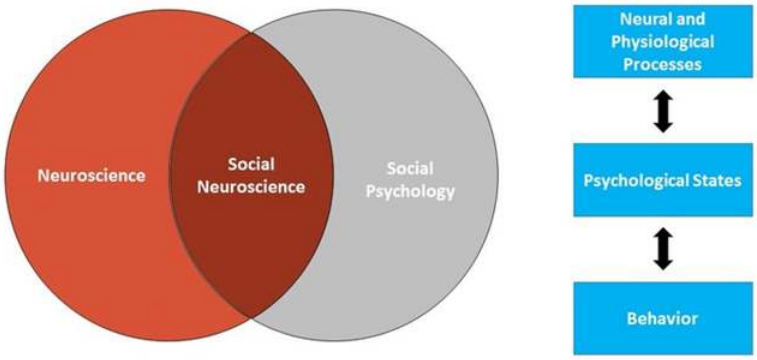


Figure 14.3.1: Social neuroscience is the intersection of social psychology and neuroscience. Under this multilevel approach, neural/physiological processes and behavior are two things we can measure or observe. Psychological states cannot be directly observed, but understanding them is the goal. Social neuroscientists use the observable neural/physiological processes and behavioral responses to make inferences about unobservable psychological states. The bidirectional arrows show that all levels of analysis are assumed to influence each other (e.g., psychological states can influence neural responses, and neural responses can influence psychological states). (Copyright; Tiffany Ito & Jennifer Kubota, via Noba Project, licensed CC BY-NC-SA 4.0)

Social neuroscience can be thought of as both a methodological approach (using measures of the brain and body to study social processes) and a theoretical orientation (seeing the benefits of integrating neuroscience into the study of social psychology). The overall approach in social neuroscience is to understand the psychological processes that underlie our social behavior. Because those psychological processes are intrapsychic phenomena that cannot be directly observed, social neuroscientists rely on a combination of measurable or observable neural and physiological responses as well as actual overt behavior to make inferences about psychological states (see Figure 14.3.1). Using this approach, social neuroscientists have been able to pursue three different types of questions: (1) What more can we learn about social behavior when we consider neural and physiological responses? (2) What are the actual biological systems that implement social behavior (e.g., what specific brain areas are associated with specific social tasks)? and (3) How are biological systems impacted by social processes?

14.3.3 How Automatically Do We Judge Other People?

Social categorization is the act of mentally classifying someone as belonging in a group. Why do we do this? It is an effective mental shortcut. Rather than effortfully thinking about every detail of every person we encounter, social categorization allows us to rely on information we already know about the person's group. For example, by classifying your restaurant server as a man, you can quickly activate all the information you have stored about men and use it to guide your behavior. But this shortcut comes with potentially high costs. The stored group beliefs might not be very accurate, and even when they do accurately describe some group members, they are unlikely to be true for every member you encounter. In addition, many beliefs we associate with groups – called **stereotypes** – are negative. This means that relying on social categorization can often lead people to make negative assumptions about others.

The potential costs of social categorization make it important to understand how social categorization occurs. Is it rare or does it occur often? Is it something we can easily stop, or is it hard to override? One difficulty answering these questions is that people are not always consciously aware of what they are doing. In this case, we might not always realize when we are categorizing someone. Another concern is that even when people are aware of their behavior, they can be reluctant to accurately report it to an experimenter. In the case of social categorization, subjects might worry they will look bad if they accurately report classifying someone into a group associated with negative stereotypes. For instance, many racial groups are associated with some negative stereotypes, and subjects may worry that admitting to classifying someone into one of those groups means they believe and use those negative stereotypes.



Figure 14.3.2: This man is wearing an elastic electrode cap into which individual electrodes (inside the white circles) are sewn into standardized locations. [Image: Hans, CC0 Public Domain, goo.gl/m25gce]

Social neuroscience has been useful for studying how social categorization occurs without having to rely on self-report measures, instead measuring brain activity differences that occur when people encounter members of different social groups. Much of this work has been recorded using the **electroencephalogram**, or **EEG**. EEG is a measure of electrical activity generated by the brain's neurons. Comparing this electrical activity at a given point in time against what a person is thinking and doing at that same time allows us to make inferences about brain activity associated with specific psychological states. One particularly nice feature of EEG is that it provides very precise timing information about when brain activity occurs. EEG is measured non-invasively with small electrodes that rest on the surface of the scalp. This is often done with a stretchy elastic cap, like the one shown in Figure 14.3.2, into which the small electrodes are sewn. Researchers simply pull the cap onto the subject's head to get the electrodes into place; wearing it is similar to wearing a swim cap. The subject can then be asked to think about different topics or engage in different tasks as brain activity is measured.

To study social categorization, subjects have been shown pictures of people who belong to different social groups. Brain activity recorded from many individual trials (e.g., looking at lots of different Black individuals) is then averaged together to get an overall idea of how the brain responds when viewing individuals who belong to a particular social group. These studies suggest that social categorization is an **automatic process** – something that happens with little conscious awareness or control – especially for dimensions like gender, race, and age (Ito & Urland, 2003; Mouchetant-Rostaing & Giard, 2003). The studies specifically show that brain activity differs when subjects view members of different social groups (e.g., men versus women, Blacks versus Whites), suggesting that the group differences are being encoded and processed by the perceiver. One interesting finding is that these brain changes occur both when subjects are purposely asked to categorize the people into social groups (e.g., to judge whether the person is Black or White), and also when they are asked to do something that draws attention away from group classifications (e.g., making a personality judgment about the person) (Ito & Urland, 2005). This tells us that we do not have to intend to make group classifications in order for them to happen. It is also very interesting to consider how quickly the changes in brain responses occur. Brain activity is altered by viewing members of different groups within 200 milliseconds of seeing a person's face. That is just two-tenths of a second. Such a fast response lends further support to the idea that social categorization occurs automatically and may not depend on conscious intention.

Overall, this research suggests that we engage in social categorization very frequently. In fact, it appears to happen automatically (i.e., without us consciously intending for it to happen) in most situations for dimensions like gender, age, and race. Since classifying someone into a group is the first step to activating a group stereotype, this research provides important information about how easily stereotypes can be activated. And because it is hard for people to accurately report on things that happen so quickly, this issue has been difficult to study using more traditional self-report measures. Using EEGs has, therefore, been helpful in providing interesting new insights into social behavior.

14.3.4 Do We Use Our Own Behavior to Help Us Understand Others?

Classifying someone into a social group then activating the associated stereotype is one way to make inferences about others. However, it is not the only method. Another strategy is to imagine what our own thoughts, feelings, and behaviors would be in a similar situation. Then we can use our simulated reaction as a best guess about how someone else will respond (Goldman, 2005). After all, we are experts in our own feelings, thoughts, and tendencies. It might be hard to know what other people are feeling and thinking, but we can always ask ourselves how we would feel and act if we were in their shoes.

There has been some debate about whether simulation should/could be used to get into the mind of others or is an effective way to get into the minds of others (Carruthers & Smith, 1996; Gallese & Goldman, 1998). Social neuroscience research has addressed this question by looking at the brain areas used when people think about themselves and others. If the same brain areas are active for the two types of judgments, it lends support to the idea that the self may be used to make inferences about others via simulation.

We know that an area in the prefrontal cortex called the **medial prefrontal cortex** (mPFC) – located in the middle of the frontal lobe – is active when people think about themselves (Kelley, Macrae, Wyland, Caglar, Inati, & Heatherton, 2002). This conclusion comes from studies using **functional magnetic resonance imaging**, or fMRI. While EEG measures the brain's electrical activity, fMRI measures changes in the oxygenation of blood flowing in the brain. Remember as discussed in chapter 2, when neurons become more active, blood flow to the area increases to bring more oxygen and glucose to the active cells. fMRI allows us to image these changes in oxygenation by placing people in an fMRI machine or scanner (Figure 14.3.3), which consists of large magnets that create strong magnetic fields. The magnets affect the alignment of the oxygen molecules within the blood (i.e., how they are tilted). As the oxygen molecules move in and out of alignment with the magnetic fields, their nuclei produce energy that can be detected with special sensors placed close to the head. Recording fMRI involves having the subject lay on a small bed that is then rolled into the scanner. While fMRI does require subjects to lie still within the small scanner and the large magnets involved are noisy, the scanning itself is safe and painless. Like EEG, the subject can then be asked to think about different topics or engage in different tasks as brain activity is measured. If we know what a person is thinking or doing when fMRI detects a blood flow increase to a particular brain area, we can infer that part of the brain is involved with the thought or action. fMRI is particularly useful for identifying which particular brain areas are active at a given point in time.



Figure 14.3.3: Functional magnetic resonance imaging (fMRI) scanner used to image the brain while people perform tasks. The scanner allows researchers to view the changes in blood oxygenation in specific locations in the brain during a task. Images are collected using powerful magnets and radio waves that shift the position of atoms in oxygenated blood that rushes to areas involved in performing the task. MRIs are non-invasive and there are no known risks from exposure to the magnetic fields or radio waves. Subjects lay on the while bed with their head inside the head coil, then the bed is moved into the scanner. [Image: Janne Moren, https://goo.gl/MKb2jn, CC BY-NC-SA 2.0, goo.gl/Toc0ZF]

The conclusion that the mPFC is associated with the self comes from studies measuring fMRI while subjects think about themselves (e.g., saying whether traits are descriptive of themselves). Using this knowledge, other researchers have looked at whether the same brain area is active when people make inferences about others. Mitchell, Neil Macrae, and Banaji (2005) showed subjects pictures of strangers and had them judge either how pleased the person was to have his or her picture taken or how symmetrical the face appeared. Judging whether someone is pleased about being photographed requires making an inference about someone's internal feelings – we call this **mentalizing**. By contrast, facial symmetry judgments are based solely on physical appearances and do not involve mentalizing. A comparison of brain activity during the two types of judgments shows more activity in the mPFC when making the mental versus physical judgments, suggesting this brain area is involved when inferring the internal beliefs of others.

There are two other notable aspects of this study. First, mentalizing about others also increased activity in a variety of regions important for many aspects of social processing, including a region important in representing biological motion (**superior temporal sulcus** or STS), an area critical for emotional processing (amygdala), and a region also involved in thinking about the beliefs of others (**temporal parietal junction**, TPJ) (Gobbini & Haxby, 2007; Schultz, Imamizu, Kawato, & Frith, 2004) (See Figure 14.3.4). This finding shows that a distributed and interacting set of brain areas is likely to be involved in social processing. Second, activity in the most ventral part of the mPFC (the part closer to the belly rather than toward the top of the head), which has been most consistently associated with thinking about the self, was particularly active when subjects mentalized about people they rated as similar to themselves. Simulation is thought to be most likely for similar others (as in other people who one assumes to be similar to oneself), so this finding lends support to the conclusion that we use simulation to mentalize about others. After all, if you encounter someone who has the same musical taste as you, you will probably assume you have other things in common with him. By contrast, if you learn that someone loves music that you hate, you might expect him to differ from you in other ways (Srivastava, Guglielmo, & Beer, 2010). Using a simulation of our own feelings and thoughts will be most accurate if we have reason to think the person's internal experiences are like our own. Thus, we may be most likely to use simulation to make inferences about others if we think they are similar to us.

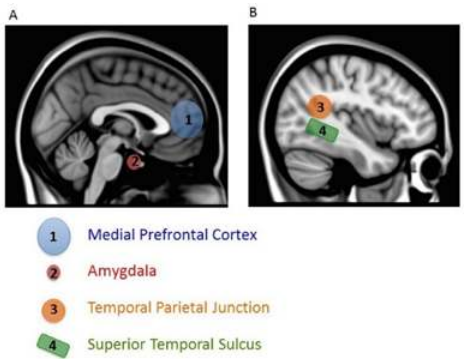


Figure 14.3.4: The areas of the brain most commonly associated with processing of self and others. Panel A is a medial sagittal view, Panel B is a lateral sagittal view. The medial prefrontal cortex (mPFC) (Structure 1) is commonly activated when thinking about one's self and when thinking about similar others. Additionally, the amygdala (Structure 2) is important for learning about and detecting important things in our environments and plays an important role in fear learning and expression. The temporal parietal junction (TPJ) (Structure 3), located at the intersection of the parietal and temporal lobes, is activated when people think about the beliefs of others. Activity in the superior temporal sulcus (STS) (Structure 4) is commonly observed when people view biological motion. The common activation of this network of regions when people think about the feelings, thoughts, and intentions of others indicates that the processing of others involves a number of complex psychological processes.

This research is a good example of how social neuroscience is revealing the **functional neuroanatomy** of social behavior. That is, it tells us which brain areas are involved with social behavior. The mPFC (as well as other areas such as the STS, amygdala, and TPJ) is involved in making judgments about the self and others. This research also provides new information about how inferences are made about others. Whereas some have doubted the widespread use of simulation as a means for making inferences about others, the activation of the mPFC when mentalizing about others, and the sensitivity of this activation to similarity between self and other, provides evidence that simulation occurs.

14.3.5 What Is the Cost of Social Stress?

Stress is an unfortunately frequent experience for many of us. **Stress** – which can be broadly defined as a threat or challenge to our well-being – can result from everyday events like a course exam or more extreme events such as experiencing a natural disaster. When faced with a stressor, **sympathetic nervous system** activity increases in order to prepare our body to respond to the challenge. This produces what Selye (1950) called a **fight or flight response**. The release of **hormones**, which act as messengers from one part of an organism (e.g., a cell or gland) to another part of the organism, is part of the stress response. This is further discussed in the next section.

A small amount of stress can actually help us stay alert and active. In comparison, sustained stressors, or chronic stress, detrimentally affect our health and impair performance (Al'Absi, Hugdahl, & Lovallo, 2002; Black, 2002; Lazarus, 1974). This happens in part through the chronic secretion of stress-related hormones (e.g., Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Dickerson, Gable, Irwin, Aziz, & Kemeny, 2009). In particular, stress activates the **hypothalamic-pituitary-adrenal (HPA) axis** to release **cortisol** (see Figure 14.3.5). Chronic stress, by way of increases in cortisol, impairs attention, memory, and self-control (Arnsten, 2009). Cortisol levels can be measured non-invasively in bodily fluids, including blood and saliva. Researchers often collect a cortisol sample before and after a potentially stressful task. In one common collection method, subjects place polymer swabs under their tongue for 1 to 2 minutes to soak up saliva. The saliva samples are then stored and analyzed later to determine the level of cortisol present at each time point.

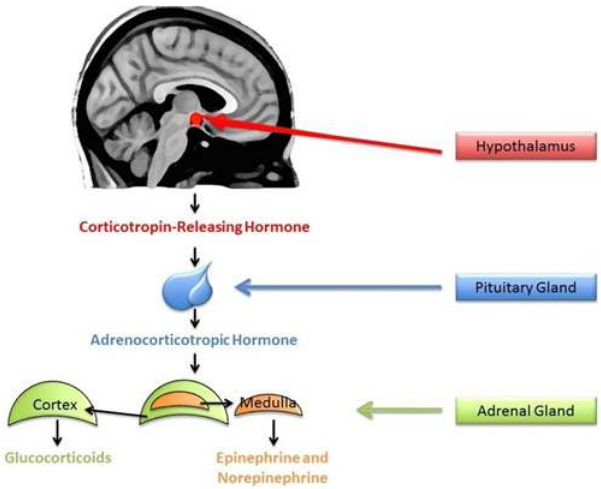


Figure 14.3.5: The Hypothalamic-pituitary-adrenal (HPA) axis. Black arrows represent the stress response pathway starting in the brain at the hypothalamus (an area within the brain). Stress triggers neurons in the hypothalamus to release corticotrophin-releasing hormone (CRH). The CRH is transported to the pituitary gland, another area in the brain, that activates the secretion of andrenocorticotropic hormone (ACTH). In turn, ACTH stimulates the adrenal glands that sit on top of the kidneys. The adrenal glands are composed of the outer adrenal cortex and inner adrenal medulla. The adrenal cortex secretes glucorcorticoids (including cortisol) and the medulla secretes epinephrine and norepinephrine. Stress, both psychological and physical, activates the HPA axis and results in the systemic release of cortisol, epinephrine, and norepinephrine.

Whereas early stress researchers studied the effects of physical stressors like loud noises, social neuroscientists have been instrumental in studying how our interactions with other people can cause stress. This question has been addressed through **neuroendocrinology**, or the study of how the brain and hormones act in concert to coordinate the physiology of the body. One contribution of this work has been in understanding the conditions under which other people can cause stress. In one study, Dickerson, Mycek, and Zaldivar (2008) asked undergraduates to deliver a speech either alone or to two other people. When the students gave the speech in front of others, there was a marked increase in cortisol compared with when they were asked to give a speech alone. This suggests that like chronic physical stress, everyday social stressors, like having your performance judged by others, induces a stress response. Interestingly, simply giving a speech in the same room with someone who is doing something else did not induce a stress response. This suggests that the mere presence of others is not stressful, but rather it is the potential for them to judge us that induces stress.

Worrying about what other people think of us is not the only source of social stress in our lives. Other research has shown that interacting with people who belong to different social groups than us – what social psychologists call **outgroup** members – can increase physiological stress responses. For example, cardiovascular responses associated with stress like contractility of the heart ventricles and the amount of blood pumped by the heart (what is called cardiac output) are increased when interacting with outgroup as compared with **ingroup** members (i.e., people who belong to the same social group we do) (Mendes, Blascovich, Likel, & Hunter, 2002). This stress may derive from the expectation that interactions with dissimilar others will be uncomfortable (Stephan & Stephan, 1985) or concern about being judged as unfriendly and prejudiced if the interaction goes poorly (Plant & Devine, 2003).

The research just reviewed shows that events in our social lives can be stressful, but are social interactions always bad for us? No. In fact, while others can be the source of much stress, they are also a major buffer against stress. Research on **social support** shows that relying on a network of individuals in tough times gives us tools for dealing with stress and can ward off loneliness (Cacioppo & Patrick, 2008). For instance, people who report greater social support show a smaller increase in cortisol when performing a speech in front of two evaluators (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007).

What determines whether others will increase or decrease stress? What matters is the context of the social interaction. When it has potential to reflect badly on the self, social interaction can be stressful, but when it provides support and comfort, social interaction can protect us from the negative effects of stress. Using neuroendocrinology by measuring hormonal changes in the body has helped researchers better understand how social factors impact our body and ultimately our health.

14.3.6 Summary

Human beings are intensely social creatures – our lives are intertwined with other people and our health and well-being depend on others. Social neuroscience helps us to understand the critical function of how we make sense of and interact with other people.

This module provides an introduction to what social neuroscience is and what we have already learned from it, but there is much still to understand. As we move forward, one exciting future direction will be to better understand how different parts of the brain and body interact to produce the numerous and complex patterns of social behavior that humans display. We hinted at some of this complexity when we reviewed research showing that while the mPFC is involved in mentalizing, other areas such as the STS, amygdala, and TPJ are as well. There are likely additional brain areas involved as well, interacting in ways we do not yet fully understand. These brain areas in turn control other aspects of the body to coordinate our responses during social interactions. Social neuroscience will continue to investigate these questions, revealing new information about how social processes occur, while also increasing our understanding of basic neural and physiological processes.

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14.3.8 Attributions

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14.4: Stress and health

Learning Objectives

- Describe basic terminology used in the field of health psychology.
- Explain theoretical models of health, as well as the role of psychological stress in the development of disease.
- Describe psychological factors that contribute to resilience and improved health.
- Defend the relevance and importance of psychology to the field of medicine.

14.4.1 Overview

Our emotions, thoughts, and behaviors play an important role in our health. Not only do they influence our day-to-day health practices, but they can also influence how our body functions. Clearly, there is a connection between stress and health - both physical and mental. This section provides an overview of health psychology, which is a field devoted to understanding the connections between psychology and health. Discussed here are examples of topics a health psychologist might study, including stress, psychosocial factors related to health and disease, how to use psychology to improve health, and the role of psychology in medicine.

14.4.2 What Is Health Psychology?

Today, we face more **chronic disease** than ever before because we are living longer lives while also frequently behaving in unhealthy ways. One example of a chronic disease is coronary heart disease (CHD): It is the number one cause of death worldwide (World Health Organization, 2013). CHD develops slowly over time and typically appears midlife, but related heart problems can persist for years after the original diagnosis or cardiovascular event. In managing illnesses that persist over time (other examples might include cancer, diabetes, and long-term disability) many psychological factors will determine the progression of the ailment. For example, do patients seek help when appropriate? Do they follow doctor recommendations? Do they develop negative psychological symptoms due to lasting illness (e.g., depression)? Also important is that psychological factors can play a significant role in *who* develops these diseases, the prognosis, and the nature of the symptoms related to the illness. Health psychology is a relatively new, interdisciplinary field of study that focuses on these very issues, or more specifically, the role of psychology in maintaining health, as well as preventing and treating illness.



Figure 14.4.1: Health psychologists are helping people to adapt behaviors to avoid disease, reduce stress, and improve overall health. [Image: Adelphi Lab Center, https://goo.gl/N9wXon, CC BY 2.0, goo.gl/BRvSA7]

Consideration of how psychological and social factors influence health is especially important today because many of the leading causes of illness in developed countries are often attributed to psychological and behavioral factors. In the case of CHD, discussed above, psychosocial factors, such as excessive stress, smoking, unhealthy eating habits, and some personality traits can also lead to increased risk of disease and worse health outcomes. That being said, many of these factors can be adjusted using psychological techniques. For example, clinical health psychologists can improve health practices like poor dietary choices and smoking, they can teach important stress reduction techniques, and they can help treat psychological disorders tied to poor health. Health psychology considers how the choices we make, the behaviors we engage in, and even the emotions that we feel, can play an important role in our overall health (Cohen & Herbert, 1996; Taylor, 2012).

Health psychology relies on the **Biopsychosocial Model of Health**. This model posits that biology, psychology, and social factors are just as important in the development of disease as biological causes (e.g., germs, viruses), which is consistent with the World Health Organization (1946) definition of **health**. This model replaces the older **Biomedical Model of Health**, which primarily considers the physical, or pathogenic, factors contributing to illness. Thanks to advances in medical technology, there is a growing understanding of the physiology underlying the **mind–body connection**, and in particular, the role that different feelings can have on our body's function (See Figure 14.4.1) . Health psychology researchers working in the fields of **psychosomatic medicine** and **psychoneuroimmunology**, for example, are interested in understanding how psychological factors can "get under the skin" and influence our physiology in order to better understand how factors like stress can make us sick.

14.4.3 What Is stress?

It is clear that stress plays a major role in our mental and physical health, but what exactly is it? The term **stress** was originally derived from the field of mechanics where it is used to describe materials under pressure. The word was first used in a *psychological* manner by researcher Hans Selye. He was examining the effect of an ovarian hormone that he thought caused

sickness in a sample of rats. Surprisingly, he noticed that almost any injected hormone produced this same sickness. He smartly realized that it was not the hormone under investigation that was causing these problems, but instead, the unpleasant experience of being handled and injected by researchers that led to high physiological arousal and, eventually, to health problems like ulcers. Selye (1946) coined the term "stressor" to label a stimulus that had this effect on the body and developed a model of the stress response called the **General Adaptation Syndrome**. Since then, psychologists have studied stress in a myriad of ways, including stress as caused by negative events (e.g., natural disasters or major life changes like dropping out of school), as caused by chronically difficult situations (e.g., taking care of a loved one with Alzheimer's), as caused by short-term hassles, as a biological fight-or-flight response, and even as clinical illness like post-traumatic stress disorder (PTSD). It continues to be one of the most important and well-studied psychological correlates of illness, because excessive stress causes potentially damaging wear and tear on the body and can influence almost any imaginable disease process.

14.4.4 Stress and Health

You probably know exactly what it's like to feel stress, but what you may not know is that it can objectively influence your health. Answers to questions like, "How stressed do you feel?" or "How overwhelmed do you feel?" can predict your likelihood of developing both minor illnesses as well as serious problems like future heart attack (Cohen, Janicki-Deverts, & Miller, 2007). To understand how health psychologists study these types of associations, we will describe one famous example of a stress and health study. Imagine that you are a research subject for a moment. After you check into a hotel room as part of the study, the researchers ask you to report your general levels of stress. Not too surprising; however, what happens next is that you receive droplets of *cold virus* into your nose! The researchers intentionally try to make you sick by exposing you to an infectious illness. After they expose you to the virus, the researchers will then evaluate you for several days by asking you questions about your symptoms, monitoring how much mucus you are producing by weighing your used tissues, and taking body fluid samples—all to see if you are objectively ill with a cold. Now, the interesting thing is that not everyone who has drops of cold virus put in their nose develops the illness. (Clearly this study was done long before COVID-19 because I can't see people checking into a hotel, or being intentionally exposed to a virus - even the common cold one - after the pandemic!) Studies like this one find that people who are less stressed and those who are more positive at the beginning of the study are at a decreased risk of developing a cold (Cohen, Tyrrell, & Smith, 1991; Cohen, Alper, Doyle, Treanor, & Turner, 2006) (see Figure 14.4.2 for an example).

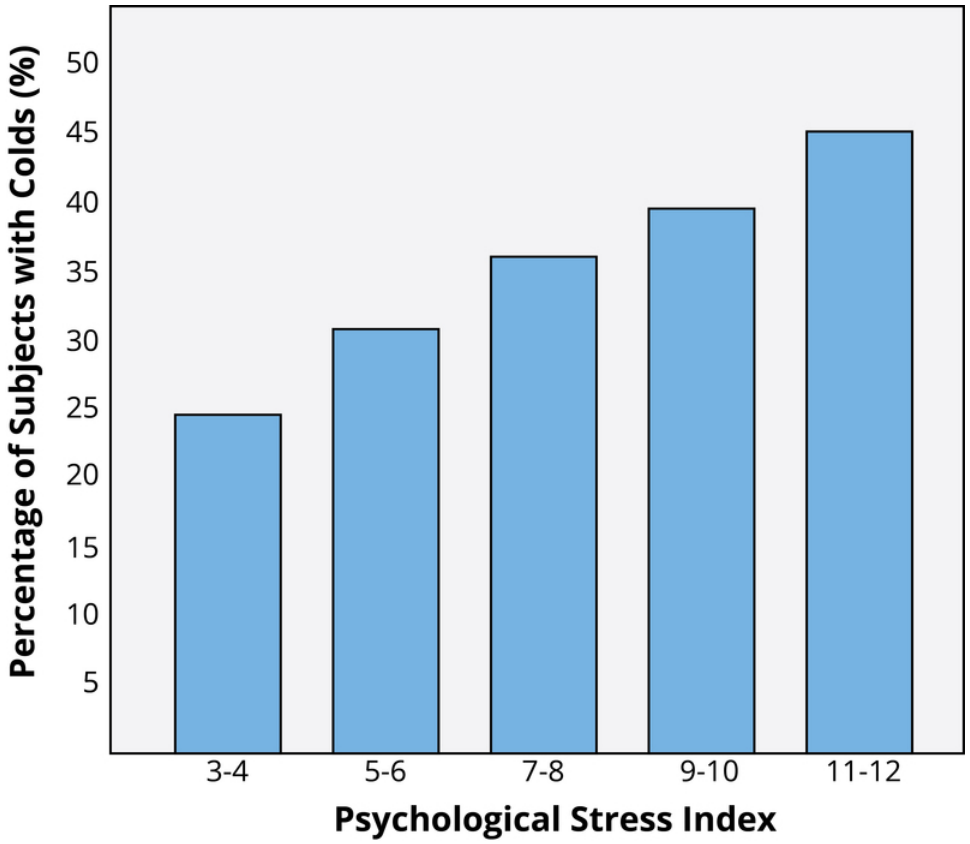


Figure 14.4.2: Adapted from Cohen et al. 1991. This graph indicates that the greater the psychological stress index, the greater the percent of subjects with colds. In fact, there is a 25% increase in percentage of subjects with a cold from those who report a psychological stress index of 3-4 versus those reporting a psychological stress index of 11-12.

Importantly, it is not just major life **stressors** (e.g., a family death, a natural disaster) that increase the likelihood of getting sick. Even small **daily hassles** like getting stuck in traffic or fighting with your girlfriend/boyfriend or partner can raise your blood pressure, alter your stress hormones, and even suppress your immune system function (DeLongis, Folkman, & Lazarus, 1988; Twisk, Snel, Kemper, & van Machelen, 1999).

14.4.5 Immune System

The immune system is a host defense system. It comprises many biological structures —ranging from individual white blood cells to entire organs — as well as many complex biological processes. The function of the immune system is to protect the host from pathogens (something that causes a disease) and other causes of disease such as tumor cells. To function properly, the immune system must be able to detect a wide variety of pathogens. It also must be able to distinguish the cells of pathogens from the host's own cells and also to distinguish cancerous or damaged host cells from healthy cells. In humans and most other vertebrates, the immune system consists of layered defenses that have increased specificity for particular pathogens or tumor cells. The layered defenses of the human immune system are usually classified into two subsystems called the innate immune system and the adaptive immune system.

14.4.5.1 Innate Immune System

Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens (which are bacteria, viruses or other microorganisms that case diseases) from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The phagocytes are the body's fast acting first line of immunological defense against organisms that have breached barrier defenses and have entered the vulnerable tissues of the body. For example, certain leukocytes (white blood cells) engulf and destroy pathogens they encounter in the process called phagocytosis. The body's response against a pathogen's breach is also called inflammation. Inflammation is discussed in detail again a few paragraphs later.

14.4.5.2 Adaptive Immune System

The adaptive immune system is activated if pathogens successfully enter the body and manage to evade the general defenses of the innate immune system. An adaptive response is specific to the particular type of pathogen that has invaded the body or to cancerous cells. It takes longer to launch a specific attack, but once it is underway, its specificity makes it very effective. An adaptive immune response is set in motion by antigens that the immune system recognizes as foreign. Unlike an innate immune response, an adaptive immune response is highly specific to a particular pathogen (or its antigen).

An important function of the adaptive immune system that is not shared by the innate immune system is the creation of immunological memory or immunity. This occurs after the initial response to a specific pathogen. It allows a faster, stronger response on subsequent encounters with the same pathogen, usually before the pathogen can cause symptoms of illness. An adaptive response also usually leads to immunity. This is a state of resistance to a specific pathogen due to the ability of the adaptive immune system to “remember” the pathogen and immediately mount a strong attack tailored to that particular pathogen if it invades again in the future.

14.4.5.2.1 Lymphatic System

The lymphatic system is a human organ system that is a vital part of the adaptive immune system. It is also part of the cardiovascular system and plays a major role in the digestive system

The primary function of the lymphatic system is to host defense as part of the immune system. This function of the lymphatic system is centered on the production, maturation, and circulation of lymphocytes. Lymphocytes are leukocytes that are involved in the adaptive immune system. They are responsible for the recognition of, and tailored defense against, specific pathogens or tumor cells. Lymphocytes may also create a lasting memory of pathogens so they can be attacked quickly and strongly if they ever invade the body again. In this way, lymphocytes bring about long-lasting immunity to specific pathogens.

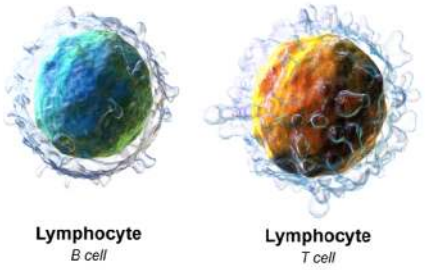


Figure 14.4.3: These are Lymphocytes - B nd T cells - Notice the large nucleus in the center of these relatively round cells.

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Lymphocytes are leukocytes that arise and mature in organs of the lymphatic system, including the bone marrow and thymus. There are two main types of lymphocytes involved in adaptive immune responses, called T cells and B cells which are illustrated in Figure 14.4.3. Both B cells and T cells are involved in the adaptive immune response, but they play different roles. T cells destroy infected cells or release chemicals that regulate immune responses. B cells secrete antibodies that bind with antigens of pathogens so they can be removed by other immune cells or processes.

14.4.5.2.2 T Cells

There are multiple types of T cells or T lymphocytes. Major types are killer (or cytotoxic) T cells and helper T cells. Both types develop from immature T cells that become activated by exposure to an antigen. T cells must be activated. After the pathogen is phagocytized and digested by macrophages, a part of the pathogen is displayed on the surface of the macrophage. Helper T cells are more easily activated than killer T cells. Activation of killer T cells is strongly regulated and may require additional stimulation from helper T cells.

14.4.5.2.3 B Cells and B Cell Activation

B cells, or B lymphocytes, are the major cells involved in the creation of antibodies that circulate in blood plasma and lymph. Antibodies are large, Y-shaped proteins used by the immune system to identify and neutralize foreign invaders. Besides producing antibodies, B cells may also function as antigen-presenting cells or secrete cytokines that help control other immune cells and responses.

14.4.5.3 Self vs. Non-Self

Both innate and adaptive immune responses depend on the ability of the immune system to distinguish between self and non-self molecules. Self molecules are those components of an organism's body that can be distinguished from foreign substances by the immune system.

14.4.5.3.1 Antigens and Antibodies

Many non-self molecules comprise a class of compounds called antigens. Antigens, which are usually proteins, bind to specific receptors on immune system cells and elicit an adaptive immune response. Some adaptive immune system cells (B cells) respond to foreign antigens by producing antibodies. An antibody is a molecule that precisely matches and binds to a specific antigen. This may target the antigen (and the pathogen displaying it) for destruction by other immune cells.

Antigens on the surface of pathogens are how the adaptive immune system recognizes specific pathogens. Antigen specificity allows for the generation of responses tailored to the specific pathogen. It is also how the adaptive immune system "remembers" the same pathogen in the future.

14.4.5.4 Immune Surveillance

Another important role of the immune system is to identify and eliminate tumor cells. This is called immune surveillance. The transformed cells of tumors express antigens that are not found on normal body cells. The main response of the immune system to tumor cells is to destroy them. This is carried out primarily by aptly named killer T cells of the adaptive immune system.

14.4.5.5 Inflammation and Fever

The inflammatory response, or inflammation, is triggered by a cascade of chemical mediators and cellular responses that may occur when cells are damaged and stressed or when pathogens successfully breach the physical barriers of the innate immune system. Although inflammation is typically associated with negative consequences of injury or disease, it is a necessary process insofar as it allows for recruitment of the cellular defenses needed to eliminate pathogens, remove damaged and dead cells, and initiate repair mechanisms. Excessive inflammation, however, can result in local tissue damage and, in severe cases, may even become deadly.

A fever is an inflammatory response that extends beyond the site of infection and affects the entire body, resulting in an overall increase in body temperature. Body temperature is normally regulated and maintained by the hypothalamus, an anatomical section of the brain that functions to maintain homeostasis in the body. However, certain bacterial or viral infections can result in the production of pyrogens, chemicals that effectively alter the "thermostat setting" of the hypothalamus to elevate body temperature and cause fever. Pyrogens may be exogenous or endogenous. For example, the endotoxin lipopolysaccharide (LPS), produced by gram-negative bacteria, is an exogenous pyrogen that may induce the leukocytes to release endogenous pyrogens such as interleukin-1 (IL-1), IL-6, interferon-γ (IFN-γ), and tumor necrosis factor (TNF). In a cascading effect, these molecules can then lead to the release of prostaglandin E2 (PGE_2) from other cells, resetting the hypothalamus to initiate fever (Figure 14.4.4:).

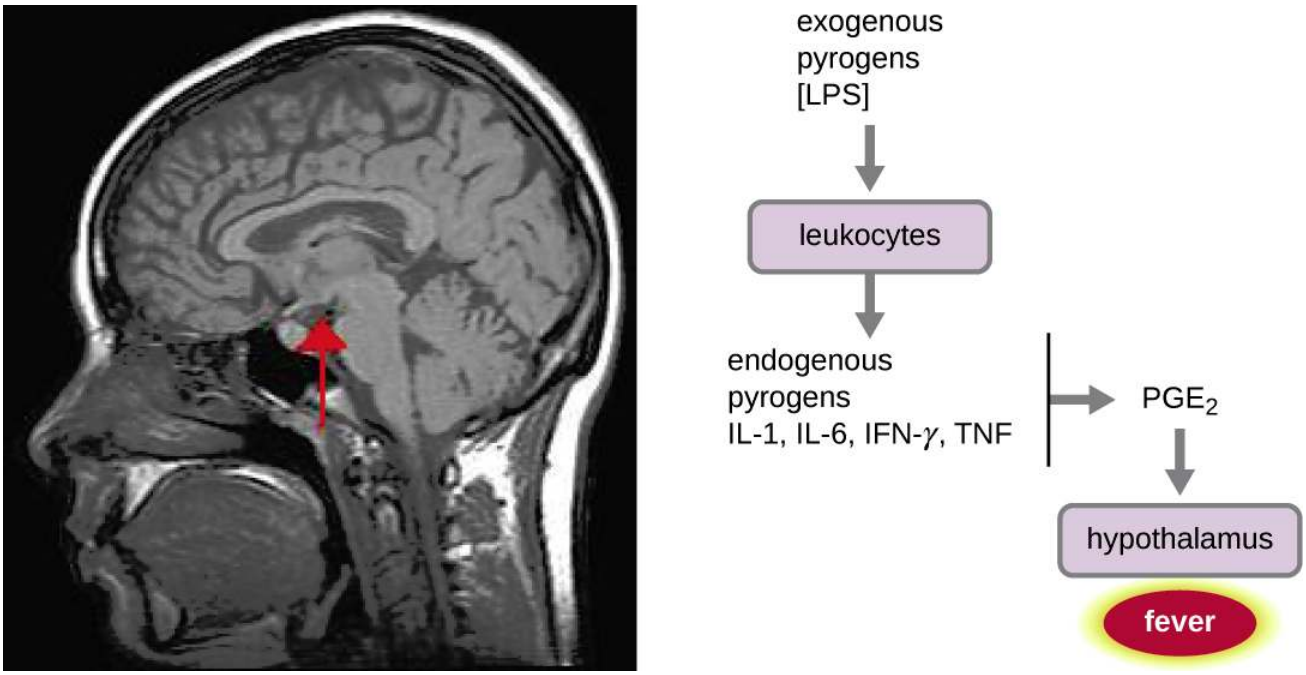


Figure 14.4.4:Macrophages recognize pathogens in an area and release cytokines that trigger inflammation. The cytokines also send a signal up the vagus nerve to the hypothalamus.

Inflammation and Fever by Openstax, licensed CC BY 4.0

Like other forms of inflammation, a fever enhances the innate immune defenses by stimulating leukocytes to kill pathogens. The rise in body temperature also may inhibit the growth of many pathogens since human pathogens are mesophiles with optimum growth occurring around 35 °C (95 °F). In addition, some studies suggest that fever may also stimulate release of iron-sequestering compounds from the liver, thereby starving out microbes that rely on iron for growth.

During fever, the skin may appear pale due to vasoconstriction of the blood vessels in the skin, which is mediated by the hypothalamus to divert blood flow away from extremities, minimizing the loss of heat and raising the core temperature. The hypothalamus will also stimulate shivering of muscles, another effective mechanism of generating heat and raising the core temperature.

The crisis phase occurs when the fever breaks. The hypothalamus stimulates vasodilation, resulting in a return of blood flow to the skin and a subsequent release of heat from the body. The hypothalamus also stimulates sweating, which cools the skin as the sweat evaporates.

Although a low-level fever may help an individual overcome an illness, in some instances, this immune response can be too strong, causing tissue and organ damage and, in severe cases, even death. The inflammatory response to bacterial superantigens is one scenario in which a life-threatening fever may develop. Superantigens are bacterial or viral proteins that can cause an excessive activation of T cells from the specific adaptive immune defense, as well as an excessive release of cytokines that overstimulates the inflammatory response. For example, *Staphylococcus aureus* and *Streptococcus pyogenes* are capable of producing superantigens that cause toxic shock syndrome and scarlet fever, respectively. Both of these conditions can be associated with very high, life-threatening fevers in excess of 42 °C (108 °F).

14.4.6 Stress and Immune Function

It is widely believed that stress suppresses immune function and increases susceptibility to infections and cancer. Paradoxically, stress is also known to exacerbate allergic, autoimmune, and inflammatory diseases. These observations suggest that stress may have bidirectional effects on immune function, being immunosuppressive (deterring the immune system) in some instances and immunoenhancing (enhancing the immune system) in others. It has recently been shown that in contrast to chronic stress that suppresses or dysregulates immune function, acute stress can be immunoenhancing. Acute stress enhances dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function and has been shown to augment innate and adaptive immune responses. Acute stress experienced prior to novel antigen exposure enhances innate immunity and memory T-cell formation and results in a significant and long-lasting immunoenhancement. Acute stress experienced during antigen reexposure

enhances secondary/adaptive immune responses. Therefore, depending on the conditions of immune activation and the immunizing antigen, acute stress may enhance the acquisition and expression of immunoprotection or immunopathology. In contrast, chronic stress dysregulates innate and adaptive immune responses by changing the type 1-type 2 cytokine balance and suppresses immunity by decreasing leukocyte numbers, trafficking, and function. Chronic stress also increases susceptibility to skin cancer by suppressing type 1 cytokines and protective T cells while increasing suppressor T-cell function. The adaptive purpose of a physiological stress response may be to promote survival, with stress hormones and neurotransmitters serving as beacons that prepare the immune system for potential challenges (eg, wounding or infection) perceived by the brain (eg, detection of an attacker). However, this system may exacerbate immunopathology (diseases/malfunction of the immune system) if the enhanced immune response is directed against innocuous or self-antigens or dysregulated following prolonged activation, as seen during chronic stress (see Figure 14.4.5). In view of the ubiquitous nature of stress and its significant effects on immunoprotection and immunopathology, it is important to further elucidate the mechanisms mediating stress-immune interactions and to meaningfully translate findings from laboratory bench to hospital bedside.

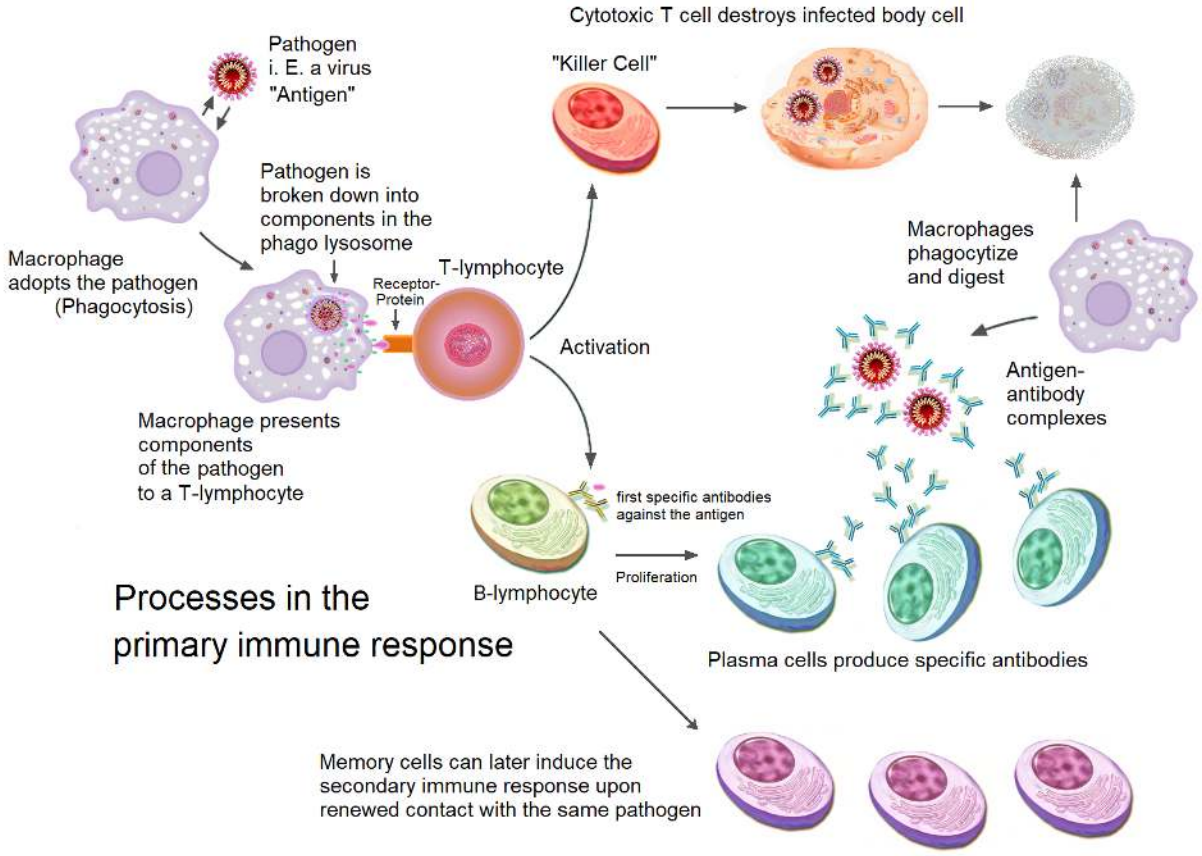


Figure 14.4.5: Macrophages break down a pathogen (virus) and present the components to a T-cell which activates killer cells that destroy the infected body cell, and flag the antigens, and also trigger B cells which create antibodies for those antigens as well as memory cells for future reference. (Copyright;Processes in the primary immune response by: Sciencia58 an the makers of the single images Domdomegg, [1], Fæ, Petr94, Manu5, CC BY-SA 4.0, via Wikimedia Commons)

An important function of physiological mediators released under conditions of acute psychological stress may be to ensure that appropriate leukocytes are present in the right place and at the right time to respond to an immune challenge that might be initiated by the stress-inducing agent (eg, attack by a predator, invasion by a pathogen, etc.). The modulation of immune cell distribution by acute stress may be an adaptive response designed to enhance surveillance and increase the capacity of the immune system to respond to challenge in compartments (such as the skin, lung, gastrointestinal and urinary-genital tracts, mucosal surfaces, and lymph nodes), which serve as defense barriers for the body. Thus, neurotransmitters and hormones released during stress may increase immunosurveillance and help enhance immune preparedness for potential (or ongoing) immune challenge. Stress-induced

immunoenhancement may increase immunoprotection during surgery, vaccination, or infection but may also exacerbate immunopathology during inflammatory (asthma, allergy, dermatitis, cardiovascular disease, gingivitis) or autoimmune (psoriasis, arthritis, multiple sclerosis) diseases that are known to be exacerbated by stress (Amkraut et al, 1971; Ackerman, 2002; Al'Abadie et al, 1994; Garg, 2001; Wright et al, 1998; Wright, 2001).

14.4.7 Protecting Our Health

An important question that health psychologists ask is: What keeps us protected from disease and alive longer? When considering this issue of **resilience** (Rutter, 1985), five factors are often studied in terms of their ability to protect (or sometimes harm) health. They are:

1. Coping
2. Control and Self-Efficacy
3. Social Relationships
4. Dispositions and Emotions
5. Stress Management

14.4.7.1 Coping Strategies

How individuals cope with the stressors they face can have a significant impact on health. Coping is often classified into two categories: problem-focused coping or emotion-focused coping (Carver, Scheier, & Weintraub, 1989). **Problem-focused coping** is thought of as actively addressing the event that is causing stress in an effort to solve the issue at hand. For example, say you have an important exam coming up next week. A problem-focused strategy might be to spend additional time over the weekend studying to make sure you understand all of the material. **Emotion-focused coping**, on the other hand, regulates the emotions that come with stress. In the above examination example, this might mean watching a funny movie to take your mind off the anxiety you are feeling. In the short term, emotion-focused coping might reduce feelings of stress, but problem-focused coping seems to have the greatest impact on mental wellness (Billings & Moos, 1981; Herman-Stabl, Stemmler, & Petersen, 1995). That being said, when events are uncontrollable (e.g., the death of a loved one), emotion-focused coping directed at managing your feelings, at first, might be the better strategy. Therefore, it is always important to consider the match of the stressor to the coping strategy when evaluating its plausible benefits.

14.4.7.2 Control and Self-Efficacy



Figure 14.4.6: Feeling a sense of control in one's life is important. Something as simple as having control over the care of a houseplant has been shown to improve health and longevity. [Image: JJ Harrison, https://goo.gl/82FsdV, CC BY-SA 2.5, goo.gl/SRAIwa]

Another factor tied to better health outcomes and an improved ability to cope with stress is having the belief that you have **control** over a situation. For example, in one study where participants were forced to listen to unpleasant (stressful) noise, those who were led to believe that they had control over the noise performed much better on proofreading tasks afterwards (Glass & Singer, 1972). In other words, even though participants *did not* have actual control over the noise, the control *belief* aided them in completing the task. In similar studies, perceived control benefited immune system functioning (Sieber et al., 1992) (See Figure 14.4.6)Outside of the laboratory, studies have shown that older residents in assisted living facilities, which are notorious for low control, lived *longer* and showed *better* health outcomes when given control over something as simple as watering a plant or choosing when student volunteers came to visit (Rodin & Langer, 1977; Schulz & Hanusa, 1978). In addition, feeling in control of a threatening situation can actually change stress hormone levels (Dickerson & Kemeny, 2004). Believing that you have control over your own behaviors can also have a positive influence on important outcomes like smoking cessation, contraception use, and weight management (Wallston & Wallston, 1978). When individuals do not believe they have control, they do not try to change. **Self-efficacy** is closely related to control, in that people with high levels of this trait believe they can complete tasks and reach their goals. Just as feeling in control can reduce stress and improve health, higher self-efficacy can reduce stress and negative **health behaviors**, and is associated with better health (O'Leary, 1985).

14.4.7.3 Social Relationships

Research has shown that the impact of social isolation on our risk for disease and death is similar in magnitude to the risk associated with smoking regularly (Holt-Lunstad, Smith, & Layton, 2010; House, Landis, & Umberson, 1988). In fact, the importance of social relationships for our health is so significant that some scientists believe our body has developed a physiological system that encourages us to seek out our relationships, especially in times of stress (Taylor et al., 2000). **Social integration** is the concept used to describe the number of social roles that you have (Cohen & Wills, 1985), as well as the lack of isolation. For example, you might be a daughter, a basketball team member, a Humane Society volunteer, a coworker, and a student. Maintaining these different roles can improve your health via encouragement from those around you to maintain a healthy lifestyle. Those in your social network might also provide you with **social support** (e.g., when you are under stress). This support might include emotional help (e.g., a hug when you need it), tangible help (e.g., lending you money), or advice. By helping to

improve health behaviors and reduce stress, social relationships can have a powerful, protective impact on health, and in some cases, might even help people with serious illnesses stay alive longer (Spiegel, Kraemer, Bloom, & Gottheil, 1989).

14.4.7.4 Dispositions and Emotions: What's Risky and What's Protective?

Negative dispositions and personality traits have been strongly tied to an array of health risks. One of the earliest negative trait-to-health connections was discovered in the 1950s by two cardiologists. They made the interesting discovery that there were common behavioral and psychological patterns among their heart patients that were not present in other patient samples. This pattern included being competitive, impatient, hostile, and time urgent. They labeled it **Type A Behavior**. Importantly, it was found to be associated with *double* the risk of heart disease as compared with **Type B Behavior** (Friedman & Rosenman, 1959). Since the 1950s, researchers have discovered that it is the **hostility** and competitiveness components of Type A that are especially harmful to heart health (Iribarren et al., 2000; Matthews, Glass, Rosenman, & Bortner, 1977; Miller, Smith, Turner, Guijarro, & Hallet, 1996). Hostile individuals are quick to get upset, and this angry arousal can damage the arteries of the heart. In addition, given their negative personality style, hostile people often lack a heath-protective supportive social network.

Positive traits and states, on the other hand, are often health protective. For example, characteristics like positive emotions (e.g., feeling happy or excited) have been tied to a wide range of benefits such as increased longevity, a reduced likelihood of developing some illnesses, and better outcomes once you are diagnosed with certain diseases (e.g., heart disease, HIV) (Pressman & Cohen, 2005). Across the world, even in the most poor and underdeveloped nations, positive emotions are consistently tied to better health (Pressman, Gallagher, & Lopez, 2013). Positive emotions can also serve as the "antidote" to stress, protecting us against some of its damaging effects (Fredrickson, 2001; Pressman & Cohen, 2005; see Figure 14.4.7:). Similarly, looking on the bright side can also improve health. Optimism has been shown to improve coping, reduce stress, and predict better disease outcomes like recovering from a heart attack more rapidly (Kubzansky, Sparrow, Vokonas, & Kawachi, 2001; Nes & Segerstrom, 2006; Scheier & Carver, 1985; Segerstrom, Taylor, Kemeny, & Fahey, 1998).

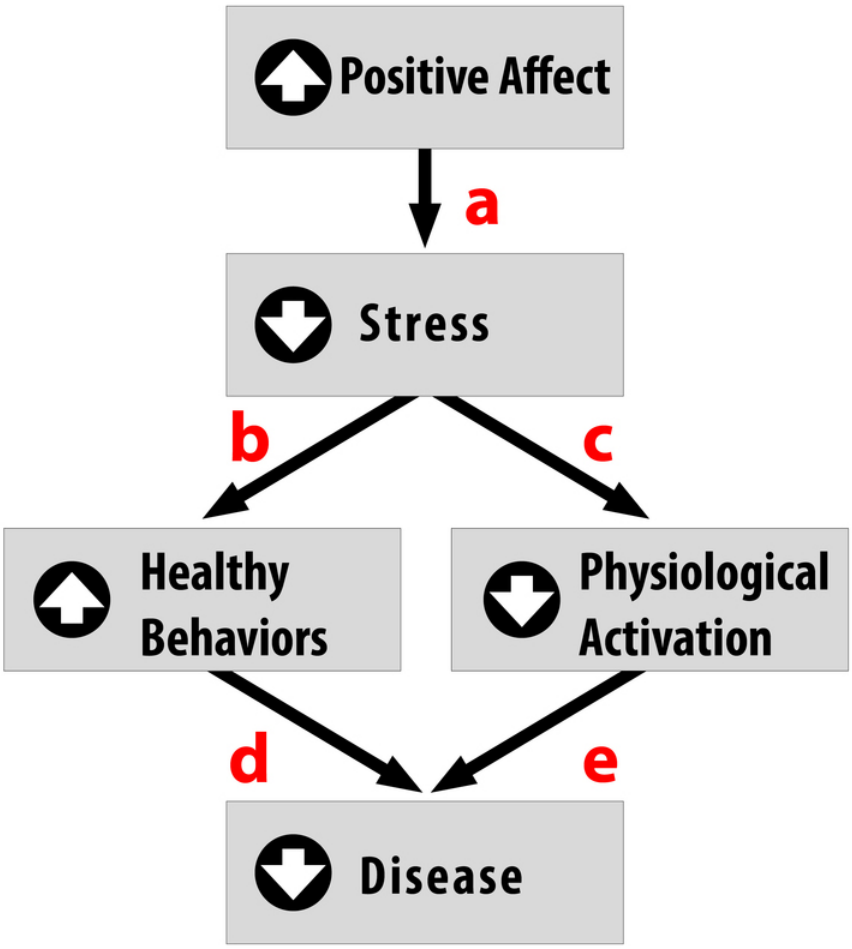


Figure 14.4.7:This figure illustrates one possible way that positive affect protects individuals against disease. Positive affect can reduce stress perceptions (a), thereby improving health behaviors (b) and lowering physiological stress responses (c) (e.g., decreased cardiovascular reactivity, lower stress hormones, non-suppressed immune activity). As a result, there is likely to be less incidence of disease (d, e). (Adapted from Pressman & Cohen, 2005)

14.4.7.5 Stress Management

About 20 percent of Americans report having stress, with 18–33 year-olds reporting the highest levels (American Psychological Association, 2012). Given that the sources of our stress are often difficult to change (e.g., personal finances, current job), a number of interventions have been designed to help reduce the aversive responses to duress. For example, relaxation activities and forms of meditation are techniques that allow individuals to reduce their stress via breathing exercises, muscle relaxation, and mental imagery. Physiological arousal from stress can also be reduced via **biofeedback**, a technique where the individual is shown bodily information that is not normally available to them (e.g., heart rate), and then taught strategies to alter this signal. This type of intervention has even shown promise in reducing heart and hypertension risk, as well as other serious conditions (e.g., Moravec, 2008; Patel, Marmot, & Terry, 1981). But reducing stress does not have to be complicated! For example, exercise is a great stress reduction activity (Salmon, 2001) that has a myriad of health benefits.

14.4.8 The Importance Of Good Health Practices

As a student, you probably strive to maintain good grades, to have an active social life, and to stay healthy (e.g., by getting enough sleep), but there is a popular joke about what it's like to be in college: you can only pick two of these things (see Figure 14.4.8: for an example). The busy life of a college student doesn't always allow you to maintain all three areas of your life, especially during test-taking periods. In one study, researchers found that students taking exams were more stressed and, thus, smoked more, drank more caffeine, had less physical activity, and had worse sleep habits (Oaten & Chang, 2005), all of which could have detrimental effects on their health. Positive health practices are *especially* important in times of stress when your immune system is compromised due to high stress and the elevated frequency of exposure to the illnesses of your fellow students in lecture halls, cafeterias, and dorms.

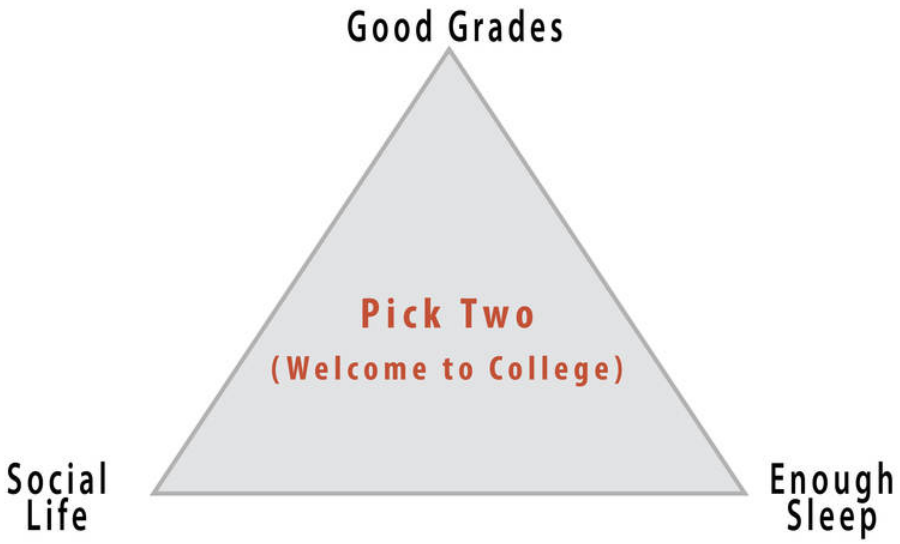


Figure 14.4.8: A popular joke about how difficult it is to stay balanced and healthy during college.

Psychologists study both **health behaviors** and health habits. The former are behaviors that can improve or harm your health. Some examples include regular exercise, flossing, and wearing sunscreen, versus negative behaviors like drunk driving, pulling all-nighters, or smoking. These behaviors become *habits* when they are firmly established and performed automatically. For example, do you have to think about putting your seatbelt on or do you do it automatically? Habits are often developed early in life thanks to parental encouragement or the influence of our peer group.

While these behaviors sound minor, studies have shown that those who engaged in more of these protective habits (e.g., getting 7–8 hours of sleep regularly, not smoking or drinking excessively, exercising) had fewer illnesses, felt better, and were less likely to die over a 9–12-year follow-up period (Belloc & Breslow 1972; Breslow & Enstrom 1980). For college students, health behaviors can even influence academic performance. For example, poor sleep quality and quantity are related to weaker learning capacity and academic performance (Curcio, Ferrara, & De Gennaro, 2006). Due to the effects that health behaviors can have, much effort is put forward by psychologists to understand *how* to change unhealthy behaviors, and to understand *why* individuals fail to act in healthy ways. Health promotion involves enabling individuals to improve health by focusing on behaviors that pose a risk for future illness, as well as spreading knowledge on existing risk factors. These might be genetic risks you are born with, or something you developed over time like obesity, which puts you at risk for Type 2 diabetes and heart disease, among other illnesses.

14.4.9 Psychology And Medicine

There are many psychological factors that influence medical treatment outcomes. For example, older individuals, (Meara, White, & Cutler, 2004), women (Briscoe, 1987), and those from higher socioeconomic backgrounds (Adamson, Ben-Shlomo, Chaturvedi, & Donovan, 2008) are all *more* likely to seek medical care. On the other hand, some individuals who need care might avoid it due to financial obstacles or preconceived notions about medical practitioners or the illness. Thanks to the growing amount of medical information online, many people now use the Internet for health information and 38% percent report that this influences their decision to see a doctor (Fox & Jones, 2009) (see Figure 14.4.9). Unfortunately, this is not always a good thing because individuals tend to do a poor job assessing the credibility of health information. For example, college-student participants reading online articles about HIV and syphilis rated a physician's article and a college student's article as *equally* credible if the participants said they were familiar with the health topic (Eastin, 2001). Credibility of health information often means how accurate or trustworthy the information is, and it can be influenced by irrelevant factors, such as the website's design, logos, or the organization's contact information (Freeman & Spyridakis, 2004). Similarly, many people post health questions on online, unmoderated forums where *anyone* can respond, which allows for the possibility of inaccurate information being provided for serious medical conditions by unqualified individuals.

Figure 14.4.9: While the Internet has increased the amount of medical information available to the public and created greater access, there are real concerns about how people are making decisions about their health based on that information. [Image: Mapbox, https://goo.gl/UNhmx5, CC BY 2.0, goo.gl/BRvSA7]

After individuals decide to seek care, there is also variability in the information they give their medical provider. Poor communication (e.g., due to embarrassment or feeling rushed) can influence the accuracy of the diagnosis and the effectiveness of the prescribed treatment. Similarly, there is variation following a visit to the doctor. While most individuals are tasked with a health recommendation (e.g., buying and using a medication appropriately, losing weight, going to another expert), not everyone *adheres* to medical recommendations (Dunbar-Jacob & Mortimer-Stephens, 2010). For example, many individuals take medications inappropriately (e.g., stopping early, not filling prescriptions) or fail to change their behaviors (e.g., quitting smoking). Unfortunately, getting patients to follow medical orders is not as easy as one would think. For example, in one study, over one third of diabetic patients failed to get proper medical care that would prevent or slow down diabetes-related blindness (Schoenfeld, Greene, Wu, & Leske, 2001)! Fortunately, as mobile technology improves, physicians now have the ability to monitor **adherence** and work to improve it (e.g., with pill bottles that monitor if they are opened at the right time). Even text messages are useful for improving treatment adherence and outcomes in depression, smoking cessation, and weight loss (Cole-Lewis, & Kershaw, 2010).

14.4.10 Being A Health Psychologist

Training as a clinical health psychologist provides a variety of possible career options. Clinical health psychologists often work on teams of physicians, social workers, allied health professionals, and religious leaders. These teams may be formed in locations like rehabilitation centers, hospitals, primary care offices, emergency care centers, or in chronic illness clinics. Work in each of these settings will pose unique challenges in patient care, but the primary responsibility will be the same. Clinical health psychologists will evaluate physical, personal, and environmental factors contributing to illness and preventing improved health. In doing so, they will then help create a treatment strategy that takes into account all dimensions of a person's life and health, which maximizes its potential for success. Those who specialize in health psychology can also conduct research to discover new health predictors and risk factors, or develop interventions to prevent and treat illness. Researchers studying health psychology work in numerous locations, such as universities, public health departments, hospitals, and private organizations. In the related field of **behavioral medicine**, careers focus on the application of this type of research. Occupations in this area might include jobs in occupational therapy, rehabilitation, or preventative medicine. Training as a health psychologist provides a wide skill set applicable in a number of different professional settings and career paths.

14.4.11 The Future of Health Psychology

Much of the past medical research literature provides an incomplete picture of human health. "Health care" is often "illness care." That is, it focuses on the management of symptoms and illnesses as they arise. As a result, in many developed countries, we are faced with several health epidemics that are difficult and costly to treat. These include obesity, diabetes, and cardiovascular disease, to name a few. The National Institutes of Health have called for researchers to use the knowledge we have about risk factors to design effective interventions to reduce the prevalence of *preventable* illness. Additionally, there are a growing number of individuals across developed countries with *multiple* chronic illnesses and/or lasting disabilities, especially with older age. Addressing their needs and maintaining their quality of life will require skilled individuals who understand how to properly treat these populations. Health psychologists will be on the forefront of work in these areas.

With this focus on prevention, it is important that health psychologists move beyond studying risk (e.g., depression, stress, hostility, low socioeconomic status) in isolation, and move toward studying factors that confer resilience and protection from disease. There is, fortunately, a growing interest in studying the positive factors that protect our health (e.g., Diener & Chan, 2011; Pressman & Cohen, 2005; Richman, Kubzansky, Maselko, Kawachi, Choo, & Bauer, 2005) with evidence strongly indicating that people with higher positivity live longer, suffer fewer illnesses, and generally feel better. Seligman (2008) has even proposed a field of "Positive Health" to specifically study those who exhibit "above average" health—something we do not think about enough. By shifting some of the research focus to identifying and understanding these health-promoting factors, we may capitalize on this information to improve public health.

Innovative interventions to improve health are already in use and continue to be studied. With recent advances in technology, we are starting to see great strides made to improve health with the aid of computational tools. For example, there are hundreds of simple applications (apps) that use email and text messages to send reminders to take medication, as well as mobile apps that allow us to monitor our exercise levels and food intake (in the growing mobile-health, or m-health, field). These m-health applications can be used to raise health awareness, support treatment and compliance, and remotely collect data on a variety of outcomes. Also exciting are devices that allow us to monitor physiology in real time; for example, to better understand the stressful situations that raise blood pressure or heart rate. With advances like these, health psychologists will be able to serve the population better, learn more about health and health behavior, and develop excellent health-improving strategies that could be specifically targeted to

certain populations or individuals. These leaps in equipment development, partnered with growing health psychology knowledge and exciting advances in neuroscience and genetic research, will lead health researchers and practitioners into an exciting new time where, hopefully, we will understand more and more about how to keep people healthy.

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CHAPTER OVERVIEW

15: Biological Bases of Psychological Disorders

15.1: Biological Factors in Psychological Disorders- An Introduction

15.2: Biological Basis of Mood Disorders- Major Depressive and Bipolar Disorders

15.3: Biological Basis of Anxiety Disorders

15.4: Biological Basis of Schizophrenia Spectrum Disorder

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15.1: Biological Factors in Psychological Disorders- An Introduction

Learning Objectives

- Describe the general role of neural structures and neurochemistry that contribute to psychological disorders.
- Describe how genetics and epigenetics contribute to psychological disorders.

15.1.1 Overview

This chapter discusses the biological perspective on psychological disorders, exploring how our brain structures, neural systems, and genetics contribute to the etiology of such disorders as schizophrenia, depression, bipolar, anxiety, and obsessive/compulsion.

15.1.2 Introduction

Although the term mental illness is often used when referring to disorders such as depression or anxiety, are these disorders really illnesses in the way that diabetes is an illness – that is a purely biological malfunction? Or are psychological disorders the product of something more intangible than a neurochemical imbalance or malfunctioning brain area, something such as a conditioned response to stress learned in childhood? The answer is both.

Within the field of psychology, it is generally acknowledged that psychological disorders develop out of a complex interaction of biological, social, and environmental factors. However, exactly how these factors interact with one another to produce a particular psychological disorder is still unclear. This is because diagnosing a psychological disorder is not like diagnosing other illnesses, such as diabetes or pneumonia.

When making a diagnosis of diabetes, a doctor may use a blood test to determine blood glucose levels. Similarly, to diagnose pneumonia, a doctor may order a chest x-ray to look for evidence of the infection. However, when it comes to diagnosing psychological disorders, there is currently no x-ray for depression or blood test for anxiety. Diagnosing psychological disorders is a more subjective process, based on the current symptoms an individual is experiencing.

The Diagnostic and Statistical Manual of Mental Disorders (**DSM**), 5th edition, (American Psychiatric Association, 2013) is the most widely accepted system used by clinicians and researchers for the classification of mental disorders, and outlines the diagnostic criteria for a specific mental disorder based on the symptoms an individual is experiencing. However, individuals suffering from the same disorder often display different symptoms while individuals suffering from different disorders may display many of the same symptoms, making the diagnosis of psychological disorders from outward symptoms alone, difficult.

Note

The American Psychological Association periodically updates the Diagnostic and Statistical Manual of Mental Disorders - also called the **DSM** - so that it will accurately reflect our current understanding of the symptoms, etiology, and treatment of psychological disorders. The revisions to the DSM-5 were released in early 2022, in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR).

The remainder of this chapter focuses on the contributions of biological factors - such as brain structure abnormalities - to the development of psychological disorders.

15.1.3 Biology of Psychological Disorders

Research into the underlying biology of psychological disorders has primarily focused on the following three areas: (1) the structures of the brain, (2) the biochemistry of the brain, and (3) genetics and epigenetics.

15.1.3.1 Structures of the Brain

Research has shown that some psychological disorders appear to involve specific structures within the brain. For example, overactivity in an area of the brain known as **Brodmann Area 25** (BA25), shown in Figure 17.1.1, is often present in individuals with clinical depression (also known as **Major Depressive Disorder**) (Mayberg et al., 2005). This area is part of a larger, limbic system structure known as the **anterior cingulate cortex** and interacts with other areas of the brain involved in mood, emotion and thinking. When this region is overactive, a person can experience an increased negative affect (e.g. sadness, anxiety) and decreased

positive affect (e.g. happiness, joy) (Jumah & Dossani, 2021). We will explore the role of brain structures in more detail as we discuss specific disorders later in this chapter.

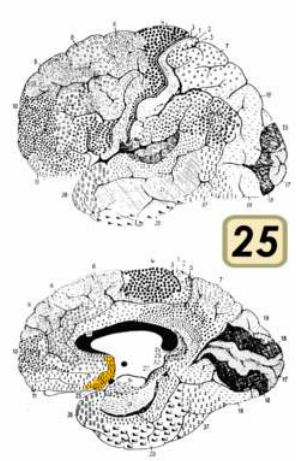


Figure 15.1.1: **Brodmann Area 25 (BA25) is a narrow region of the brain located in the anterior cingulate cortex and is a part of the limbic system. BA25 is shown here colored in yellow.** (Public Domain; By Brodmann; Colored by was_a_bee, via Wikimedia Commons)

Dig Deeper

Check out the following article from Harvard Health for more on the brain and the biological factors that play a role in depressive disorders:
https://www.health.harvard.edu/mind-and-mood/what-causes-depression

15.1.3.2 Biochemistry of the Brain

In addition to the individual structures of the brain, researchers are also interested in what role our chemical communication systems – hormones and neurotransmitters –play in the development of psychological disorders.

The primary communication in the brain occurs between neurons (neurotransmission) using neurotransmitters at the junctions between neurons known as synapses. Many factors can influence synaptic communication in ways that may lead to maladaptive alterations or disruptions of this important form of communication. Such disruptions can then result in a display of symptoms associated with various psychological disorders.

For example, researchers believe that disruptions in the neurotransmitters, particularly dopamine, play an important role in schizophrenia (NIH, 2007). This link between dopamine and schizophrenia arose out of several observations including the benefit from drugs that blocked dopamine action. Later it was also observed that individuals addicted to cocaine or amphetamine sometimes showed symptoms very similar to those seen in cases of schizophrenia. Cocaine works by reducing the amount of monoamine neurotransmitters (dopamine, norepinephrine, epinephrine, and serotonin) that are taken back into the presynaptic neuron (Richards & Laurin, 2021), as shown in Figure 2. When this happens, more monoamine neurotransmitters, crucially dopamine, are available in the synapse for binding to the receptors on the postsynaptic neuron. We will discuss the dopamine theory of schizophrenia in more detail later in this chapter.

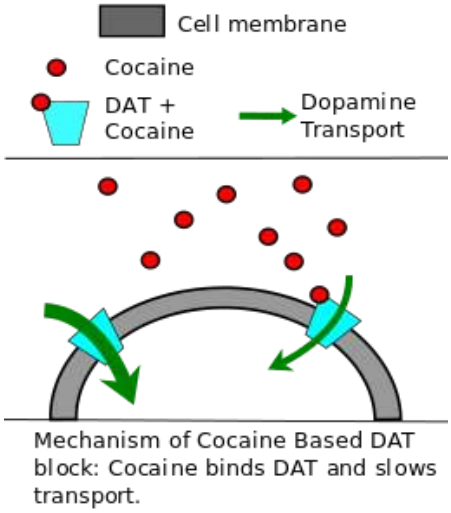


Figure 15.1.2: **How cocaine increases the amount of dopamine in the synapse by reducing the activity of the dopamine reuptake transporter (DAT)**; (CC BY-SA 3.0; Hard-59 via Wikimedia Commons.)

In addition to neurotransmitters, the brain also communicates via hormones, which are released by the endocrine system, and activate behaviors such as alertness or sleepiness, concentration, and reactions to stress. Elevated or depleted levels of certain hormones may be responsible for some of the symptoms seen in psychological disorders. For example, elevated levels of cortisol, a stress hormone, interfere with learning and memory as well as increase the risk of depression. High levels of cortisol have been shown to alter the function of serotonin receptors in the brain, leading to symptoms of depression (Qin et al., 2018).

15.1.3.3 Genetics and Epigenetics

Researchers have long recognized that many psychological disorders tend to run in families, suggesting a potential genetic factor. In family and twin studies, schizophrenia is significantly more likely to be present in an identical twin than a fraternal twin (Coon & Miller, 2007) and in individuals with a first-degree relative (e.g. mother or father) with schizophrenia.

Researchers have also linked several genetic variations, or mutations, to psychological disorders, including variations in two genes which code for the cellular machinery that helps regulate the flow of calcium into neurons (NIH, 2013). One of these calcium channel genes, CACNA1C, is known to affect the brain circuitry involved in emotion, thinking, attention and memory. Variations in this gene have been linked to disorders such as bipolar disorder, schizophrenia, and major depression.

Although individual genes, such as CACNA1C, have been linked to psychological disorders, most disorders are believed to be polygenic; that is linked to abnormalities in many genes, rather than just one. It is the complex interaction between multiple genes which may trigger a psychological disorder.

Furthermore, while researchers currently believe that genetic factors are implicated in all psychological disorders, they are not believed to be the sole cause. There are important gene-environment interactions, also known as epigenetic factors, unique to each individual (even identical twins) which may explain why some individuals with a genetic predisposition toward a certain disorder develop that disorder while others do not (e.g., why one identical twin develops schizophrenia, but the other does not).

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15.1.5 Attributions

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Biology of Psychological Disorders, Original material written by Amy E. Coren, Ph.D., Pasadena City College, Pasadena, CA and adapted by Alan Keys, Ph.D., Sacramento City College, Sacramento, CA.

Figure 15.1.1 Brodman Area 25. By Brodmann; Colured by was_a_bee; File:Brodmann_Cytoarchitectonics.PNG, Public Domain, via Wikimedia Commons.

Figure 15.1.2 Cocaine and DAT. RicHard-59, CC BY-SA 3.0, via Wikimedia Commons.

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15.2: Biological Basis of Mood Disorders- Major Depressive and Bipolar Disorders

Learning Objectives

- Describe what is meant by the term “mood disorder”.
- Describe the differences between depressive and bipolar disorders.
- Identify the biology thought to underlie the etiology of Major Depressive Disorder.
- Identify the biology thought to underlie the etiology of Bipolar Disorder (I & II).

15.2.1 Overview

Mood disorders are a broad category of psychological disorders characterized by severe disturbances in mood and emotion. While these disorders share common features of extreme mood alteration, most research suggests that they have different biological origins (Cuellar et al., 2005).

15.2.2 An Introduction to Mood Disorders

The classification, **mood disorders,** is used by mental health professionals to describe a broad group of psychological disorders characterized by severe disturbances in mood and emotion. Also known as **affective disorders**, disorders in this category are typically classified into two distinct groups: depressive disorders and bipolar disorders (Figure 15.2.1).

Depressive disorders typically include **major depressive disorder (MDD)**, also known as clinical depression, which is characterized by episodes of profound sadness and loss of interest or pleasure in usual activities, among other features, and persistent depressive disorder (formerly **dysthymia**), a milder but long-term, chronic form of depression. **Bipolar disorders** are characterized by mood states that vacillate between sadness and euphoria and include bipolar disorder **types I and II**, as well as cyclothymic disorder (APA, 2013).

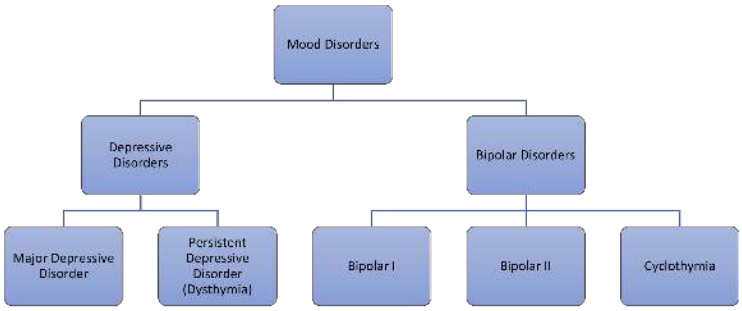


Figure 15.2.1: Mood disorders are typically grouped in two categories: (1) Depressive disorders, which include Major Depressive Disorder and Persistent Depressive Disorder (Dysthymia) and (2) Bipolar disorders which includes Bipolar I & II and Cyclothymia. (CC BY-NC-SA 4.0; by Amy E. Coren, Ph.D.)

15.2.3 Depressive Disorders

Depressive disorders are a group of disorders whose main features include a **depressed mood** for most of the day and/or feelings of **anhedonia** (the inability to feel pleasure from activities usual found enjoyable) (Post & Warden, 2018).

The DSM-5 describes the main features of depressive disorders as “the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function.” (APA, 2013) Depressed people often report feeling sad, discouraged, and hopeless (Figure 17.2.2) These individuals lose interest in activities they once enjoyed, and often experience a decrease in drives such as hunger and sex, and frequently doubt their personal worth. When these features are triggered by a traumatic or negative experience (e.g. death of close loved one), it is called **reactive depression**. When there is no apparent reason or cause, it is known as **endogenous depression.**

Depressive disorders are often highly **comorbid** (meaning more than one health condition is present in the same person at the same time) with other psychological disorders. Depressive disorders are often seen occurring alongside anxiety disorders, bipolar disorders, and OCD and related disorders (Groen, et al., 2020).

Perhaps the most well-known example of a depressive disorder is **Major Depressive Disorder (MDD)**, also known as **clinical depression**. Major depressive disorder is believed to affect about 2-5% of the global population each year (Han, et al., 2019). According to the DSM-5, the defining symptoms of **major depressive disorder** include "depressed mood most of the day, nearly every day" (feeling sad, empty, hopeless, or appearing tearful to others) and loss of interest and pleasure in usual activities (APA, 2013). When these symptoms last for longer than 2 weeks, and significantly impair an individual's ability to function, that individual is said to be suffering from MDD.

Researchers and mental health professionals both agree that there is no single cause responsible for any of the depressive disorders. Rather it is thought that depressive disorders arise from the interaction between multiple biological and environmental factors. However, this interaction is thought to be extremely complex and is still not well understood. As such, the biology underlying depressive disorders continues to be a major subject of ongoing research and is explored in more detail below.

15.2.3.1 The Genetics and Epigenetics of Depressive Disorders

Historically, evidence from family, twin, and adoption studies has seemed to support the idea that genetic factors play an important role in the development of depressive disorders, although which genes are involved and the how these genes interact to contribute to the development of depressive disorders is still not understood (Lohoff, 2010).

In 2015, several genome-wide association studies (GWASs), which involve scanning the genomes of large groups of people to find genetic variations associated with a disorder, identified over 100 possible genes which may play a role in increasing an individual's risk for developing a depressive disorder (Ormel, et al., 2019, Shadrina, et al., 2018).

As a result of these studies, and others, it is now believed that an individual's genetic predisposition to a depressive disorder is determined by (1) the coordinated action of many genes, (2) the genes' interactions with each other, and (3) their interactions with environmental factors through epigenetic mechanisms (Shardina, et al., 2018).

Current research is now focusing on the role of epigenetics - how behaviors and environment can cause changes that affect the way our genes work, in the development of depressive disorders such as MDD (Barbu, et al., 2020).

Dig Deeper

To learn more about the interaction of biology and environment in the development of depressive disorders, check out this video lecture provided by Stanford Univeristy professor, Dr. Robert Sapolsky:



15.2.3.2 The Role of Neurotransmitters in Depressive Disorders

Until relatively recently, low levels of neurotransmitters in the brain were believed to be the main culprits behind depressive disorders. However, current research now suggests that, while neurotransmitters do play an important role, the reality is much more complicated than previously thought.

15.2.3.2.1 *Monoamine Theory of Depression*

It has historically been believed that **low activity levels of monoamine neurotransmitters** (norepinephrine, serotonin, and dopamine) contribute to the symptoms associated with depressive disorders (Nutt, 2008). The discovery that certain drugs which increased levels of serotonin and norepinephrine in the brain, alleviated depressive symptoms, lead to formulation of the monoamine theory of depression by Joseph Schildkraut in the 1960s. According to the monoamine theory, low levels of serotonin, norepinephrine, and/or dopamine in the central nervous system are primarily the basis for the development of depressive disorders (Hirschfeld, 2000). This theory prevailed for more than 50 years before being challenged by an increasing number of research studies and clinical observations.

Today, most current research acknowledges that while monoamine neurotransmitters are important, they are by far not the *only* neurotransmitters involved in depressive disorders. The following video from Yale Medicine explains why the monoamine theory of depression is no longer believed to be fully accurate and what alternative theories researchers are currently exploring. For example, other neurotransmitters, such as glutamate and GABA, are increasingly being investigated for their role in the development of depression.



Furthermore, research is increasingly focused not only on individual neurotransmitters, but also on the *interactions* between the various neurotransmitters themselves as well as how they interact with other biological systems such as the endocrine system (Ding et al., 2014). For example, serotonin production and activity are affected by the hormones secreted by the endocrine system, such as cortisol, in response to threat or stress.

15.2.3.3 The role of neural structures in MDD

Research into the neural basis of MDD has focused on examining the neural architecture of individuals with MDD by using a variety of both structural and functional neuroimaging techniques. Structural techniques, such as CT scans and magnetic resonance imaging (MRI), take static pictures of the brain to determine whether any specific neural structures are different in subjects with MDD than control subjects.

By using these static neuroimaging techniques, researchers have discovered several areas of the brain where the volume of **grey matter** is significantly decreased in those individuals with MDD (Filatova, et al., 2021). These areas include the **prefrontal cortex (PFC), hippocampus, amygdala, and cingulate cortex** (Ancelin, et al. 2019).

Importantly, these areas comprise most of the major structures in the brain's **corticolimbic system**, a system responsible for regulating multiple behavioral and cognitive functions, including decision making, motivation, emotional processing, and our response to stress and pain (Vachon-Presseau, 2018) (Figure 16.2.3.).

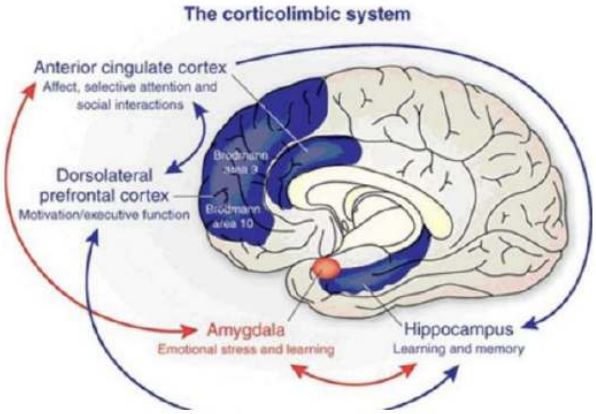


Figure 15.2.2: The corticolimbic system in the brain regulates several important behavioral and cognitive functions, including our reactions to stress and pain. (CC BY-SA 4.0; Benes 2010 via Wikimedia Commons)

In addition to looking at the overall structure of the brain, researchers also use functional neuroimaging techniques, such as positron emission tomography (PET) scans and functional magnetic resonance imaging (fMRI), to examine the brain in action, looking for any areas of atypical activation.

For example, a meta-analysis of neuroimaging studies showed that when viewing negative stimuli (e.g., picture of an angry face, picture of a car accident), participants with MDD have *greater* activation in brain regions involved in stress response, such as the amygdala and anterior cingulate cortex, and *reduced* activation in brain regions involved in positively motivated behaviors, such as the prefrontal cortex, compared with healthy control participants. (Hamilton, et al., 2012).

Other functional imaging studies have examined alterations in the **functional connectivity** - the strength of the connections between regions of the brain. These connections allow multiple brain regions to properly "talk" to one another; that is to perceive, generate, and encode information in concert. By examining these neural connections, researchers can see if there are problems in the way the brain processes specific types of information in individuals with MDD, and where these "faulty" connections may occur (Goldstein-Peikarski, et al. 2018).

Several studies have noted differences in the neural networks of individuals with MDD, compared to those without. For example, abnormally low activity in brain regions related to stopping thoughts and shifting to new ones, referred to in the research as "cognitive control," and hyperactivity in other brain regions that "process emotional thoughts and feelings" has consistently been found in individuals with MDD (Janiri, et al., 2019).

15.2.4 Bipolar Disorders

Some people who suffer from clinical depression may also experience what are known as **manic** or **hypomanic** episodes. When this occurs, the individual is usually diagnosed with **bipolar disorder**.

Hypomanic episodes are fairly short– around 4 days in duration, and are characterized by a positive mood, reduced need for sleep, and high energy. Individuals experiencing a hypomanic episode are often talkative, impulsive, energetic, and very confident. It is important to note that by definition, hypomanic episodes cannot cause impairment, distress, or the need for hospitalization. If any of these three features are present the episode is considered to be manic, rather than hypomanic.

Manic episodes are longer, at least 1 week in duration, and have features similar to hypomania but taken to an extreme. In addition, manic episodes are often characterized by delusions of grandeur, psychosis, and distractibility. Additionally, for an episode to be considered manic, it must cause impairment in functioning, significant distress, or require the individual to be hospitalized.

Bipolar I disorder, previously known as manic-depressive disorder, is diagnosed when there is at least one manic episode. This manic episode may be preceded by or followed by a major depressive episode but that is not required for the Bipolar I diagnosis. In contrast, a diagnosis of **bipolar II disorder** is made when the individual has experienced *both* a hypomanic episode and a depressive episode, but no manic episodes. Alternatively, an individual may suffer from **cyclothymic disorder**, which characterized by multiple, alternating periods of hypomania and depression, lasting at least two years. To qualify for cyclothymic

disorder, the person must experience symptoms at least half the time with no more than two consecutive symptom-free months; and the symptoms must cause significant distress or impairment (APA, 2013).

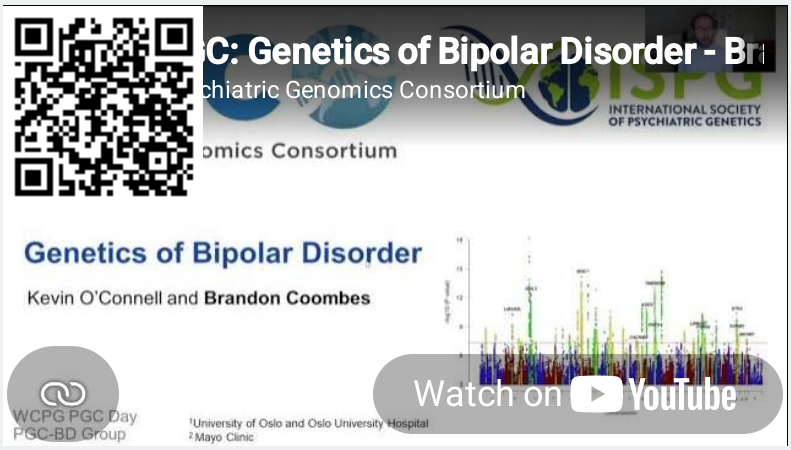
15.2.4.1 The Genetics and Epigenetics of Bipolar Disorders

Numerous twin and family studies have shown that there is a strong genetic component to bipolar disorders, especially Bipolar I (Edvardsen et al., 2008, Escamilla & Zavala, 2008). However, the exact nature of this genetic component remains elusive – numerous studies, include a genome-wide association study (GWAS) of more than 40,000 bipolar disorder cases, have identified hundreds to thousands of genes associated with bipolar disorder (Gandal, et al. 2018).

Given the complicated genetic component, recent research has focused on the identifying epigenetic mechanisms which may play role in the risk and development of bipolar disorders (Duffy, et al. 2019).

Dig Deeper

Genome-wide association studies, or GWAS, have become an increasingly popular tool for exploring the genetic and epigenetic factors involved in psychological disorders, such as Biopolar Disorders. To learn more about GWAS and their use in Bipolar disorder research, check out the following video:



15.2.4.2 The Role of Neurotransmitters and Neural Structures in Bipolar Disorders

As depression was often a characteristic of bipolar disorders, researchers initially believed that norepinephrine, serotonin, and dopamine were all implicated in the development of bipolar disorder. It was thought that manic episodes were the result of drastic increases in serotonin. Unfortunately, research did not support this hypothesis. It is now believed that manic episodes may, in fact, be explained by low levels of serotonin and high levels of norepinephrine (Soreff & McInnes, 2014).

In addition, consistent decreases in gray matter volume in both the prefrontal cortex and areas of the limbic system, such as the hippocampus, have been reported, as have enlargement of the ventricles (Jiang, et al. 2020).

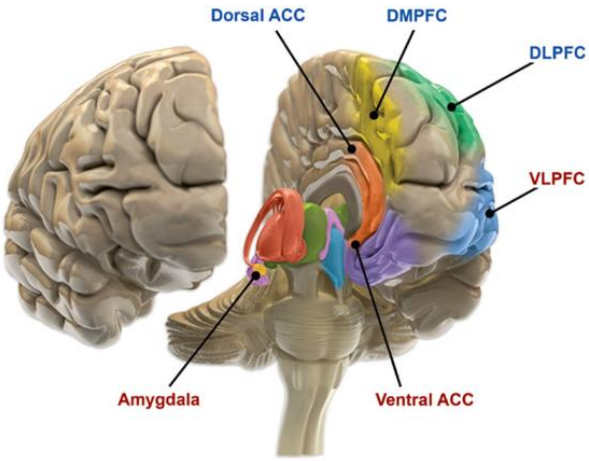


Figure 15.2.3: Regions of the brain implicated in Bipolar disorders. (CC BY-SA 4.0; Maletic V, Raison C via Wikimedia Commons)

Studies of brain activity have led to the view that bipolar disorder may be a suite of related neurological issues with interconnected functional abnormalities that often appear early in life and worsen over time. In support of this hypothesis, fMRI techniques have noted atypical activation of the frontal cortex and basil ganglia, as well as disruption in the connectivity between these structures (Maletic & Rasion, 2014). The issues in connectivity seem to cluster around those networks in the brain associated with emotional processing. See Figure 15.2.3.

15.2.5 References

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15.2.6 Attributions

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15.3: Biological Basis of Anxiety Disorders

Learning Objectives

- Describe the principal features of anxiety disorders.
- Describe the difference between fear and anxiety.
- Identify the major biological systems involved in anxiety and fear.
- Identify the biology thought to underlie the etiology of anxiety disorders.

15.3.1 Overview

Anxiety disorders are the most prevalent of all psychological disorders. Large scale surveys estimate that around 33% of the population is likely to suffer from an anxiety disorder at some point in their lives (Bandelow & Michaelis, 2015). The category of anxiety disorders encompasses a broad range of disorders marked by severe levels of fear and anxiety. Similar to the other disorders discussed in this chapter, the etiology of anxiety disorders is thought to be a complex combination of biological and environmental factors.

15.3.2 Introduction to Anxiety Disorders

The main feature common to all individuals suffering from an anxiety disorder is the experience of excessive **anxiety**. Similar to the emotion, fear, anxiety acts as a signal of danger, threat, or motivational conflict, and prepares the body for action. While *fear* is a physical and emotional response to a real or external imminent threat, *anxiety* is a **generalized response to an unknown threat or internal conflict**, often accompanied by bodily symptoms such as increased heart rate, muscle tension, a sense of unease, and apprehension about the future (APA, 2013). The category of anxiety disorders includes generalized anxiety disorder, panic disorder, specific phobia, and social anxiety disorder (social phobia) (APA, 2013).

Like many psychological disorders, anxiety disorders are believed to arise from a complex blend of factors, both biological and environmental, that when combined with stress, lead to the development of a particular anxiety disorder.

Although all the anxiety disorders share the feeling of anxiety as a symptom, there are many different ways in which this anxiety may manifest in an individual, leading to the diversity seen among the disorders in this category.

15.3.3 Genetic and epigenetic factors in anxiety disorders

Anxiety disorders are believed to be highly complex and polygenic (Meier & Decker, 2019). While genetics have been known to contribute to the presentation of anxiety symptoms, the interaction between genetics and stressful environmental influences accounts for more anxiety disorders than genetics alone (Bienvenu, et al., 2011). Nevertheless, several genes have been identified that may contribute to the increased risk of the development of anxiety disorders.

One of the first promising genes to be identified was a **serotonin transporter** or **SERT** gene. The serotonin transporter is of major importance in regulating levels of serotonin in the synapse. Serotonin synapses play a central role in the neural circuitry controlling mood and temperament (Houwing, et al., 2017). Disturbances in the serotonin system are known to contribute to many psychological disorders (Andrews et al., 2015). Mutation of the SERT gene have been found to be related to a reduction in serotonin activity and an increase in anxiety-related personality traits (Munafo, et al, 2008).

In 2020, a large research study of over 200,000 participants identified a gene known as SATB1 (Levey, et al. 2020). This gene is believed to influence the activity ("expression") of multiple other genes involved in neuronal development, including a gene known as CRH1. The CRH1 gene codes for the protein, Corticotropin Releasing Hormone (*CRH*), which is a hormone that plays an essential role in our body's hypothalamic-pituitary-adrenal (HPA) axis, the pathway that modulates our stress and fear/anxiety responses.

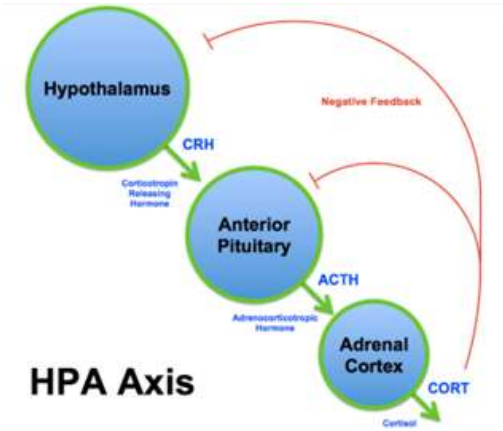


Figure 15.3.1: The body's HPA axis regulates stress responses. Genes which help maintain this system, may play a role in the risk of developing an anxiety disorder. (CC BY-SA 3.0; BrianMSweis via Wikimedia Commons)

15.3.4 Neural structures and neurotransmitters involved anxiety disorders

Researchers have identified several brain structures and pathways that are may be responsible for the excessive anxiety responses often seen in anxiety disorders. In particular, the atypical activation in the prefrontal cortex, hippocampus, and amygdala has been implicated in anxiety disorders (Shin & Liberzon, 2010, Maron & Nutt, 2017).

A region of the brain called the **locus coeruleus** has been of particular interest to researchers studying panic disorder. Located in the brainstem, the locus coeruleus is the brain's major source of norepinephrine, a neurotransmitter that triggers the body's fight-or-flight response (Figure 16.3.4.1). Research with nonhuman primates has shown that stimulating the locus coeruleus either electrically or through drugs produces panic-like symptoms (Charney et al., 1990). Such findings have led to the theory that individuals with panic disorder may have a hyperactive locus coeruleus, leaving them an increased likelihood of experiencing more intense and frequent physiological arousal than the general public (Gorman, et al., 2000). This theory is supported by studies in which individuals experienced increased panic symptoms following injection of norepinephrine (Bourin, et al., 1995).

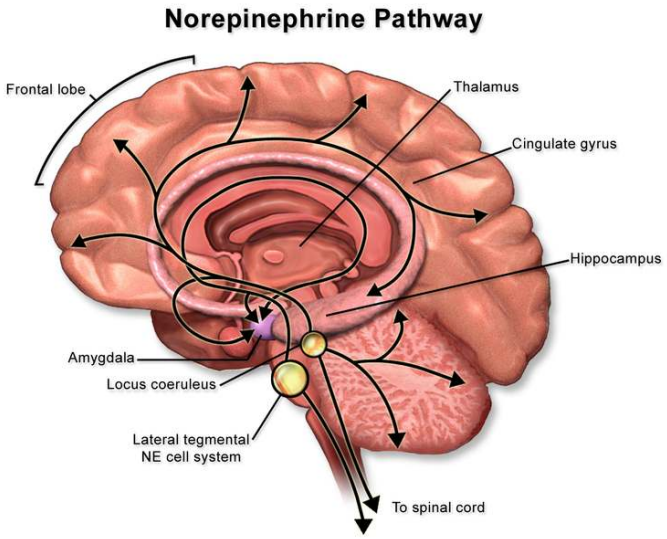


Figure 15.3.2: The locus coeruleus and the norepinephrine pathway. (CC BY-SA 4.0; BruceBlaus via Wikimedia Commons)

Unfortunately, norepinephrine and the locus coeruleus fail to fully explain the development of panic disorder, and a more complex neuropathway is likely implicated in the development of panic disorder. More specifically, the corticostriatal-thalamocortical (CSTC) circuit, also known as the fear-specific circuit, is theorized as a major contributor to panic symptoms (Gutman, et al., 2004). When an individual is presented with a frightening object or situation, the amygdala is activated, sending a fear response to the anterior cingulate cortex and the orbitofrontal cortex. Additional projections from the amygdala to the hypothalamus activate endocrinologic responses to fear- releasing adrenaline and cortisol to help prepare the body to fight or flight (Gutman, et al. 2004).

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15.3.6 Attributions

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15.4: Biological Basis of Schizophrenia Spectrum Disorder

Learning Objectives

- Describe the principal features of schizophrenia spectrum disorders.
- Identify the difference between positive and negative symptoms in schizophrenia.
- Identify the biology thought to underlie the etiology of schizophrenia.
- Describe the dopamine and glutamate hypotheses of schizophrenia.
- Explain the key elements of the neurodevelopmental theory of schizophrenia
- Evaluate the influence of the prefrontal cortex in the etiology and symptoms of schizophrenia

15.4.1 Overview

Schizophrenia spectrum and other psychotic disorders are a category of psychological disorders encompassing an incredibly diverse range of characteristics, including distortions in perception, impairments in cognition, and abnormal motor activity. In addition, the symptoms vary greatly among individuals, as there are rarely two cases similar in presentation, course, or responsiveness to treatment (APA, 2013).

This category also includes schizophreniform disorder (a briefer version of schizophrenia), schizoaffective disorder (a mixture of psychosis and depression/mania symptoms), delusional disorder (the experience of only delusions), and brief psychotic disorder (psychotic symptoms that last only a few days or weeks). However, as many of the symptoms of these disorders overlap with schizophrenia, this disorder is the primary focus of this section.

15.4.2 Schizophrenia Symptomology

Originally termed *dementia praecox* (Latin for premature dementia), schizophrenia involves a diverse and complex set of symptoms, such as delusions, hallucinations, disorganized speech and behavior, abnormal motor behavior (including catatonia), anhedonia/amotivation and blunted affect/reduced speech (APA, 2013). Given this diversity of symptoms, and the fact that the presentation of symptoms can vary widely from case to case, it has been difficult for researchers and clinicians to precisely define schizophrenia as a disorder (Tandor, 2013). Growing evidence suggests that schizophrenia represents a broad and heterogenous syndrome, rather than a specific disorder, and is better classified along a psychosis spectrum (APA, 2013, Cuthbert & Morris, 2021).

When considering the symptoms of schizophrenia, it is common practice to divide the symptoms into **positive symptoms** (symptoms that demonstrate an excess of function) and **negative symptoms** (symptoms that represent a loss or reduction in function) (see Figure 15.4.1).

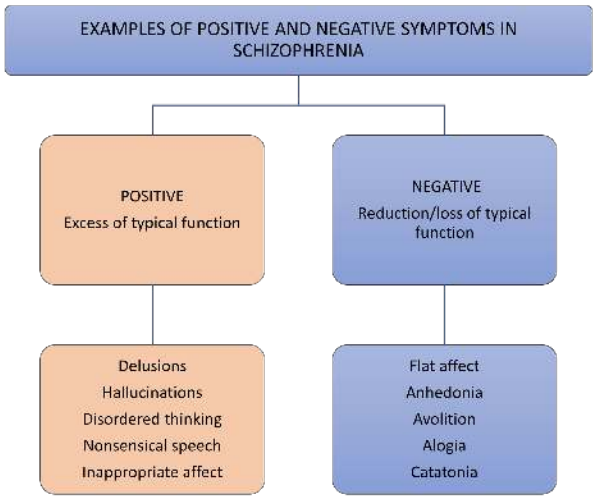


Figure 15.4.1: Schizophrenia symptoms are often classified as positive (an excess of typical function) or negative (a loss/reduction in typical function). (CC BY-SA 4.0; Amy E. Coren, Ph.D.)

The most common positive symptoms are **delusions** and **hallucinations**. Delusions are “fixed beliefs that are not amenable to change in light of conflicting evidence” (APA, 2013, pp. 87). An individual suffering from delusions remains convinced in their belief, even when presented with clear, contradicting evidence. Researchers believe that delusions primarily relate to the social, emotional, educational, and cultural background of the individual (Arango & Carpenter, 2010). For example, an individual with schizophrenia who comes from a highly religious family is more likely to experience religious delusions (delusions of grandeur) than another type of delusion.

Hallucinations are perceptual experiences with no external stimulus (such as hearing voices when no one else is present). Hallucinations can occur in any sensory modality: auditory, visual, olfactory (smell), gustatory (taste), or somatic (touch), however the most common type are auditory hallucinations (APA, 2013). The content of these auditory hallucinations is frequently negative, making critical comments (“you’re worthless”) or telling the person what to do.

Negative symptoms typically involve an impairment in functions – cognitive, physical, and/or emotional. For example, anhedonia reflects a lack of apparent drive to engage in social or recreational activities. Importantly, this does not seem to reflect a lack of enjoyment in pleasurable activities or events (as is often seen in Depressive Disorders) (Llerena, et al., 2012) but rather a reduced drive or ability to take the steps necessary to obtain the potentially positive outcomes (Barch & Dowd, 2010). Flat affect and reduced speech (alogia) reflect a lack of showing emotions through facial expressions, gestures, and speech intonation, as well as a reduced amount of speech and increased pause frequency and duration.

15.4.3 Genetics and Epigenetics in Schizophrenia

Numerous family and twin studies have provided evidence that genetics play a significant role in an individual’s risk of developing schizophrenia (Henriksen, et al., 2017). However, as is the case with many psychological disorders, the genetics underlying schizophrenia have proven to be highly complex, heterogeneous, and polygenic. Furthermore, the wide variations in symptoms among cases (i.e., one individual may demonstrate only negative symptoms, while another may present only positive symptoms) makes it even more challenging to identify specific genes associated with risk for schizophrenia.

Genome-wide studies have identified more than 70 genes suspected of playing a role in producing schizophrenia (Flint & Munafò, 2014), and it is believed that the development of schizophrenia involves the cumulative effects of multiple genes, with most of these having only a small effect by themselves.

While our understanding of the genetic basis underlying schizophrenia is still developing, recent research has noted several genes associated with various aspects of brain development, including myelination and synaptic transmission (Smigielski, et al. 2020), that are also associated with an increased susceptibility to schizophrenia (Gürel, et al. 2020). It is now believed that this genetic susceptibility may be triggered by early environmental factors, through epigenetic mechanisms, and alter the course of neural development, leading to the later development of schizophrenia. (Gürel, et al. 2020.) This theory is sometimes referred to as the **Neurodevelopmental Hypothesis** of schizophrenia since it requires epigenetic activation of genes during early development to set the stage for latter presentation of the disorder. "The influential neurodevelopmental hypothesis of schizophrenia proposes that pathological neurodevelopmental processes, beginning as early as the first and second trimesters, result in neuronal circuits that are primed to generate psychotic symptoms during adolescence or young adulthood, often in the context of heightened biological and psychological stress" (Nour and Howes, 2015). See the section below on the Neurodevelopmental Hypothesis for more details.

15.4.4 The Role of Neurotransmitters in Schizophrenia

Since the 1960s, it has been believed that many of the symptoms of schizophrenia were the result of an overactivity of dopamine. As with many of the psychological disorders, it is now understood that the biochemistry underlying schizophrenia is complex and involves multiple biological systems.

15.4.4.1 Dopamine Hypothesis of Schizophrenia

Although the first **antipsychotic** drugs appeared in the 1950s, it was not well understood how these drugs were alleviating some of the symptoms of schizophrenia, nor why they also produced side effects, similar to those seen in patients with Parkinson’s disease (muscular rigidity, tremors, decrease in voluntary movement). It wasn’t until the late 1960s when further research made the notable discovery that the striatums of individuals with Parkinson’s disease were completely depleted of dopamine (Goetz, 2011). This discovery led researchers to further speculate that antipsychotic drugs might be producing their rigidity and tremor side effects by reducing dopamine activity, which then implied that many of the psychotic symptoms alleviated by these drugs were being caused by the overactivity of dopamine in the brain. These speculations developed into what eventually became known as the **dopamine theory of schizophrenia** (see Brisch, et al., 2014).

Almost since this theory became accepted, the development of newer antipsychotics had generally followed the dopamine hypothesis. In other words, since patients with schizophrenia were assumed to have increased dopaminergic activity, dopamine antagonist drugs, particularly those that targeted the dopamine D2 receptor could treat their symptoms.

The antagonism of dopamine D2 receptors in the mesolimbic pathway is thought to be the main mode of action of antipsychotic medication in treating psychotic symptoms. See Figure 15.4.2. In addition to the mesolimbic brain areas, **dopamine dysregulation** has also been observed in the **amygdala and prefrontal cortex**, which are important for emotional processing, and differences in dopamine contents in the prefrontal cortex, cingulate cortex, and hippocampus between schizophrenia patients and healthy control subjects (Patel, et al., 2010). In particular, the dopamine system in the hippocampus is overactive in schizophrenia patients (Grace, 2012).

However, a dopamine receptor antagonist is not clinically effective at treating cortical-related symptoms, such as cognitive deficits, in schizophrenia. Although the exact mechanism underlying these cognitive deficits remains largely unknown, factors such as deficits in cortical dopamine function , dysfunction in the glutamate, NMDA receptor, or synaptic elimination are likely to play a contributing role.

Molecular imaging studies have supported an association of increased subcortical dopamine transmission with the positive symptoms of schizophrenia with some exceptions. Although hyperactivity in subcortical dopaminergic function most likely contributes substantially to positive symptoms, the original dopamine hypothesis must be extended to include contributions of other neurotransmitter systems in the pathophysiology of schizophrenia [13].

As researchers came to better understand the biological complexities of schizophrenia, the original version of the dopamine hypothesis no longer fit with our understanding of the disorder. This has led to the “revised dopamine hypothesis” (Brisch, et al., 2014). This revised hypothesis proposes that the increased dopamine transmission in the mesocorticolimbic areas (see Figure 15.4.2) and decreased dopamine transmission in the prefrontal cortex seen in individuals with schizophrenia account for many of their symptoms. (Pogarell, et al. 2012).

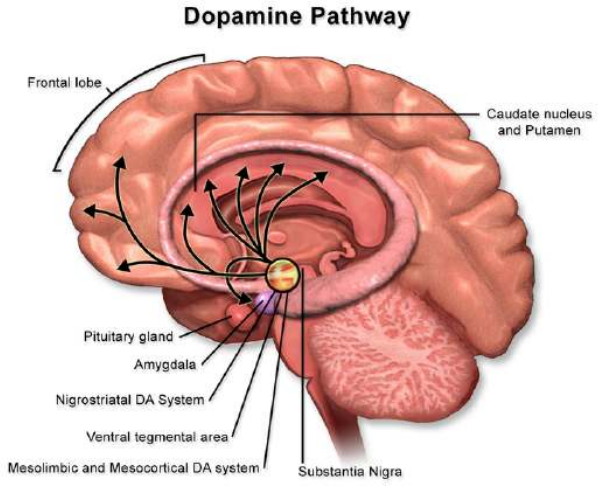


Figure 15.4.2: The mesocorticolimibic dopamine pathway. The revised dopamine hypothesis proposes that many of the symptoms of schizophrenia arise from dopamine dysfunction in this pathway. (CC BY-SA 4.0; BruceBlaus via Wikimedia Commons)

15.4.4.2 Glutamate Hypothesis of Schizophrenia

As noted above, schizophrenia has been primarily associated with dopamine dysfunction, and treatments have been developed that target the dopamine pathway in the central nervous system. However, accumulating evidence has shown that the core pathophysiology of schizophrenia might involve dysfunction in dopaminergic, glutamatergic, serotonergic, and gamma-aminobutyric acid (GABA) systems. This broad range of dysfunction may lead to the diverse cognitive, behavioral, and social alterations observed in this disorder (Yang & Tsai, 2017)

Glutamate is one of the excitatory and most abundant neurotransmitters in the brain. Glutamate pathways link to the cortex, the limbic system, and the thalamus regions, all of which have been implicated in schizophrenia. The association of glutamate dysfunction with schizophrenia could originate from the observation that the cerebrospinal fluid of patients with schizophrenia had decreased glutamate levels . Furthermore, patients who abuse certain glutamate antagonists, such as phencyclidine or ketamine,

frequently show psychotic symptoms. Dysfunction of glutamate action can be a promising treatment target for its essential role in the pathophysiology of schizophrenia, especially in terms of negative symptoms and cognitive impairment (Yang & Tsai, 2017).

15.4.5 Neurodevelopment Hypothesis of Schizophrenia

Almost three decades ago Weinberger proposed a **neurodevelopmental hypothesis** for the etiology of schizophrenia. Weinberger's hypothesis synthesized emerging findings from the field of schizophrenia research, attaching particular importance to the observation that symptoms of the disease often surface in adolescence and are associated with stressful life events. Weinberger suggested that '…a fixed 'lesion' from early in life may interact with normal brain maturational events that occur much later.' This vision of the pathogenesis of schizophrenia was prescient. At the time, the field of neuropathology in schizophrenia was in its infancy. The only evidence for structural brain pathology was the finding of enlarged ventricular volume in patients with schizophrenia. There was not yet any hard evidence linking early brain insult to schizophrenia, and the concept that the late adolescent maturational process of synaptic elimination might contribute to schizophrenia had only recently been proposed (Selemon & Zecevic, 2015)

In the ensuing years, a wealth of evidence has accumulated from epidemiologic studies to indicate that prenatal and perinatal factors contribute to the risk of developing schizophrenia, leading to virtual universal acceptance of schizophrenia as a neurodevelopmental disease. Over this same period, neuroimaging studies of schizophrenia subjects have found widespread cortical gray matter loss due to impoverished neural connectivity that is particularly pronounced in certain areas such as the prefrontal cortex. Taken together, these diverse research findings strengthen the basic tenets of the neurodevelopmental hypothesis: (1) that schizophrenia is a disease associated with early abnormal brain development and (2) that schizophrenia-associated neuropathology, for example, reduction of neuropil in the prefrontal cortex, could be unmasked by the late adolescent process of synaptic pruning. (Selemon & Zecevic, 2015)

15.4.6 Neural Structures in Schizophrenia

There is a long and reliable history of research into the neural basis of schizophrenia. Neuroimaging studies have found a **significant reduction** in overall and **specific brain region volumes**, as well as tissue density of individuals with schizophrenia compared to healthy controls (Brugger & Howes, 2017). Additionally, there has been evidence of **ventricle enlargement** (See Figure 15.4.3) as well as **volume reductions** in the **medial temporal lobe**, which contains such structures as the **amygdala** (involved in emotion regulation), the **hippocampus** (involved in memory), as well as the **neocortical surface** of the temporal lobes (processing of auditory information) (Kurtz, 2015). Additional studies also indicate a reduction in the **orbitofrontal regions** of the brain, a part of the frontal lobe that is responsible for **response inhibition** (Kurtz, 2015).

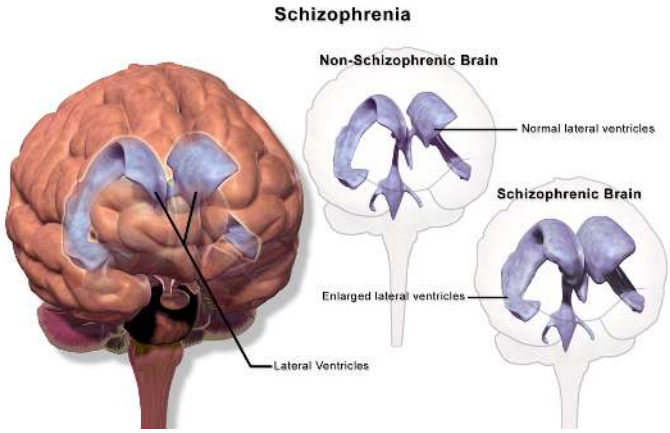


Figure 15.4.3: The enlarged ventricles are often seen in the brains of individuals diagnosed with Schizophrenia. (CC BY-SA 4.0; BruceBlaus via Wikimedia Commons)

15.4.6.1 Focus on Prefrontal Cortex Alterations in Schizophrenia

One of the brain regions most consistently implicated in the pathophysiology of schizophrenia is the **dorsolateral prefrontal cortex** (See Figure 15.4.4). Dysfunction of the dorsolateral prefrontal cortical is thought to be an underlying substrate for thought disorder in schizophrenia. Patients with schizophrenia perform poorly on an array of cognitive tasks that depend on prefrontal cortical function, for example, Continuous Performance (attention), Stroop (cognitive inhibition), Wisconsin Card Sort (cognitive flexibility), Delayed Response (working memory) and N-Back (working memory) tasks. Moreover, a meta-analysis of magnetic

resonance imaging findings has reaffirmed that the dorsolateral prefrontal cortex is a hotspot for gray matter volume deficit in the brains of schizophrenia patients. (Selemon & Zecevic, 2015)

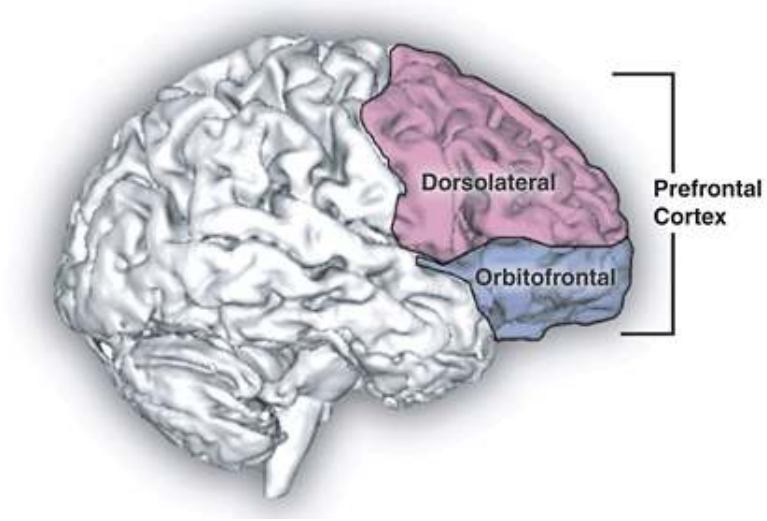


Figure 15.4.4: Dorsolateral Prefrontal Cortex - A major component of the frontal lobe involved with higher cognitive functions and shown to be altered in studies of schizophrenia. From Zahr, N.M.., Sullivan, E.V., (2008) Translational Studies of Alcoholism Bridging the Gap. *Alcohol Research & Health*, 31 (3). NIH, Public Domain.

Interestingly, a review of recent research confirms the influence of the neurodevelopmental hypothesis on prefrontal cortex development, especially in terms of two developmental periods, early gestation and adolescence, that have been implicated in the etiology of schizophrenia. Guided by knowledge of basic human neurodevelopment, this research has identified two developmental processes, cell proliferation in early gestation and synaptic pruning in adolescence, that are prominent during these critical time periods and are essential to normative prefrontal cortical development. The results of this body of research suggests that diverse environmental insults may converge on these processes and perturb normal development of the prefrontal cortex, resulting in a heightened risk of schizophrenia. (Selemon & Zecevic, 2015)

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