NBL 356-656 Module 3 Review Q&A

1. *What is the spinocerebellar tract and what does it transmit?*

The spinocerebellar tract is a tract originating in the spinal cord and terminating in the same side (ipsilateral) of the cerebellum. Proprioceptive information is obtained by Golgi tendon organs and muscle spindles. Golgi tendon organs consist of a fibrous capsule enclosing tendon fascicles and nerve endings that respond to tension in the tendon by causing action potentials in type Ib afferents/axons. These fibers/axons are relatively large, myelinated, and quickly conducting. Muscle spindles monitor the length within muscles and send information via fast Ia afferents/axons, type Ib (from both nuclear bag fibers/axons and nuclear chain fibers/axons) and type II afferents/axons (solely from nuclear chain fibers/axons). All of these neurons are sensory (first order, or primary) neurons that have cell bodies that lie in the dorsal root ganglia. They send an axon into the spinal cord. The axon branches and one set of branches is involved in the spinal stretch reflex in which the axon synapses with either a motor neuron or spinal interneuron as describe in the reflex lectures. Another branch forms a synapse with a second order (secondary) neuron in the dorsal horn. These secondary sensory neurons send their axons to the ipsilateral cerebellum forming the spinocerebellar tracts. There are four divisions of the spinocerebellar tract called the dorsal (posterior), ventral (anterior), and rostral spinocerebellar tracts and the cuneocerebellar tract. They transmit information from muscle spindles and/or Golgi tendon organs from either the caudal body and legs or the arms. The secondary neuron axons travel in different regions in the spinal cord white matter. (You will not be tested on these divisions now.)

1. *What are the functions of the cerebellum?*

From Wikipedia: “In humans, the cerebellum plays an important role in motor control. It may also be involved in some cognitive functions such as attention and language as well as in regulating fear and pleasure responses, but its movement-related functions are the most solidly established. The human cerebellum does not initiate movement, but contributes to coordination, precision, and accurate timing: it receives input from sensory systems of the spinal cord and from other parts of the brain, and integrates these inputs to fine-tune motor activity. The cerebellum is also involved in encoding some types of procedural/motor memory. The cerebellum has also been implicated in several cognitive functions including some aspects of language and emotion. Cerebellar damage produces disorders in fine movement, equilibrium, posture, and motor learning in humans.”

1. *Describe the main inputs to and outputs from the cerebellum involved in control of movement. (Note you will not be responsible for knowing which specific tracts travel through which specific peduncles.)*

The great majority of inputs to and outputs from cerebellum travel through the cerebellar peduncles. Inputs to cerebellum. (You do not need to memorize which specific tracts travel in which specific cerebellular peduncles):

1. Input from the spinocerebellar tracts (see above). The axons from these tracts travel to the cerebellum through the cerebellar peduncles. Specifically, the dorsal/posterior spinocerebellar tract and cuneocerebellar tract travel in the inferior cerebellar peduncle. The ventral/anterior spinocerebellar tract enters the cerebellum via the superior cerebellar peduncle. The rostral spinocerebellar tract enters the cerebellum partially through the inferior and partially through the superior cerebellar peduncle.
2. Input from the vestibular nuclei in the brainstem. The vestibulocerebellar tract enters the cerebellum through the inferior cerebellar peduncle. It’s involved in balance and vestibular reflexes.
3. Input from the inferior olivary nucleus in the medulla. The olivocerebellar tract transmits information about the current commands for execution of motion, and is involved in motor coordination and learning. It enters via the inferior cerebellar peduncle.
4. Input from the cerebral cortex. All information from the cerebral cortex to the cerebellum occurs by way of the corticopontocerebellar tracts. Axons originate in the cortex and synapse on pontine nuclei involved in motor activity. Axons from pontine nuclei travel through the middle peduncle to the cerebellum. The cortical inputs include a) sensory inputs from the parietal lobe (primary and secondary somatosensory cortex and secondary visual cortex), b) input from the cingulate cortex (part of the limbic system), and c) input from both primary and secondary motor cortex. Hence axons from the projection/principal cortical neurons form the corticopontine tracts.

Outputs from the cerebellum:

The cerebellum transmits information to the thalamus and the brain stem, including the red nucleus, vestibular nuclei and reticular formation. (Note that the cerebellum does not provide a direct input to the cerebral cortex.) Axons to the thalamus form the cerebello-thalamic tract, axons to the red nucleus form the cerebello-rubral tract, and axons to the reticular formation form the cerebello-reticular tract. Both the cerebello-thalamic and cerebello-rubral tracts, and part of the cerebello-reticular tract travel via the superior cerebellar peduncle. The cerebello-vestibular outputs and some of the cerebello-reticular tracts travels through the inferior cerebellar peduncle.”

The following information was described in the videos and helps in understanding the function of the cerebellum, and some of you may have already learned this. “Three lobes can be distinguished within the cerebellum: the anterior lobe (above the primary fissure), the posterior lobe (below the primary fissure), and the flocculonodular lobe (below the posterior fissure). The smallest region, the flocculonodular lobe, is often called the vestibulocerebellum. It is the oldest part in evolutionary terms (archicerebellum) and participates mainly in balance and spatial orientation; its primary connections are with the vestibular nuclei, although it also receives visual and other sensory input. The medial zone of the anterior and posterior lobes constitutes the spinocerebellum, also known as paleocerebellum. This sector of the cerebellum functions mainly to fine-tune body and limb movements. It receives proprioceptive input from the dorsal columns of the spinal cord (including the spinocerebellar tract) and from the cranial trigeminal nerve, as well as from visual and auditory systems. It sends fibers to deep cerebellar nuclei that, in turn, project to both the cerebral cortex and the brain stem, thus providing modulation of descending motor systems. The lateral zone, which in humans is by far the largest part, constitutes the cerebrocerebellum, also known as neocerebellum. It receives input exclusively from the cerebral cortex (especially the parietal lobe and motor cortex) via the pontine nuclei (forming cortico-ponto-cerebellar pathways), and sends output mainly to the ventrolateral thalamus (in turn connected to motor areas of the premotor cortex and primary motor area of the cerebral cortex) and to the red nucleus. There is disagreement about the best way to describe the functions of the lateral cerebellum: It is thought to be involved in planning movement that is about to occur, in evaluating sensory information for action, and in a number of purely cognitive functions, such as determining the verb which best fits with a certain noun (as in "sit" for "chair").”) The cerebellum is also involved in encoding some types of procedural/motor memory.

1. *The basal ganglia is also called the basal nuclei. What are the main functions and components of the basal ganglia/nuclei involved in movement?*

From Wikipedia: “Popular theories implicate the basal ganglia primarily in action selection – in helping to decide which of several possible behaviors to execute at any given time. In more specific terms, the basal ganglia's primary function is likely to control and regulate activities of the motor and premotor cortical areas so that voluntary movements can be performed smoothly. Experimental studies show that the basal ganglia exert an inhibitory influence on a number of motor systems, and that a release of this inhibition permits a motor system to become active. The "behavior switching" that takes place within the basal ganglia is influenced by signals from many parts of the brain, including the prefrontal cortex, which plays a key role in executive functions.” The basal nuclei is also said to be involved in action initiation and suppression of unwanted movement.

The caudate and putamen have similar functions, and are often considered as one. Together the caudate and putamen are called the neostriatum or simply striatum. All input to the basal ganglia circuit comes via the striatum. For the motor functions of the basal ganglia, it’s the dorsal striatum that is involved. The input to the striatum comes mainly from cortical areas, with major inputs from motor cortex to the dorsal striatum. Medial to the putamen is the globus pallidus (GP). The globus pallidus has two parts, a lateral, external (or outer) segment abbreviated GPe and a medial, internal (or inner) segment abbreviated GPi. GPi contains the output neurons of the basal ganglia circuit. They project to the ipsilateral motor thalamus, called the VA and VL nuclei in the thalamus. (Note that the ventral striatum contains the nucleus accumbens and is involved in motivation and reward.)

All cortical areas involved in the planning and execution of movements project to the dorsal striatum, though other cortical areas also project to the striatum. Striatal neurons receiving these cortical inputs then project to the globus pallidus, which in turn projects to the VA/VL (thalamus). VA/VL in turn projects to the motor cortex. So, the caudate and putamen (striatum) and globus pallidus act on the motor thalamus, which acts on the motor cortex. The other two components of the basal ganglia are the subthalamic nucleus (STN), the substantia nigra pars compacta (SNc) and substantia nigra pars reticulata (SNr). The SNc is the source of the striatal input of dopamine, which plays an important role in basal ganglia function. The subthalamic nucleus receives input mainly from the striatum and cerebral cortex, and projects to the globus pallidus. The SNr contains output GABAergic neurons that also project to the VA/VL thalamus. The roles of the STN and SNc are described next.

1. *Describe the direct and indirect pathways. Note that the  projection neurons in cortex, subthalamic nucleus (STN) and VA/VL (motor nucleus) in thalamus use glutamate; their effects are excitatory. The projection neurons in striatum and both segments (internal and external) of globus pallidus use GABA; their effects are inhibitory.*

There are two important pathways through which striatal information reaches GPi - the direct pathway and the indirect pathway. These two pathways have opposite effects on motor activity and help explain many clinical symptoms of basal ganglia diseases. In the direct pathway, striatal  neurons project directly to GPi.  The consequence of this  pathway is to increase the excitatory  drive from motor nuclei in the thalamus to the motor cortex. How is this accomplished? The cortical  projections to the striatum use the  excitatory transmitter glutamate. When  they are activated, these cortical  projections excite striatal neurons. These striatal cells use the  inhibitory transmitter GABA and their  axons project to, and inhibit neurons in  GPi. The neurons in GPi   also use GABA and they project to the VA/VL (motor nuclei) in the thalamus.  So, the cortical signal excites striatal neurons, which results in MORE inhibition from striatum to GPi. More inhibition of GPi neurons means LESS inhibition of motor thalamus (VA/VL). Since the motor thalamus receives LESS inhibition, the VA/VL neurons will INCREASE their firing (VA/VL cells are not just receiving the inhibitory pallidal input, but have other excitatory inputs [one source is from the cerebellum). This decrease in inhibition is called dis-inhibition.  Though not the same as direct excitation, it similarly leads to an increase in activity. So the end result of cortical excitatory input to striatal neurons in the direct pathway is INCREASED FIRING OF VA/VL NEURONS AND IN TURN MOTOR CORTEX. This results in increased activity in the corticospinal tract and eventually increased muscle contraction. THE DIRECT PATHWAY INCREASES MOTOR ACTIVITY.

The Indirect Pathway: Instead of projecting to GPi, the striatal neurons of the indirect pathway project to the globus pallidus external GPe. In this pathway, there is another nucleus, the subthalamic nucleus (STN). This nucleus lies just above the rostral portion of the substantia nigra. Neurons in GPe project to the STN. Neurons in the STN project to GPi, which in turn projects to VA/VL in thalamus. So, the indirect pathway is striatum to GPe to STN to GPi to VA/VL thalamus to motor cortex. In the indirect pathway, cortical fibers excite striatal neurons that project to GPe. The increased activity of the GABAergic striatal neurons decreases activity in GPe. The GABAergic cells in GPe inhibit neurons in the STN, so the decrease in activity in GPe results in less inhibition of neurons in the STN. That is, STN neurons are dis-inhibited and increase their activity. The “return” projection from the STN to GPi is excitatory, so the increased activity in the STN results in more excitation to cells in GPi. Thus, the end result of actions of the indirect loop is an increase in activity of the GABAergic cells in GPi that project to VA/VL thalamus, hence an INCREASE in INHIBITION of the VA/VL thalamic neurons. The Indirect Pathway turns DOWN the excitatory drive from the motor thalamus and, in turn, motor cortex. Thus, the effect of indirect pathway is to TURN DOWN motor activity.

Many neurons in the substantia nigra pars compacta (SNc) are dopaminergic neurons that project to the striatum, forming the nigrostriatal pathway. Their axons are called nigrostriatal axons and their terminals release dopamine into the striatum. Dopamine has an EXCITATORY effect upon neurons in the striatum that are part of the Direct Pathway. This is via D1 receptors. Dopamine has an INHIBITORY effect upon striatal cells associated with the Indirect Pathway. This is via D2 receptors. Hence, the direct pathway (which turns up motor activity) is excited by dopamine while the indirect pathway (which turns down motor activity) is inhibited. Both of these effects lead to increased motor activity. DOPAMINE EXCITES THE DIRECT AND INHIBITS THE INDIRECT PATHWAY. THE EFFECT OF THE DOPAMINERGIC NIGROSTRIATAL PROJECTION IS TO INCREASE MOTOR ACTIVITY.

1. *What is Parkinson’s Disease? What are the causes and treatments?*

From Wikipedia: Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. As the disease worsens, non-motor symptoms become more common. The symptoms usually emerge slowly. Early in the disease, the most obvious symptoms are shaking, rigidity, slowness of movement, and difficulty with walking. Thinking and behavioral problems may also occur. Dementia becomes common in the advanced stages of the disease. Depression and anxiety are also common, occurring in more than a third of people with PD. Other symptoms include sensory, sleep, and emotional problems.”

The cause of Parkinson's disease is unknown, but is believed to involve both genetic and environmental factors. Those with a family member affected are more likely to get the disease themselves. There is also an increased risk in people exposed to certain pesticides and among those who have had prior head injuries, while there is a reduced risk in tobacco smokers and those who drink coffee or tea. The motor symptoms of the disease result from the death of cells in the substantia nigra, a region of the midbrain. This results in not enough dopamine in this region of the brain. The cause of this cell death is poorly understood, but it involves the build-up of proteins into Lewy bodies in the neurons. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging used to rule out other diseases.

PD is caused by the loss of dopaminergic neurons in the midbrain in the region/nucleus called the substantia nigra pars compacta (SNc). As described above, the substantia nigra is one of the components of the basal ganglia/nuclei, together with the striatum (caudate nucleus and putamen), globus pallidus internal and external (GPi and GPe) and the subthalamic nucleus (STN). The loss of dopaminergic neurons in PD leads to a decrease in dopamine levels and dopamine transmission within the basal ganglia circuitry. Since dopamine normally increases motor activity, the loss of dopaminergic input to the striatum leads to the hypokinesia effects observed in PD.

There is no cure for Parkinson's disease. Treatment aims to improve the symptoms. Initial treatment is typically with the antiparkinson medication levodopa (L-DOPA), followed by dopamine agonists when levodopa becomes less effective. As the disease progresses and neurons continue to be lost, these medications become less effective while at the same time they produce a complication marked by involuntary writhing movements. Diet and some forms of rehabilitation have shown some effectiveness at improving symptoms. Surgery to place microelectrodes for deep brain stimulation has been used to reduce motor symptoms in severe cases where drugs are ineffective. Evidence for treatments for the non-movement-related symptoms of PD, such as sleep disturbances and emotional problems, is less strong.

In 2015, PD affected 6.2 million people and resulted in about 117,400 deaths globally. Parkinson's disease typically occurs in people over the age of 60, of whom about one percent are affected. Males are more often affected than females at a ratio of around 3:2. When it is seen in people before the age of 50, it is called early-onset PD. The average life expectancy following diagnosis is between 7 and 15 years. The disease is named after the English doctor James Parkinson, who published the first detailed description in An Essay on the Shaking Palsy, Public awareness campaigns include World Parkinson's Day and the use of a red tulip as the symbol of the disease. People with Parkinson's who have increased the public's awareness of the condition include actors Michael J. Fox, Katherine Hepburn and Alan Alda, Olympic cyclist Davis Phinney, and professional boxer Muhammad Ali.

1. *What is the autonomic nervous system (ANS) and what are its two divisions?*

The ANS regulates the functions of our internal organs and glands (the viscera) such as the heart, blood vessels, stomach and intestines. The ANS is regulated by the CNS and is considered part of the peripheral nervous system (PNS). The ANS controls smooth muscles, cardiac muscles and glands. We are usually unaware and unconscious of the ANS because it functions involuntary and reflexively, though we can become acutely aware of its effects, such as our heart beating faster. Though the ANS is unconscious, some people can train to consciously control some functions of the ANS such as heart rate or blood pressure. The ANS plays an essential role in maintaining physiological homeostasis and regulating the responses of acute stress and/or emergency. There are actually two components to the ANS, the motor ANS and the sensory ANS, typically called the visceral sensory system. In this module, we’ll be discussing the motor ANS, hereafter just ANS. When we learn about sensory systems in the next modules, the visceral sensory system will be introduced.

The ANS has two main divisions, the sympathetic nervous system (SNS), also called the sympathetic division and the parasympathetic nervous system (PSNS), also called the parasympathetic division. The SNS is also called the “fight or flight” or “fright, flight or flight” system. The PSNS is also called the “rest and digest” or “feed and breed” system. Most, but not all target tissues that receive ANS input are innervated by BOTH the sympathetic and parasympathetic systems. And thus the organs/glands that are innervated by both the SNS and PSNS are said to have “dual innervation.” The organs/glands that receive only single innervation by the SNS include the adrenal medulla, sweat glands and much of the vascular system. The majority of blood vessels (arteries and veins) in the body are innervated by only the SNS, with the SNS causing vasoconstriction of most blood vessels leading to an increase in blood pressure. (Note that in skeletal muscle blood vessels, norepinephrine and epinephrine, released into the blood by SNS action, have the opposite effect and cause vasodilation, which increases blood flow to skeletal muscles.) A few blood vessels that are innervation by the PSNS are located in the salivary glands, lungs, GI glands, genitalia, and coronary vessels. PSNS stimulation causes vasodilation in these tissues.

The sympathetic and parasympathetic divisions typically function in opposition to each other. But this opposition is better termed complementary in nature rather than antagonistic. One may think of the sympathetic division as the accelerator and the parasympathetic division as the brake. The sympathetic division typically functions in actions requiring quick responses. The parasympathetic division functions with actions that do not require immediate reaction. The two divisions work together to ensure that the body responds appropriately to different situations. It should be noted that the ANS is always working. It is NOT only active during "fight or flight" or "rest and digest" situations. Rather, the autonomic nervous system acts to maintain normal internal functions at all times. Thus the SNS and PSNS can work antagonistically, synergistically, or independently to balance the functions of autonomic effector organs. In a few rare functions the ANS works with the somatic nervous system to control processes, such as breathing (though the two systems work on different targets to produce its control.)

1. *What organs does the ANS innervate and what are the functions of the ANS?*

The ANS innervates and controls internal organs and tissues, including the blood vessels, stomach, intestine, liver, kidneys, bladder, genitals, lungs, pupils, heart, and sweat, salivary, and digestive glands. The autonomic nervous system controls internal body processes including the following: blood pressure, heart rate and force of heart beat, breathing rates, body temperature, digestion, metabolism (thus affecting body weight), balance of water and electrolytes (such as sodium and calcium), the production of body fluids (saliva, sweat, and tears), urination and defecation, and sexual responses.

1. *Describe the overall circuitry in the ANS.*

Unlike the somatic nervous system where the lower motor neurons innervate skeletal muscle directly, the autonomic pathway involves two neurons. The first neuron is located in the [brain stem](https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/biology-of-the-nervous-system/brain#v733460) or lateral horn of the spinal cord. This is called the preganglionic neuron and is a type of motor neuron. The preganglionic neurons extend their axon out of the spinal cord or brain stem, and the axon forms a component of the spinal nerve or some cranial nerves. This axon forms a synapse on the second neuron, called the postganglionic neuron, which is located in the cluster of neurons called the autonomic ganglion. It is the axon from the postganglionic neuron that extends to and innervates the internal organs.

All the preganglionic neurons in the ANS are cholinergic. In the ganglia, ACh acts by binding to activating [nicotinic ACh receptors](http://www.scholarpedia.org/article/Nicotinic_Acetylcholine_Receptors). The nicotinic receptors are a type of ionotropic receptor that lead to depolarization of the membrane in the postganglionic neurons. Many preganglionic autonomic neurons also release neuropeptides, usually acting as co-transmitters that mediate slow excitatory post-synaptic potentials, facilitating cholinergic transmission. The postganglionic neurons in the ANS are either cholinergic or noradrenergic. Because there is more branching of the axons in the SNS than in the PSNS, activation of the SNS cause more widespread effects than does PSNS activation. A single sympathetic preganglionic fiber has many axon collaterals (branches) and synapses with 20 or more postganglionic neurons, whereas a parasympathetic preganglionic neurons synapses with only 4 or 5 postganglionic neurons.

1. *Describe the function and anatomy of the SNS.*

The SNS prepares the body for stressful or emergency situations. The sympathetic division increases heart rate and the force of heart contractions and dilates the airways to make breathing easier. It causes the body to release stored energy. Muscular strength is increased. This division also causes palms to sweat, pupils to dilate, and hair to stand on end. It slows body processes that are less important in emergencies, such as digestion and urination.

The cell bodies of the preganglionic neurons of the SNS are located in the lateral horn in the thoracic and lumbar regions of the spinal cord, terminating around L2-3. Hence the SNS is said to have “thoraco-lumbar” outflow. In most cases, this neuron makes a synapse with the postganglionic neuron in the sympathetic ganglion, called paravertebral ganglia of the sympathetic chain. A few preganglionic neurons extend to other ganglia outside of the sympathetic chain, called the prevertebral ganglia and synapse there. The postganglionic neuron then project to the either a smooth or cardiac muscle or a gland. The great majority of postganglionic neurons in the SNS are noradrenergic and release norepinephrine as their primary neurotransmitter at their synapses on their target organ or gland. Many release co-transmitters such as adenosine triphosphate (ATP) and neuropeptides. The receptors for norepinephrine on the organ/gland targets are called adrenergic receptors. These are a type of metabotropic (G protein coupled) receptor, and the two main types are called alpha adrenergic and beta adrenergic receptors. These metabotropic receptors function by the activation of G proteins, which can interact with and regulate ion channels, and also produce second messengers that lead to changes in phosphorylation of proteins in the target cells to produce effects. A few preganglionic SNS neurons do not synapse on ganglia but rather directly innervate the adrenal gland, which stimulates the release of norepinephrine and epinephrine into the blood. Generally norepinephrine has a stimulatory effect on its targets. Norepinephrine and epinephrine are removed from the synapse by neurotransmitter transporters.

A few SNS neurons (that innervate many sweat glands and hair follicles) are cholinergic and stimulate sweating or make hair stand on end. Similar to the parasympathetic system, acetylcholine released by postganglionic sympathetic neurons activates muscarinic acetylcholine receptors in the target organs/glands (see below).

*Here is another overview:*

The SNS division of the ANS is typically known as the fight or flight response. The sympathetic division has a high degree of neuronal divergence meaning that one preganglionic neuron can synapse onto approximately 20 postganglionic neurons. They typically have a 1:20 ratio and therefore their effects tend to be more widespread compared to the parasympathetic division of the ANS (explained in the next question). The main functions of the SNS are to increase cardiac output, accelerate the respiratory rate, release stored energy, and dilate the pupils in intense situations. The SNS also inhibits the processes that are less important in intense situations such as digestion and urination. The preganglionic neurons releases acetylcholine to stimulate action potentials in the postganglionc neurons which innervates and releases the neurotransmitter, norepinephrine from postganglionic neurons to control its target. One exception are the sweat glands, they release acetylcholine from postganglionic neurons. The cholinergic neurons in generalized sweat glands mainly regulate body temperature; the localized sweat glands like the soles, palms, armpits, and genitalia are adrenergic thereby using norepinephrine as their hormones. Hormones are released into the bloodstream for widespread distribution. Norepinephrine can be inhibitory and excitatory, an example would be the fact that the hormone can increase blood flow to the legs, but reduce blood flow to the gut. It all depends on the receptors receiving the hormone, in this case it would be the smooth muscles involved.

The adrenal sympathetic pathway is a unique pathway classified under the autonomic nervous system. The response is also known as the sympatho-adrenal response of the body. The preganglionic fibers extend from the CNS to nicotinic receptors on the adrenal gland and are cholinergic (acetylcholine). The adrenal gland controls the release of epinephrine as a hormone into the bloodstream. This leads to an increase or decrease of blood vessel constriction. The binding of epinephrine to alpha receptors on blood vessels leads to blood constriction (ex: in the stomach), whereas the binding of epinephrine to beta receptors on blood vessels leads to more blood flow (ex: in muscles).

1. *Describe the function and anatomy of the PSNS.*

The PSNS controls body process during ordinary situations. The parasympathetic division conserves and restores. It slows the heart rate and decreases blood pressure. It stimulates the digestive tract to process food and eliminate wastes. Energy from the processed food is used to restore and build tissues. The cell bodies of the parasympathetic preganglionic neurons are located in the brainstem, in the nuclei for four of the cranial nerves. The following cranial nerves have parasympathetic components: [cranial nerves](https://faculty.washington.edu/chudler/cranial.html) III (oculomotor never), VII (facial nerve), IX (glossopharyngeal nerve), and X (vagus nerve) and their axons form the autonomic motor components of these cranial nerves. The vagus nerve (cranial nerve X) is the largest cranial nerve and provides the largest parasympathetic innervation, extending throughout the body. Preganglionic fibers emerge from Cranial Nerves III, VII, and IX and synapse on ciliary, pterygopalatine, otic, or submandibular postganglionic neurons. The vagus nerve has preganglionic fibers in the thoracic viscera and the abdominal viscera. In the spinal cord the preganglionic parasympathetic neurons are located in [sacral](https://en.wikipedia.org/wiki/Sacral_vertebrae) regions (S2-S4). Hence the parasympathetic division is said to have “cranio-sacral” outflow.

The preganglionic axons from the brain stem or spinal cord project to ganglia that are located very close to or within the target organ and make a synapse. Hence, in the PSNS, the preganglionic axons are longer and the postganglionic axons are shorter. As mentioned above, the preganglionic synapse uses the neurotransmitter acetylcholine. From this ganglion, the postganglionic neuron projects to the target organ and also uses acetylcholine at its terminal. As stated above, the ganglia for the PSNS are located near or in the target organs they connect with. As the postganglionic neurons in the PSNS are cholinergic, they release acetylcholine at their synapses on organs and glands. Acetylcholine binds to the muscarinic type of acetylcholine receptors on the target organ/gland. These receptors are G protein coupled receptors. Postganglionic PSNS neurons often co-release nitric oxide and co-transmitter neuropeptides. Generally, acetylcholine has inhibitory effects on its targets. Acetylcholine is removed from the synapse by acetylcholine esterase.

*Here is another overview:*

The parasympathetic nervous system is typically known as the rest and digest response. The degree of divergence in the PNS is about 1:4. Meaning that one preganglionic neuron can synapse on typically four postganglionic neurons, thereby, their effects tend to be more localized, specific responses. The rest and digest response entails the slowing of the heart rate, decreased respiratory rate, stimulation of digestion, stores energy, and removes waste. Collectively, the PNS allows an organism to calm down after a stressful situation and allows the organism to digest food, reproduce, excrete waste, and fight off infections allowing the organism to do the basic functions of living. In the PNS, neurons release acetylcholine in their preganglionic synapses similarly to SNS; however, the majority of postganglionic synapses release acetylcholine to effector organs. The PNS is craniosacral meaning that nerves arise from the brainstem and sacral region of the spinal cord. The cranial nerves synapse almost directly on their effectors due to their proximity.

1. *What is autonomic tone?*

Autonomic tone, also known as dual autonomic innervation, is the balance between the parasympathetic nervous system and the sympathetic nervous system. The balance changes accordingly to the immediate needs of the organism, therefore one may dominate over the other. Generally speaking, the parasympathetic tone will be more prevalent since it is heavily associated with normal bodily functions for an organism.

1. *What does the ANS receive information from? In other words, what is the central autonomic control?*

The autonomic nervous system receives information about the body and external environment. Preganglionic neurons for parasympathetic and sympathetic autonomic outflow are located in the brainstem and in thoracic, upper lumbar and sacral regions of the spinal cord. Several different brain centers control these preganglionic neurons, including the hypothalamus and other neurons in the brainstem. Many of the brainstem regulatory neurons use a monoamine (noradrenaline, adrenaline, dopamine or serotonin) as neurotransmitter. The neurons in the hypothalamus and brainstem that control the ANS are themselves regulated by inputs from diverse regions of the brain, including other regions of the brainstem and hypothalamus, the [amygdala](http://www.scholarpedia.org/article/Amygdala), [basal ganglia](http://www.scholarpedia.org/article/Basal_ganglia), anterior cingulate cortex, insular cortex, visual centers, and prefrontal cortical centers involved in emotional processing, for example.

  Within the brain, the autonomic nervous system is regulated by the hypothalamus. Autonomic tone is the general activity rate of the autonomic nervous system, both the sympathetic and parasympathetic aspects of the system, and autonomic tone is regulated by the hypothalamus. The [hypothalamus](https://en.wikipedia.org/wiki/Hypothalamus), located just above the [brain stem](https://en.wikipedia.org/wiki/Brain_stem), acts as an integrator for autonomic functions, receiving ANS [regulatory](https://en.wikipedia.org/wiki/Regulatory) input from the [limbic system](https://en.wikipedia.org/wiki/Limbic_system) to do so. The most important hypothalamic nucleus of the central autonomic network is the **paraventricular nucleus (PVN).** The PVN has two morphological classes of neurons that fall into three functional categories. A group of parvocellular neurons comprise the functional group of PVN neurons involved in central autonomic control. These hypothalamic neurons extend axons to the brain stem or spinal cord where they can directly and/or indirectly modulate the preganglionic neurons of the ANS.

Other important hypothalamic nuclei in the central autonomic network include the dorsomedial nucleus, the lateral hypothalamic area, the posterior hypothalamic nucleus and the mammillary nucleus. These nuclei send and receive projections from the PVN, the dorsal motor nucleus of the vagus, the central gray matter, the parabrachial nucleus, the nucleus of the solitary tract, the lateral and ventral medulla and the intermediolateral spinal columns. The lateral hypothalamus is especially involved in cardiovascular control as well as in control of feeding, satiety and insulin release. Many nuclei in the brain stem are associated with control of sympathetic and parasympathetic outflow. The extra-hypothalamic sites associated with control of parasympathetic outflow also include the central nucleus of the amygdala. Limbic cortices, including the cingulate, orbitofrontal, insular and rhinal cortices, and the hippocampus, influence both sets of autonomic outflow. Finally, somatosensory and visceral sensory afferent neurons also project into the dorsal horn of the spinal cord or into cranial nerve nuclei in the brainstem, which can provide indirect sensory input into the ANS. (Note you are not responsible for memorizing the specific brainstem nuclei involved in control of the ANS.)

*Another overview:*

The cerebral cortex and limbic system send input to the hypothalamus (as well as to each other). This input includes cognitive processing and emotional responses, although this happens subconsciously. This explains why you cry (lacrimation) when you’re sad or your blood pressure increases when you’re angry. This information is sent to the hypothalamus, which is the major center of integration for the autonomic nervous system. Based on the input it receives, neurons in the hypothalamus can signal to brainstem centers responsible for autonomic control. The autonomic control centers in the brainstem, specifically the medulla, integrate information from the hypothalamus, along with sensory feedback. This regulates the activity for centers which control the heartbeat, blood vessel contraction, salivation, sweating, and many other autonomic reflexes. Some of these outputs may be sent out via cranial nerves to effectors, and some neurons go on to synapse with reflex centers in the spinal cord. The spinal cord has its own autonomic reflex centers at different levels, which help to control all ANS reflexes below the neck. They also integrate sensory feedback in addition to input from the brainstem. This integration determines whether preganglionic neurons will fire, leading to autonomic motor output.

1. *What are the inputs to and functions of the hypothalamus?*

The main functions of the hypothalamus are 1) maintaining homeostasis of the body such as regulating body temperature, food intake, daily physiological cycles, and neuroendocrine output and 2) regulating the activities of the autonomic nervous system. The hypothalamus receives input from several brain structures: hippocampus, amygdala, cingulate cortex, limbic and olfactory systems, retina, and the brainstem. The hypothalamus receives many sensory inputs in order to detect changes in the internal and external environments. The hypothalamus receives inputs from the 1) nucleus of the solitary tract - this nucleus collects all of the visceral sensory information from the vagus and relays it to the hypothalamus and other targets. Information includes blood pressure and gut distension; 2) reticular formation - this nucleus in the brainstem receives a variety of inputs from the spinal cord. Among them is information about skin temperature, which is relayed to the hypothalamus; and the 3) retina - some fibers from the optic nerve go directly to a small nucleus within the hypothalamus called the suprachiasmatic nucleus. This nucleus regulates circadian rhythms, and couples the rhythms to the light/dark cycles.

The outputs of the hypothalamus can be split into two: neural projections and endocrine hormones. Neural projections are nerve fibers that run to various control sites and are usually bidirectional. The hypothalamus releases hormones into the blood in the capillaries which then stimulate hormone release in the pituitary gland. Stated another way, he hypothalamus has two major outputs: endocrine signals to/through the pituitary and neural signals to the autonomic system - the (lateral) hypothalamus projects to the (lateral) medulla, where the cells that drive the autonomic systems are located. These include the parasympathetic vagal nuclei and a group of cells that descend to the sympathetic system in the spinal cord. With access to these systems, the hypothalamus can control heart rate, vasoconstriction, digestion, sweating, etc. For endocrine signals, magnocelluar neurons send axons directly to the posterior pituitary and secrete oxytocin and vasopressin directly into bloodstream, while parvocellular neurons secrete peptides that regulate release of anterior pituitary hormones.

1. *Explain why the sympathetic division of the ANS has more widespread and longer-lasting effects than the parasympathetic division.*

A single sympathetic preganglionic fiber has many axon collaterals (branches) and

synapses with 20 or more postganglionic neurons, whereas a parasympathetic preganglionic

neuron synapses with only 4 or 5 postganglionic neurons. The sympathetic neurotransmitter,

norepinephrine is removed (since it is taken up by transporters) more slowly than acetylcholine (which is degraded by acetylcholine esterase), so postganglionic cells are stimulated longer. Also, the sympathetic division stimulates release of epinephrine and norepinephrine from the adrenal medulla, thus enhancing the sympathetic effects via the endocrine system. Also, more visceral effectors have receptors for catecholamines (norepinephrine and epinephrine) than for acetylcholine.

1. *Describe disorders that affect the ANS. What is dysautonomia? What is the treatment? What causes it?*

Almost 10% of the population (or > 30 million people in the US) may acquire an autonomic disorder requiring medical attention. Because the autonomic nervous system maintains internal physiologic homeostasis, disorders of this system can be present with both central as well as peripheral nervous system localization. The etiology of autonomic dysfunction can be primary or idiopathic and secondary causes. Autonomic dysfunction is called autonomic neuropathy or dysautonomia.

Autonomic failure is seen in multiple system atrophy, pure or progressive autonomic failure, Parkinson and other neurodegenerative diseases, metabolic diseases such as Wernicke and cobalamin deficiency, diabetes mellitus, hyperlipidemia, trauma, vascular diseases, neoplastic diseases, and multiple sclerosis. In addition, autonomic dysfunction is associated with various medications. In addition to diabetes, autonomic dysfunction is associated with other neuropathies, including Guillain-Barré syndrome, Lyme disease, human immunodeficiency virus (HIV) infection, leprosy, acute idiopathic dysautonomia, amyloidosis, porphyria, uremia, and alcoholism. Besides nerve localization in the peripheral nervous system, it occurs in diseases of the presynaptic neuromuscular junction such as botulism and myasthenic syndrome.

Dysautonomia refers to a disorder of the autonomic nervous system that usually involves the failure of the sympathetic or parasympathetic divisions, but can also include an overactive autonomic nervous system too. Dysautonomia is also referred to as autonomic neuropathy and common symptoms range from lightheadedness to erectile dysfunction to loss of appetite. This is due to the fact the autonomic nervous system is such a major role in the body so a disorder of it will affect practically every body system. Treatment for dysautonomia is increasing quality of life and standard of care. This can be water bolus, elevation of the head in bed, or even medications such as midodrine. Primary causes of autonomic neuropathy can be familial dysautonomia (Riley-Day Syndrome) or Parkinson’s syndrome with autonomic failure. Secondary causes can include a multitude of things such as diabetes, alcoholism, chemotherapy, or autoimmune neuropathies such as myasthenia gravis or rheumatoid arthritis.

1. *What about the ANS and the enteric nervous system?*

Complex autonomic ganglia in the walls of the stomach and small intestine control the [enteric nervous system](http://www.scholarpedia.org/article/Enteric_nervous_system). Most of the neural pathways in the enteric plexuses lack direct preganglionic inputs and can operate independently of central control. Indeed, uniquely within the ANS, the enteric plexuses contain primary sensory neurons that connect to extensive networks of [interneurons](http://www.scholarpedia.org/article/Interneurons) as well as excitatory and inhibitory enteric motor neurons.

1. *What types of receptors are used in the sympathetic and parasympathetic nervous systems?*

Both the sympathetic and parasympathetic nervous systems have cholinergic preganglionic neurons. However, the sympathetic nervous system has adrenergic postganglionic neurons, while the parasympathetic nervous system has cholinergic postganglionic neurons. Because the preganglionic neurons are cholinergic, they release acetylcholine, and cholinergic receptors are located on the dendrites and cell bodies of the postganglionic neurons they synapse. These receptors are called nicotinic-2 or N2 receptors. The acetylcholine receptors located on effector organs of the parasympathetic nervous system are known as muscarinic or M receptors. Conversely, because the postganglionic neurons of the sympathetic nervous system are adrenergic, they release norepinephrine, and adrenergic receptors are located on effector organs of the sympathetic nervous system. These receptors are either alpha or beta adrenergic receptors.

1. *How do the sympathetic and parasympathetic nerve pathways differ?*

The autonomic nerve pathway for both is composed of two neurons (pre- and postganglionic neurons) that meet and synapse at an autonomic ganglion. Preganglionic neurons of the sympathetic nervous system arise from the thoracic and lumbar regions of the spinal cord. The sympathetic nervous system has short preganglionic and long postganglionic fibers, so autonomic ganglia reside near the spinal cord. Furthermore, the effects of the sympathetic nervous system tends to be widespread, since one preganglionic neuron can synapse with up to 20 postganglionic neurons. On the other hand, preganglionic neurons of the parasympathetic nervous system arise from the brainstem and the sacral region of the spinal cord. The preganglionic fibers exit either the brainstem via several cranial nerves or exit the spinal cord via spinal nerves, which form the pelvic splanchnic nerves. The parasympathetic nervous system has long preganglionic and short postganglionic fibers, so autonomic ganglia either reside near or within the effector organs. Moreover, there is a much lower degree of neuronal divergence in the parasympathetic nervous system compared to the sympathetic nervous system, so responses tend to be more specific and localized.

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