SCIENCE MAGAZINES

Issue 1: Neuroanatomy

Magazine 1: Neuroanatomy Primer

12US17IUS0017 November 2017

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NEUROANATOMY PRIMER

Serves as a foundation for understanding the anatomy of the brain and how it works. This issue will allow you to become familiar with the structure and function of the brain, the method it uses to send signal to nearby nerve cells and to other parts of the body and how therapeutic agents can be used to modify those signals.

ANATOMY OF CNS

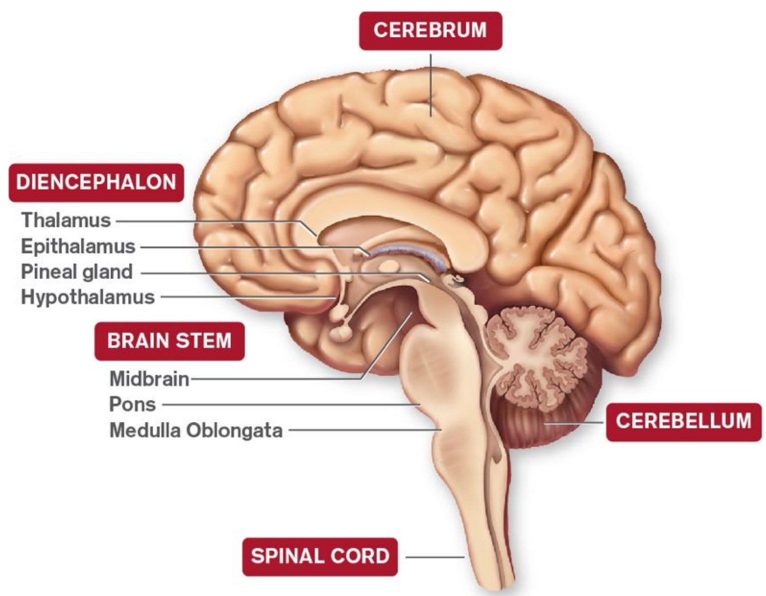
ANATOMICAL REGIONS OF THE BRAIN[6]

The science of how the brain works is interesting. We think we know quite a bit about it—and you are going to be exposed to some of what is known—but it is likely that the way the brain works is far more complex and mysterious than we actually know now. So just keep in mind that there is probably a lot more to learn in the future, but what you will learn here will be an interesting journey. One thing to keep in mind is that we will use much of the language that is part of the neuroscientists' lexicon. This is important because when you are speaking to healthcare professionals that work in the neuroscience field, this is how they talk—so use this opportunity to learn a little bit of a new language.

The nervous system is the network of interlinked nerve cells that coordinates all the sensory and motor activities of the body. It is responsible for controlling our speech and behavior and for regulating the activity of all internal organs and body systems. Anatomically, the nervous system is often considered as two parts: the central nervous system—CNS—and the peripheral nervous system.[1,2] The brain is part of the CNS.

Cerebrum

The cerebrum includes the cerebral cortex, the underlying cerebral white matter, and a complex of deep, gray matter masses, the basal ganglia. There are multiple "maps" (motor, somatosensory, visual) of the body and the external world within the cerebral cortex. The cerebral cortex is responsible for a variety of higher brain functions, including manual dexterity (the "opposing thumb" and the ability to move the fingers individually so as to, for example, play the piano); conscious, discriminative aspects of sensation; and cognitive ability, including language, reasoning, planning, and many aspects of learning and memory.[7]



Diencephalon

The diencephalon includes the thalamus and its geniculate bodies, the hypothalamus, the subthalamus, and the epithalamus. The third ventricle lies between the halves of the diencephalon.[8] The thalamus can be divided into five functional nuclear groups: sensory, motor, limbic, multimodal, and intralaminar.[8]

Cerebellum

The cerebellum is located behind the dorsal aspect of the pons and the medulla (divisions of the brain stem).[9]

The cerebellum has several main functions: coordinating skilled voluntary movements by influencing muscle activity and controlling equilibrium and muscle tone through connections with the vestibular system and the spinal cord and its motor neurons.[9]

The cerebellum is an important part of the circuitry that links sensory to motor areas of the brain, and it functions to coordinate movement. It provides corrections during movement, which are the basis for precision and accuracy, and it is critically involved in motor learning and reflex modification. It receives information from peripheral receptors and from the cerebral cortex. Cerebellar output is directed predominantly to the thalamus and then to the motor cortex.[10]

Brain stem

Three major external divisions of the brain stem are recognizable: the medulla (medulla oblongata), the pons together with the cerebellum, and the midbrain (mesencephalon).[9]

Spinal cord

The spinal cord, which sits just below the brain stem, is essentially a segmental structure, giving rise to 31 bilaterally paired spinal nerves.[11]

The spinal cord provides innervation for the trunk and limbs via spinal nerves and their peripheral extensions. It receives primary afferent fibers from peripheral receptors located in somatic and visceral structures and sends motor axons to skeletal muscle.[11]

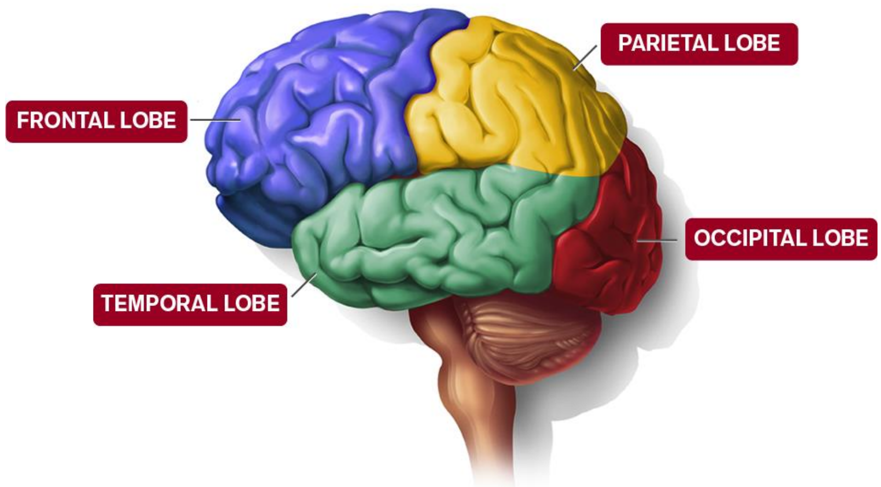
LOBES OF THE BRAIN[6]

If we could gently pull the brain out of its protected surroundings, called the skull, we would see an organ that is pretty much three colors, a combination of brown, white and gray. Those colors don't help differentiate the parts of the brain, so we are going to take the liberty of adding our own color. This will help us see where one lobe ends and another lobe begins. Take a look!

Each cerebral hemisphere is divided into lobes. Although some sources list two additional—small—lobes, the four that are most important are shown below.

Frontal lobe

The frontal lobe includes the motor cortex, as well as frontal association areas responsible for initiative, judgment, abstract reasoning, creativity, and socially appropriate behavior (inhibition of socially inappropriate behavior). These latter parts of the cortex are the phylogenetically newest and the most uniquely "human." The frontal lobe extends from the frontal pole to the central sulcus and the lateral fissure.[7]



The prefrontal cortex includes the higher-order association cortex, which is involved in judgment, reasoning, initiative, higher-order social behavior, and similar functions. The prefrontal cortex is located anterior to the primary motor cortex within the precentral gyrus and the adjacent premotor cortex.[7]

Parietal lobe

The parietal lobe extends from the central sulcus to the parieto-occipital fissure; laterally, it extends to the level of the lateral cerebral fissure.[7] Its primary function is somatosensory processing.[7]

Temporal lobe

The temporal lobe lies below the lateral cerebral fissure and extends back to the level of the parieto-occipital fissure on the medial surface of the hemisphere.[7] Its major functions are processing of auditory stimuli and language comprehension.[7]

Occipital lobe

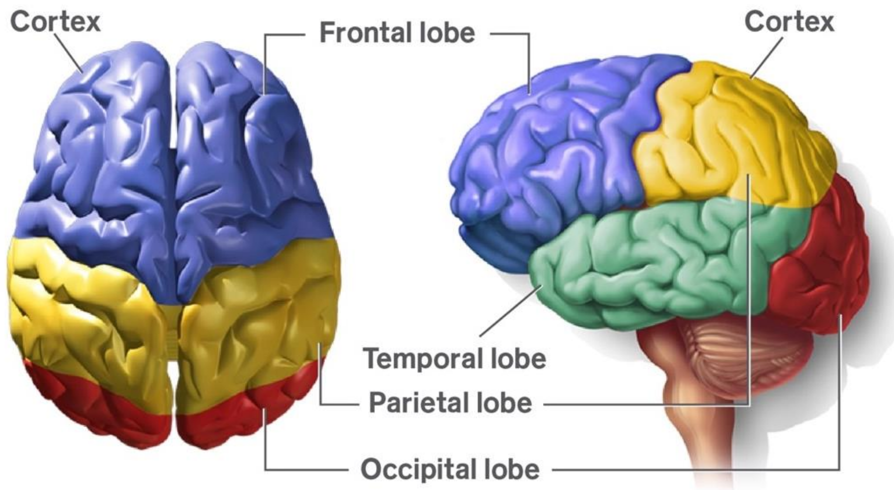
The occipital lobe houses the primary visual cortex and other components.[7] Its major function is processing of visual stimuli.[7]

THE CEREBRUM[6]

The word cerebrum is used in everyday language to refer to the part of the brain that is used to think. Well, it's not really that simple, but the cerebrum is one of the important parts of the brain that is involved in cognition—the brain experts' term for thinking. The cerebrum plays several different roles in our daily lives—and these roles are often employed together to accomplish what we want to do.

Although the two hemispheres seem to be mirror images of each other, they are different. For instance, the ability to form words seems to lie primarily in the left hemisphere, while the right hemisphere seems to control many abstract reasoning skills. Nearly all of the signals from the brain to the body, and vice versa, cross over on their way to and from the brain.[13]

The cerebral cortex consists of frontal, parietal, temporal, occipital, insular, and limbic lobes on each side of the brain. It also contains underlying cerebral white matter and a complex of deep gray matter masses called the basal ganglia. The cortex is particularly well developed in humans. Different parts of the cortex are responsible for a variety of higher brain functions, including manual dexterity, the conscious aspects of sensation, and cognitive activity, such as language, reasoning, learning, and memory.[2,14]



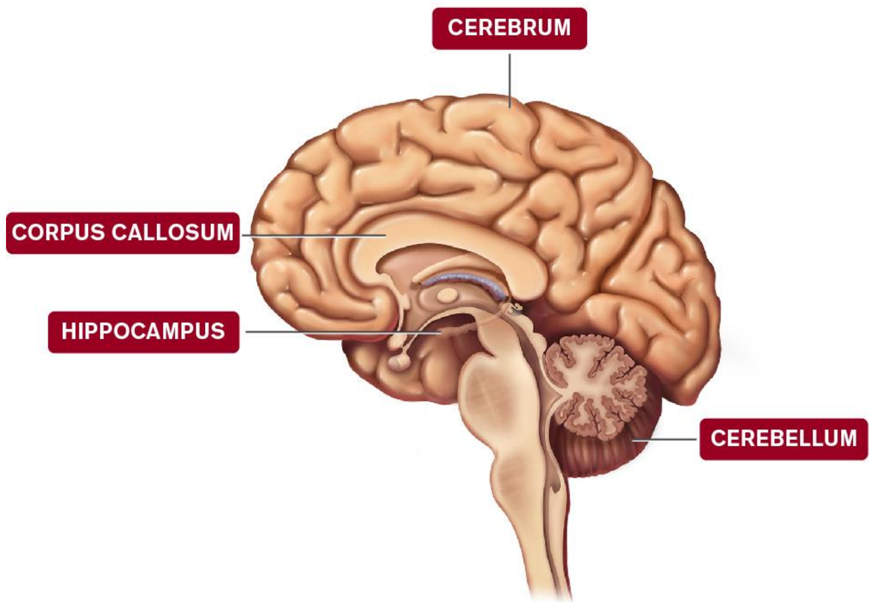
INTERNAL STRUCTURES OF THE BRAIN[6]

If we go down just a little deeper into the brain, we could see four different structures that work with the cerebrum to accomplish both conscious and subconscious tasks during the day and night. One of these, the corpus callosum, has an interesting job of connecting the left side of the brain with the right side. Can you imagine what it would be like if the two hemispheres were not connected? A lot of things would be nearly impossible to do.

Internally, each hemisphere is made up of the structures listed below.

Cerebrum

The cerebrum includes the cerebral cortex, the underlying cerebral white matter, and a complex of deep gray matter masses, the basal ganglia. There are multiple “maps” (motor, somatosensory, visual) of the body and the external world within the cerebral cortex. The cerebral cortex is responsible for a variety of higher brain functions, including manual dexterity (the “opposing thumb” and the ability to move the fingers individually so as, for example, to play the piano); conscious, discriminative aspects of sensation; and cognitive ability, including language, reasoning, planning, and many aspects of learning and memory.[7]



Corpus callosum

The corpus callosum connects the left and right hemispheres.[7]

Hippocampus

The hippocampus has several functions. It helps control corticosteroid production. It also makes a significant contribution to understanding spatial relations within the environment. Additionally, the hippocampus is critically involved in many declarative memory functions.[15]

The hippocampus also mediates the signals that are responsible for processing and retrieving memories.[16]

Cerebellum

The cerebellum is located behind the dorsal aspect of the pons and the medulla (divisions of the brain stem).[9]

The cerebellum has several main functions: coordinating skilled voluntary movements by influencing muscle activity, and controlling equilibrium and muscle tone through connections with the vestibular system and the spinal cord and its motor neurons.[9]

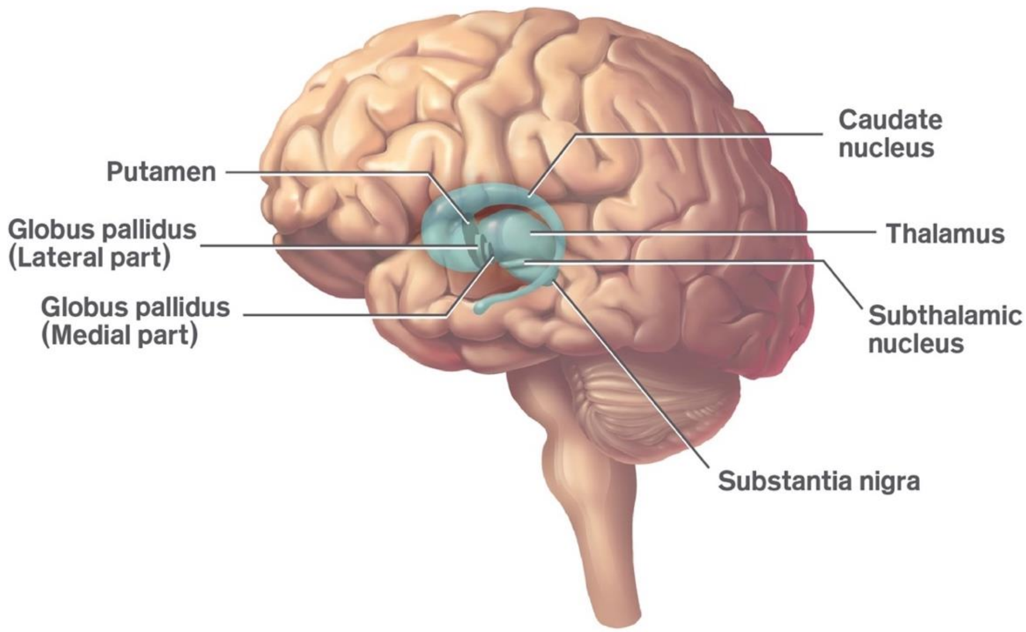
One of the things we take for granted is the ability to walk smoothly, left foot after right foot and so on. This coordinated smooth style of walking is thanks to the cerebellum.

The cerebellum is an important part of the circuitry that links sensory to motor areas of the brain, and it functions to coordinate movement. It provides corrections during movement, which are the basis for precision and accuracy, and it is critically involved in motor learning and reflex modification. It receives information from peripheral receptors and from the cerebral cortex. Cerebellar output is directed predominantly to the thalamus and then to the motor cortex.[10]

BASAL GANGLIA[6]

Now we are getting in to the parts of the brain that have names that are a little more difficult to remember. These were given Latin names way back when scientists were discovering the parts of the brain and the names haven't changed since then. But try not to let this get in the way! Maybe you can think of a common way to remember them based on what they sound like.

The basal ganglia consist of several nuclei of gray matter found buried within the white matter of the cerebral hemispheres. There are four principal nuclei: subthalamic nucleus, substantia nigra, striatum, and globus pallidus. The basal ganglia help initiate and terminate movements of the body. They also suppress unwanted movements and regulate muscle tone. In addition, the basal ganglia influence many aspects of cortical function, including sensory, limbic, cognitive, and linguistic functions.[2]



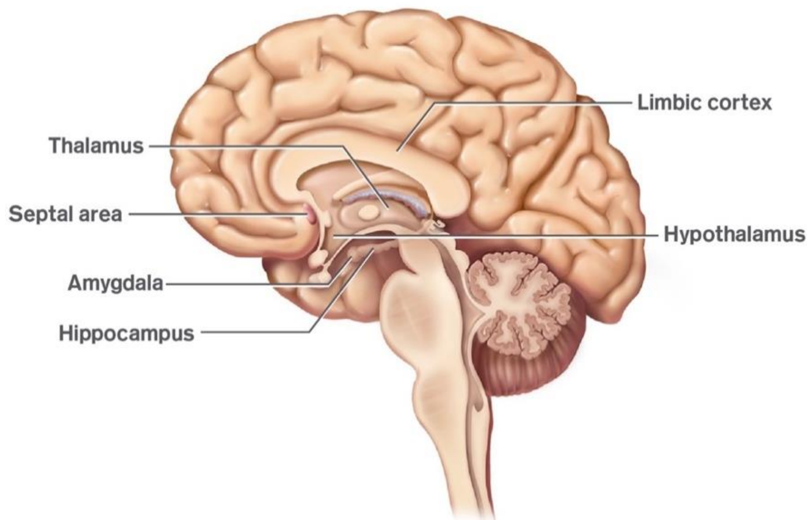
THE LIMBIC SYSTEM[6]

Now the limbic system is connected to many other parts of the brain and it is almost always busy. It helps in sensation, hearing, and many other functions that require transmitting messages through circuits to other parts of the brain. Think of it as a branch of the government: each part has its own role, but it works best when all parts communicate!

The limbic system is a functional network rather than an anatomical structure. Nerve fibers are contributed to it from several parts of the brain. The circuitry of the limbic system includes parts of the prefrontal cortex, basal ganglia, the thalamus, and a structure called the amygdala. This set of structures, together with the hippocampus and cingulate cortex, is generally referred to as the limbic system.[15,17]

In some cases, mental health involves emotions of some type. This is where the amygdala comes in—and its connections to several other parts of the brain.

The amygdala clearly plays a major role in the experience and expression of emotional behavior. The amygdala links cortical regions that process sensory information with hypothalamic and brain stem effector systems. Cortical inputs provide information about highly processed visual, somatic sensory, visceral sensory, and auditory stimuli. Projections from the amygdala to the hypothalamus and brain stem allow it to play an important role in the expression of emotional behavior.[15,17]

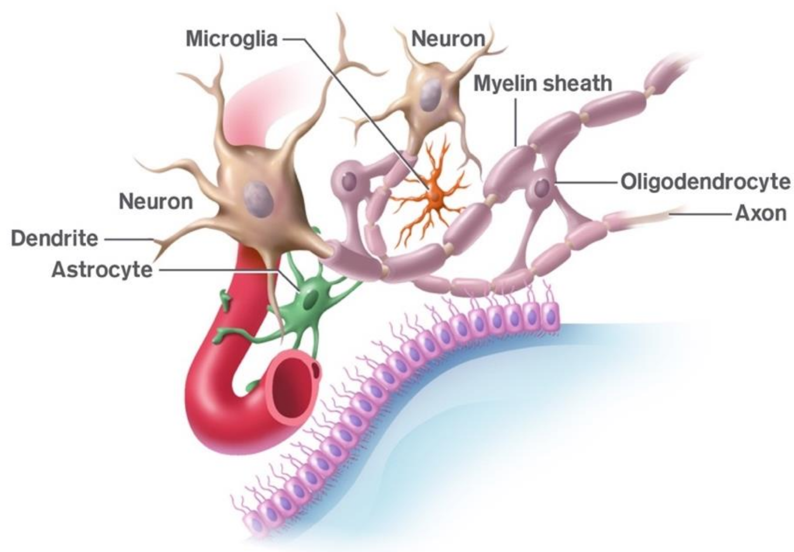


MICROSTRUCTURES OF THE BRAIN[6]

Of course, every part of the brain we have already talked about is made up of tissues and cells. Although we are not going to cover every single type of cell in the brain, there are a few cell types that are almost ubiquitous and that you should know about.

The cerebral cortex contains neurons and supporting cells called neuroglial cells. There are several different types of neurons, and we will focus on these in the next screen. Neuroglial cells—sometimes just called glial cells—are non-neuronal cells in the brain, and they perform a variety of functions. The different types of glial cells include oligodendrocytes, microglia, and astrocytes.

Oligodendrocytes wrap around individual nerve axons to form the protective myelin sheath of nerve fibers.[3] Microglia are cells that may become phagocytic in areas of neural damage or inflammation.[3] A phagocytic cell is capable of ingesting and digesting other cells, bacteria, bits of necrotic tissue, or foreign particles.[3] Astrocytes, also called macroglia, perform many functions, including biochemical support, provision of nutrients to the nervous tissue, immune defense, neurotransmission, and maintenance of ionic balance.[4] Now let's look more specifically at the cell type that has the greatest interest for understanding the neurobiology of schizophrenia, the neuron.



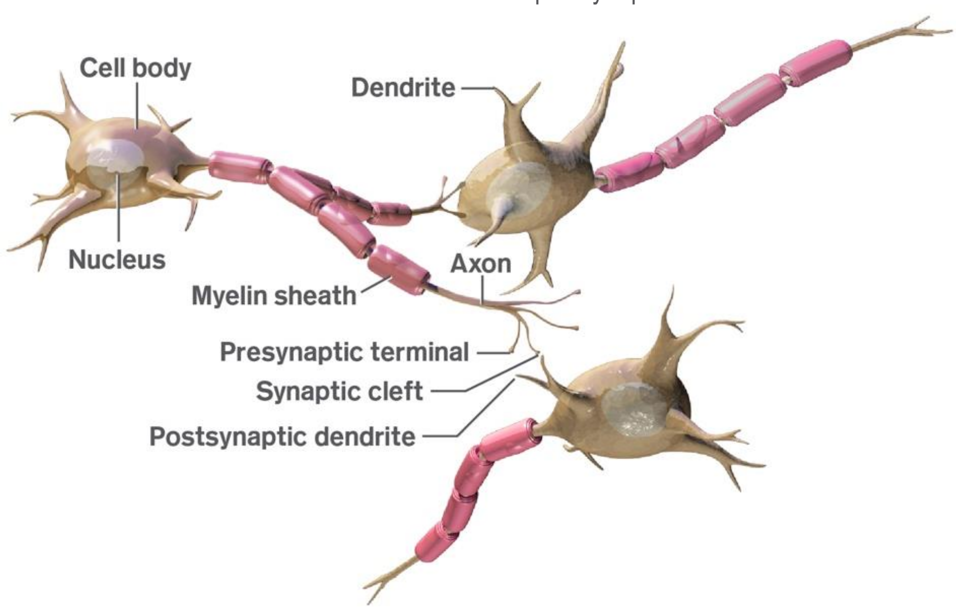
NEURONS[6]

Like cerebrum, neuron is a term that is often used in everyday language to refer to the essential component of a larger structure. It basically means nerve cell and it almost never rests, even when we are sleeping. Let's take a look at what the neuroscientists say about neurons.

A neuron is a nerve cell that is the basic building block of the nervous system. Neurons are similar to other cells in the human body in a number of ways, but there is one key difference between neurons and other cells: neurons are specialized to transmit information throughout the body.[18]

These highly specialized nerve cells are responsible for communicating information as both chemical and electrical stimuli. There are also several different types of neurons responsible for different tasks in the human body. Sensory neurons carry information from the sensory receptor cells throughout the body to the brain. Motor neurons transmit information from the brain to the muscles of the body. Interneurons are responsible for communicating information between different neurons in the body.[18]

There are three basic parts of a neuron: the dendrites, the cell body, and the axon. Some neurons have few dendritic branches, while others are highly branched in order to receive a great deal of information. Some neurons have short axons, while others can be quite long.[18] The longest extension of the neuron, the axon, leaves the cell body as a single arm and most often branches into multiple tips called synaptic terminals, where the stimulus, also called an "action potential," is passed to dendrites of the neighboring neurons. All neurons are separated by a gap, known as a synaptic cleft. Since an action potential cannot "jump" across a synaptic cleft, it must be converted into a chemical signal for communication between neurons to occur.[19] The synapse is a juncture formed by the axon terminals of one neuron—a presynaptic neuron—and the dendrites of a downstream neuron—the postsynaptic neuron.



PROGRESS CHECK QUESTIONS

Answers to these questions can be found on page 24.

Question 1

Which of the following is a true statement about the cerebral hemispheres? *(More than one answer may be correct)*

A. The two cerebral hemispheres communicate with each other

B. The right and left hemispheres are mirror images of each other

C. Nearly all signals from the brain to the body cross over to and from the brain

D. The ability to form words, for most people, is a function of the right hemisphere

Question 2

Which of the following lobes are primarily involved in controlling or processing emotions? *(More than one answer may be correct)*

A. Temporal lobe

B. Parietal lobe

C. Frontal lobe

D. Occipital lobe

Question 3

Which of the following is primarily in control of motor movements?

A. Basal ganglia

B. Thalamus

C. Substantia nigra

D. Putamen

Question 4

Which of the following is part of the circuitry of the limbic system? *(More than one answer may be correct)*

A. Prefrontal cortex

B. Hypothalamus

C. Basal ganglia

D. Amygdala

Question 5

The axon leaves the cell body of a neuron as a single arm and most often branches into multiple tips called what?

A. Myelin

B. Synaptic terminals

C. Astrocytes

D. Dendrites

Question 6

Which of the following is a true statement about neurons? *(More than one answer may be true)*

A. The longest extension of the neuron is called the dendrite

B. They transmit information

C. Only neurons in the brain have a cell body

D. The synapse is a juncture formed by the axon terminals of one neuron and the dendrites of another neuron

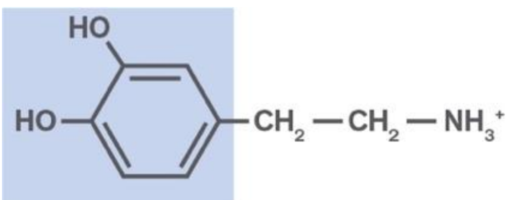
NEUROTRANSMITTERS AND NEUROPHARMACOLOGY

WHAT IS A NEUROTRANSMITTER?[6]

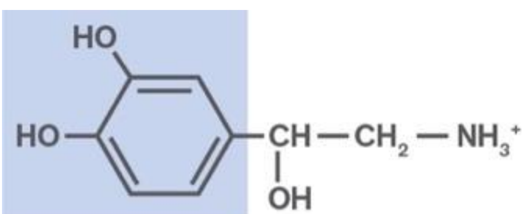
A neurotransmitter is a chemical messenger that carries, boosts, and modulates signals between neurons and other cells in the body. Neurotransmitters released from synaptic vesicles located in presynaptic axon terminals act on a large variety of receptor molecules to elicit fast excitation or inhibition as well as slower modulatory effects on neuronal excitability and responsiveness to other neurotransmitters. In addition to electrophysiologic effects, chemical transmission triggers long-term effects on function, protein expression, and structure of the target cell. These effects are critical for dynamic, use-dependent, long-term changes in the efficacy of synaptic transmission.[5]

You may have seen those old-fashioned mail tubes that were used to send messages from one office to another—in the same building. The sender would put some papers inside a capsule, screw on the top, pop it into the tube and send it on its way to the recipient. Somehow the vacuum inside that mail tube could control the direction of the capsule so it would end up in the right place. Well, that is kind of what a neurotransmitter does. It is a special kind of messenger that one nerve cell uses to communicate with another—and there are several different types, each with its own function.

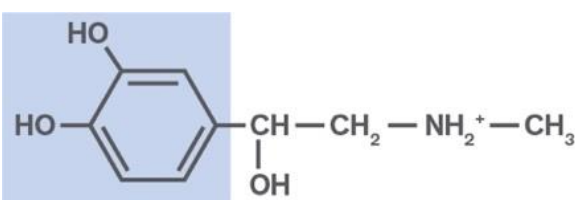
Three Neurotransmitters



DOPAMINE
(derived from tyrosine)



NOREPINEPHRINE
(derived from tyrosine)



EPINEPHRINE
(derived from tyrosine)

THE SYNAPSE[6]

There are two major types of neurotransmission: (1) chemical neurotransmission; and (2) electrochemical neurotransmission. In chemical neurotransmission, the first neuron secretes at its nerve-ending synapse a chemical substance called a neurotransmitter (or often called simply a transmitter substance). The neurotransmitter binds to the receptor proteins in the membrane, either activating, inhibiting, or modulating the activity of the receptors.[19]

> The synapse is like a gap or space between the sender and the receiver in the nervous system. If all of the nerves were physically connected, it is possible that the messages to and from the brain would be sent too fast for a proper response. What the synapse does is provide a little buffer space so that the neurotransmitter (the messenger) has to take the time to travel across before the receiver gets the message. Now this isn't very long in reality, but it allows for some pacing of messages that works better for timing purposes.

Synapse

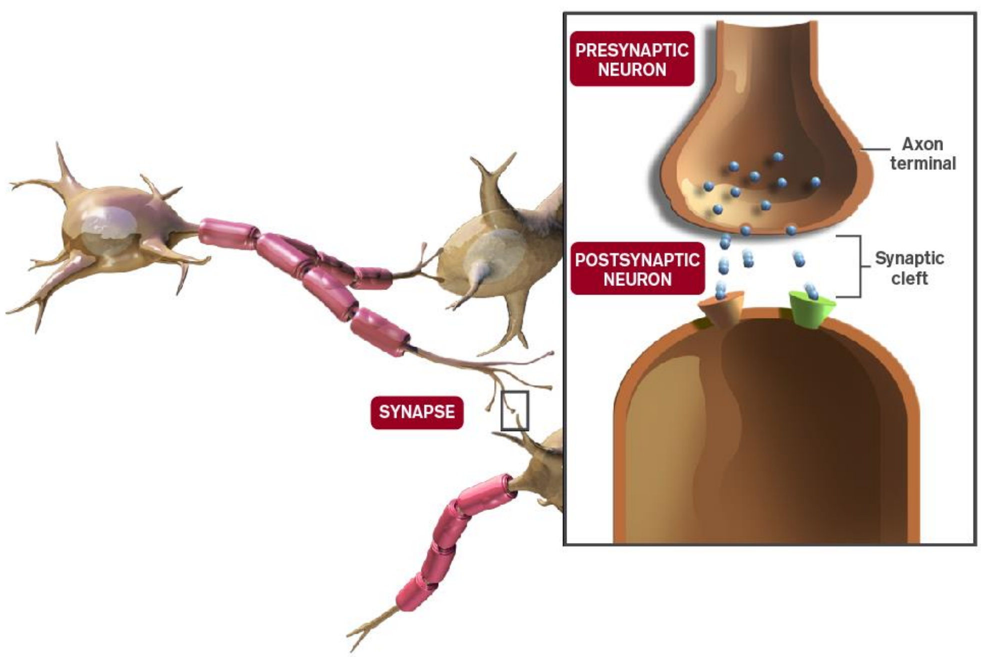
There are two major types of neurotransmission: (1) chemical neurotransmission; and (2) electrochemical neurotransmission. In chemical neurotransmission, the first neuron secretes at its nerve-ending synapse a chemical substance called a neurotransmitter (or often called simply a transmitter substance). The neurotransmitter binds to the receptor proteins in the membrane, either activating, inhibiting, or modulating the activity of the receptors.[19]

Presynaptic neuron

The presynaptic neuron releases neurotransmitters that travel across the synaptic cleft.[19] This is the nerve that sends the message. Although very small, the synaptic cleft creates a physical barrier for the electrical signal that is carried by one neuron and which then needs to be transferred to another neuron.[18]

Postsynaptic neuron

A postsynaptic neuron has receptors to which neurotransmitters bind.[19] This is the nerve that receives the message once it crosses the synapse.

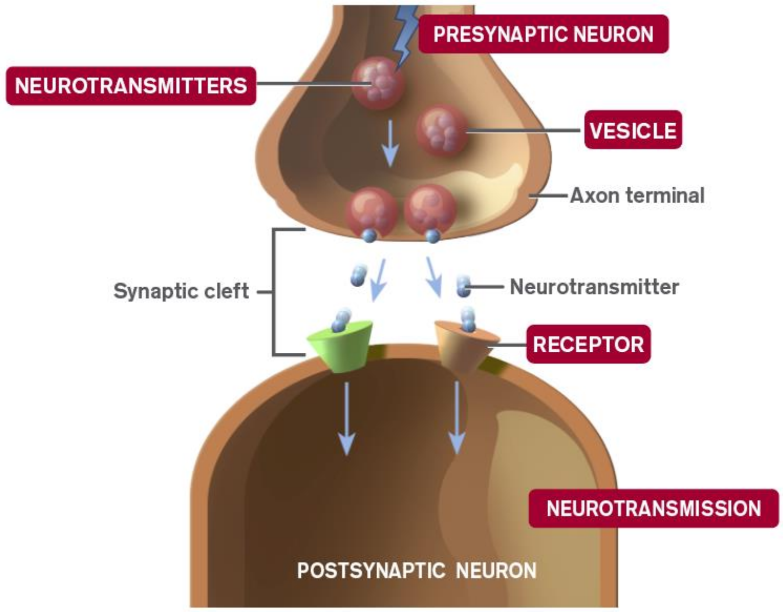


CHEMICAL TRANSMISSION[6]

Chemical neurotransmission is a process by which a presynaptic cell, on excitation, releases a specific chemical agent—a neurotransmitter—to cross a synapse to activate, inhibit, or modify receptors in the postsynaptic cell.[3]

Presynaptic neuron

A potential electrical signal reaches the axon terminal of the presynaptic neuron.[1]



Vesicle

A vesicle is a membrane-enclosed sac that stores or transports substances. Vesicles fuse with the cell membrane of the presynaptic neuron to release stored neurotransmitters into the synaptic cleft.[1]

Neurotransmitters

The neurotransmitters cross the synaptic cleft and bind to specific receptors on the postsynaptic neuron.[1]

There are two main classes of chemical substances that serve as neurotransmitters and neuromodulators: small-molecule transmitters and large-molecule transmitters. Small-molecule transmitters include amino acids, such as glutamate, GABA, and glycine; acetylcholine; monoamines, such as norepinephrine, epinephrine, dopamine, and serotonin; and adenosine triphosphate or ATP. Large molecule transmitters include a group of substances called neuropeptides, which will not be covered in this module.[20]

Receptor

This is a protein molecule within a cell membrane that has specific binding sites for select neurotransmitters or drugs and which produces a specific physiological effect.[2]

DOPAMINE AND DOPAMINE RECEPTORS[6]

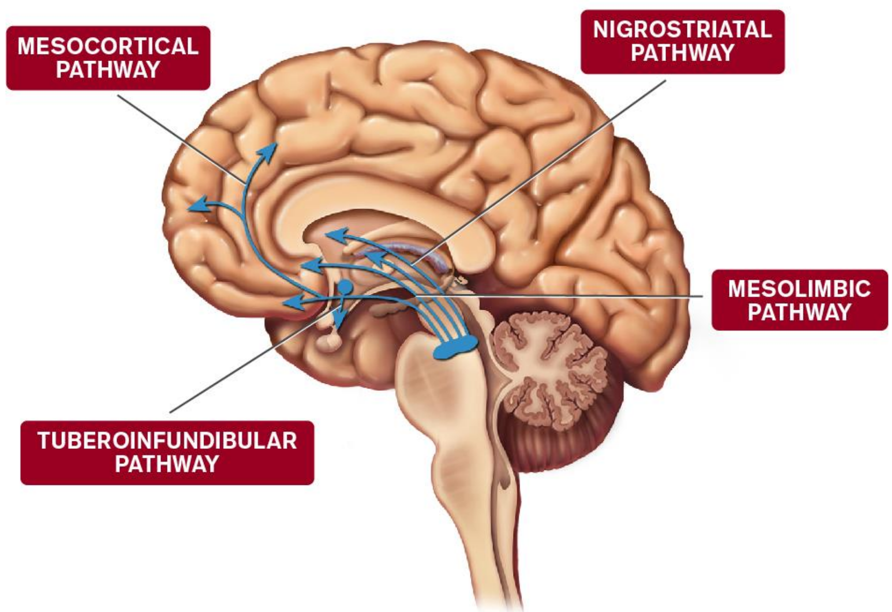
One basic concept to note when we talk about neurotransmitters like dopamine, serotonin, and norepinephrine is that they don't just float around inside the brain and make things happen. Each of these three neurotransmitters must be matched up with the proper receptor, the receiving unit that allows the neurotransmitter to bind. The binding creates some type of reaction in the receptor. Sometimes it is responsible for a new event, such as moving the leg. Other times it may slow or stop those actions. But in all 3 cases, in order to work, the neurotransmitter has to bind to a specific receptor.

Dopamine is an important neurotransmitter involved in the pathophysiology of schizophrenia and major depressive disorder (MDD) and is involved in four different neural pathways: mesocortical, mesolimbic, nigrostriatal, and tuberoinfundibular.[21]

There are two major types of dopamine receptors. The neurotransmitter receptor proteins are integral components in the communication between adjacent cells of the nervous system, spanning the width of the postsynaptic membrane and protruding into the synaptic cleft and cell cytoplasm. They mediate the effects of neurotransmitters between adjacent neurons.[22]

Although it was initially believed that each neurotransmitter interacted with a single type of receptor, it is now clear that there exists a family of neurotransmitter receptors for each neurotransmitter, called subtypes.[22] Thus, depending on which receptor subtype the neurotransmitter binds with on the postsynaptic neuron, dopamine can increase or decrease cellular activity.[23]

DOPAMINE PATHWAYS



Mesocortical pathway

The neurons associated with this pathway are implicated in the reward circuitry of the brain and are important in cognition, motivation, drug addiction, and several psychiatric disorders. This is the pathway that is associated with negative psychotic symptoms, such as alogia and affective flattening.[21,24]

Mesolimbic pathway

The mesolimbic pathway is thought to be involved in emotion, pleasurable sensations and reward, and the euphoric effects of addictive substances, as well as positive psychotic symptoms, such as delusions and hallucinations.[21,24]

Nigrostriatal pathway

The nigrostriatal pathway influences control of fine movements and initiation of movement.[24]

Tuberoinfundibular pathway

Neurons in the tuberoinfundibular pathway normally inhibit the release of prolactin. Dopamine antagonists would be expected to counteract that inhibition, leading to an increase in prolactin secretion.[24]

SEROTONIN AND SEROTONIN RECEPTORS[6]

Serotonin—also known as 5-HT—is a neurotransmitter that is found throughout the body.[25]

There are multiple receptor subtypes for serotonin; the roles of these receptor subtypes are not fully elucidated. Serotonergic neurons project widely throughout the brain from their origin in the brain stem.[1,21]

The wide dispersal of serotonergic neurons throughout the brain enables serotonin to be involved in modulating diverse body functions.

High concentrations of serotonin are found in the CNS, platelets, and certain cells in the gastrointestinal tract.[25]

The raphe nuclei are the group of nuclei in the brain stem that releases serotonin into the brain.[26]

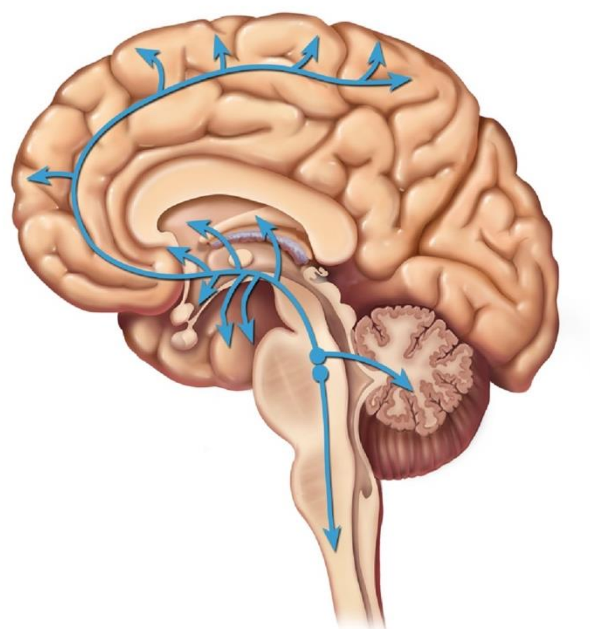
SEROTONIN PATHWAYS

Body Functions

Body functions modulated by serotonin include sleep, cognition, mood, sensory perception, pain perception, movement, regulation of internal temperature, appetite, sexual behavior, and hormone secretion.[25]

Clearly, serotonin has many different jobs in the nervous system. Think about what would happen if there were too much serotonin, or too little, when you read about its functions.

The neurotransmitter serotonin, or 5-hydroxytryptamine, mediates a wide range of physiological functions by interacting with multiple receptors, and these receptors have been implicated in certain pathological and psychopathological conditions. As previously mentioned, seven distinct families of 5-HT receptors have been identified—5-HT$_1$ to 5-HT$_7$), and subpopulations have been described for several of these.[27]



NOREPINEPHRINE AND NOREPINEPRHINE RECEPTORS[6]

Noradrenergic neurons project widely throughout the brain.

> There is another term you may hear that also means norepinephrine—noradrenaline. In the United States we typically use norepinephrine, but you may hear noradrenaline used if you are speaking with a healthcare professional who trained in Europe.

NOREPINEPHRINE PATHWAYS

Prefrontal cortex

Some noradrenergic projections to the prefrontal cortex are thought to help regulate mood; others are thought to mediate attention.[21]

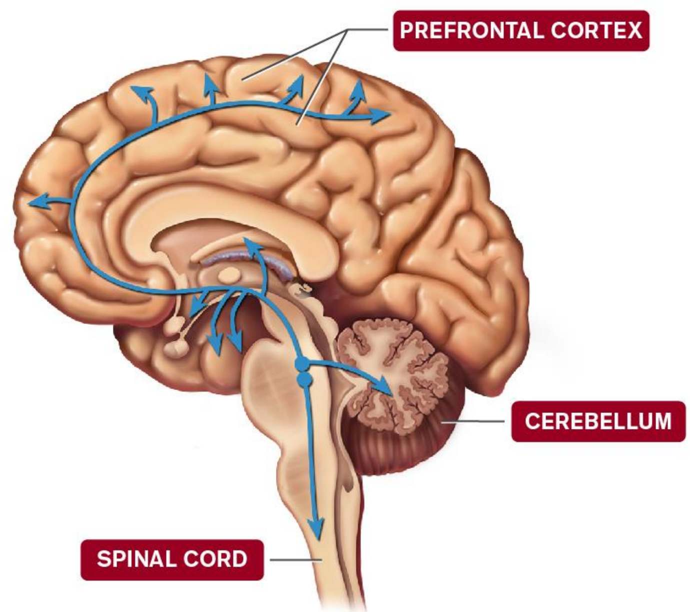
The noradrenergic projection to the limbic cortex is thought to mediate emotions, energy, fatigue, and psychomotor agitation/retardation.[21]

Cerebellum

The noradrenergic projection to the cerebellum is thought to mediate motor movements, especially tremor.[21]

Spinal cord

The noradrenergic projection to the brain stem controls blood pressure.[21]



RECEPTOR SUBTYPES[6]

Dopamine	Dopaminergic receptors (D_{1-5} subtypes)
Serotonin	5-HT receptors (5-HT_{1A-F}, 5-HT_{2A-C}, 5-HT_{3-7} subtypes)
Noradrenaline	α-adrenergic receptors (α_{1A-C}, α_{2A-C} subtypes)
Glutamate	β-adrenergic receptors (β_{1-3} subtypes)
GABA	Ionotropic receptors: non-NMDA (AMPA, kainate), NMDA receptors

Neurotransmitters are released and diffuse across the synapse and bind to structures called receptors located within the cell membrane of the dendrite of the adjacent nerve cell. The table shown on this screen shows the types of receptors—and receptor subtypes—to which the major neurotransmitters bind. Note that for each neurotransmitter there are several important receptor subtypes. Keep this in mind as you learn about how an imbalance in neurotransmitters plays a role in MDD and schizophrenia and the rationale for the design of various drugs to treat these disorders.

The neurotransmitters act as chemical messengers, which transmit information from one neuron to another. The binding of a neurotransmitter to its receptor on the postsynaptic neuron triggers specific downstream physiological consequences, such as increasing neurotransmitter release to the next neuron in the pathway or increasing the production of functional proteins in the cell. These downstream events are mediated either through a change in electrical properties of the neuron and/or through a series of interactions between intracellular proteins—second messengers.[20,24]

DRUG-RECEPTOR INTERACTION[6]

These are some of the important basic principles that apply to many different types of drugs that are used by mental health specialists such as psychiatrists. Learn these functions now so you will be better able to understand how specific classes of drugs and individual drugs act.

DRUG CLASSIFICATIONS

The classification of a drug as an agonist, antagonist, or partial agonist is based on the characteristic activity of the receptor after the drug binds to the receptor. This classification is determined in vitro. [28,29]

Agonist Full Activation

An agonist binds with the receptor and increases downstream activity.

Antagonist Inhibits Activation

An antagonist binds with the receptor and inhibits downstream activity of receptor stimulation by an agonist.

Partial Agonist and Partial Activation

But sometimes an agent can act as an agonist to a certain extent that produces less than the maximal response of a full agonist. This kind of drug is called a partial agonist. In other words, after a partial agonist binds to the receptor, the receptor functions at a preset level—not fully activated but not fully blocked. For example, a partial agonist with 20% intrinsic activity allows the receptor to function at a preset level of 20% activity, or agonism, whereas a partial agonist with an intrinsic activity of 40% allows the receptor to function at a preset level of 40% activity, or agonism. The partial agonist with the higher intrinsic activity—40%—functions more like an agonist than the partial agonist with lower intrinsic activity. Importantly, a drug with lower intrinsic activity functions more like an antagonist than a drug with higher intrinsic activity.[29,30]

AGONISM, ANTAGONISM, AND PARTIAL AGONISM[6]

Type of Agent	Action	Effect
Full agonist (Dopamine)	Full receptor stimulation (eg, 100 out of 100)	A full agonist, like the neurotransmitter dopamine, causes complete activation.
Partial agonist (Example #1)	Partial receptor stimulation (eg, 80 out of 100)	For this partial agonist, the ratio of agonism to antagonism is high. This may cause activation, worsening of psychosis, nausea, and vomiting.
Partial agonist (Example #2)	Partial receptor stimulation (eg, 60 out of 100)	For this partial agonist, the ratio of agonism to antagonism is lower, but the patient may still have side effects.
Partial agonist (Example #3)	Partial receptor stimulation (eg, 40 out of 100)	For this partial agonist, the balance between agonism to antagonism results in better tolerability.
Antagonist	No receptor activity (0 out of 100)	A full antagonist may result in sedation, EPS, akathisia, and hyperprolactinemia.

PROGRESS CHECK QUESTIONS

Answers to these questions can be found on page 24.

Question 7

The noradrenergic projection to the limbic cortex is thought to do which of the following?

E. Control blood pressure

F. Mediate emotions and energy

G. Mediate attention

H. Mediate psychomotor agitation

Question 8

The noradrenergic projection to the prefrontal cortex is thought to do which of the following?

A. Control blood pressure

B. Mediate motor movements

C. Regulate mood

D. Control somnolence

Question 9

Which of the following terms describes the strength of the attraction between the drug and the receptor?

A. Affinity

B. Intrinsic activity

C. Occupancy

D. Agonism

Question 10

Which of the following terms is the degree to which a drug activates a receptor?

A. Affinity

B. Intrinsic activity

C. Occupancy

D. Agonism

PROGRESS CHECK ANSWERS

1. A, C
2. C
3. A
4. A, C, D
5. B
6. B, D
7. B
8. C
9. A
10. B

REFERENCES

1. Purves D, Augustine G, Fitzpatrick D, Hall W, LaMantia A, White L. *Neuroscience*. Sunderland, MA: Sinauer Associates, Inc.; 2004.
2. Tortora G, Derrickson B. *Principles of Anatomy & Physiology*. Hoboken, NJ: John Wiley & Sons, Inc.; 2009.
3. Stedman's Online (Medical Dictionary). 2017. http://www.stedmansonline.com. Accessed September 9, 2017.
4. Oberheim N, Goldman S, Nedergaard M. Heterogeneity of astrocytic form and function. *Methods Mol Biol*. 2012:814:23-45.
5. Benarroch E. Chapter 8: Neurotransmitters. In: Waldman S, Terzic A, eds. *Pharmacology and Therapeutics: Principles To Practice*. 1st ed. Philadelphia, PA: Elsevier; 2009.
6. 11US15IBS0060 Brex Training Program: HS103 Neuroanatomy Module April 2015.
7. Chapter 10: Cerebral Hemispheres/Telencephalon. In:Waxman SG, ed. *Clinical Neuroanatomy.* 27th ed. New York, NY: McGraw-Hill; 2013.
8. Chapter 9. Diencephalon. In: Waxman SG, ed. *Clinical Neuroanatomy.* 27th ed. New York, NY: McGraw-Hill; 2013.
9. Chapter 7. The Brain Stem and Cerebellum. In: Waxman SG, ed. *Clinical Neuroanatomy.* 27th ed. New York, NY: McGraw-Hill; 2013.
10. Crossman AR, Neary D. Chapter 20. Cerebellum. In: Standring S, ed. *Gray's Anatomy*. 40th ed. London: Elsevier Health Sciences UK; 2008.
11. Crossman AR, Neary D. Chapter 18. Spinal Cord: internal organization. In: Standring S, ed. *Gray's Anatomy*. 40th ed. London: Elsevier Health Sciences UK; 2008.
12. Martin J. Chapter 1. Introduction to the central nervous system. In: Martin J, ed. *Neuroanatomy*. 3rd ed. New York, NY: McGraw-Hill; 2003.
13. Brain Basics. National Institute of Neurological Disorders and Stroke. April 2001. https://catalog.ninds.nih.gov/pubstatic//01-3440A/01-3440A.pdf. Accessed September 9, 2017.
14. Hartwig M, Wilson L. Chapter 50. Anatomy and physiology of the nervous system. Price S, Wilson L, eds. *Pathophysiology: Clinical Concepts of Disease Processes*. 6th ed. St. Louis, MO: Mosby; 2003.
15. R. Chapter 9. Limbic System. In: Swenson R, ed. *The Review of Clinical and Functional Neuroscience*. 2006. http://www.dartmouth.edu/~rswenson/NeuroSci/chapter_9.html. Accessed September 9, 2017.
16. Guyton A, Hall J. Behavioral and motivational mechanisms of the brain—the limbic system and the hypothalamus. In: Guyton A, Hall J, eds. *Textbook Of Medical Physiology*. 11th ed. Philadelphia, PA: Elsevier Saunders; 2007:Chapter 58.
17. Purves D, Williams S. The limbic system. In: Purves D, Augustine GJ, Fitzpatrick D, et al, eds. *Neuroscience.* 2nd ed. Sunderland MA: Sinauer Associates; 2001. https://www.ncbi.nlm.nih.gov/books/NBK10799/. Accessed September 12, 2017.
18. Stufflebeam R. Neurons, synapses, action potentials, and neurotransmission. The Mind Project [Web site]. http://www.mind.ilstu.edu/curriculum/neurons_intro/neurons_intro.php. Accessed September 10, 2017.
19. Hall J. Chapter 45. Organization of the Nervous System, Basic Functions of Synapses, and Neurotransmitters. In: Hall J, ed. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia, PA: Saunders; 2011.
20. K, Barman S, Boitano S, Brooks H. Chapter 7. Neurotransmitters & neuromodulators. In: Barrett K, Barman S, Boitano S, Brooks H, eds. *Ganong's Review of Medical Physiology*. 24th ed. New York, NY: McGraw-Hill Medical Publishing Division; 2012.
21. Stahl S. In: Stahl S, ed. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge: Cambridge University Press; 2013.
22. Stephenson F, Hawkins L. Neurotransmitter receptors in the postsynaptic neuron. *Encyclopedia of Life Sciences*. John Wiley & Sons, Ltd.; 2001. http://www.els.net/WileyCDA/ElsArticle/refId-a0000284.html. Accessed September 12, 2017.
23. Hall J. Chapter 58. Behavioral and Motivational Mechanisms of the Brain—The Limbic System and the Hypothalamus. In: Hall J, ed. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia, PA: Saunders; 2011.

24. Meltzer H. Chapter 29. Antipsychotic agents & lithium. In: Katzung B, Masters S, Trevor A, eds. *Basic & Clinical Pharmacology*. 12th ed. New York, NY: McGraw-Hill; 2012.
25. Buxton I. Chapter 1. Pharmacokinetics and pharmacodynamics: the dynamics of drug absorption, distribution, action, and elimination. In: Brunton L, Parker K, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. New York: McGraw-Hill; 2006.
26. Nordquist N, Oreland L. Serotonin, genetic variability, behaviour, and psychiatric disorders - a review. *Ups J Med Sci*. 2010;115(1):2-10.
27. Glennon R, Dukat M, Westkaemper R. Serotonin receptor subtypes and ligands. In: Bloom F, Kupfer D, eds. *Psychopharmacology – 4th Generation of Progress*. American College of Neuropsychopharmacology Web site. https://www.acnp.org/g4/GN401000039/Ch039.html. Accessed September 12, 2017.
28. Tamminga C. Partial dopamine agonists in the treatment of psychosis. *J Neural Transm*. 2002;109(3):411-420.
29. Gründer G, Carlsson A, Wong D. Mechanism of new antipsychotic medications: occupancy is not just antagonism. *Arch Gen Psychiatry*. 2003;60(10):974-977.
30. Blumenthal D, Garrison J. Chapter 3. Pharmacodynamics: molecular mechanisms of drug action. In: Goodman L, Brunton L, Chabner B, Knollmann B, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill Medical; 2011.