NBL 355-655 Module 13 Review Q&A

1. *Describe conventional and unconventional transmitters.*

As was described in the past few modules, the chemical messengers that act as conventional neurotransmitters (which include the small molecule neurotransmitters and neuropeptides) share certain basic features. They are stored in vesicles (either synaptic or secretory/dense core), are released when Ca2+ enters the axon presynaptic region in response to an action potential, and act by binding to receptors on the membrane of the postsynaptic, presynaptic or nearby synaptic membranes.

Several classes of neurotransmitters have been identified that don’t follow all of the conventional neurotransmitter rules. These are considered “unconventional” neurotransmitters: the endocannabinoids and gasotransmitters. These signaling molecules are unconventional in that they are not stored in vesicles, are often produced in response to conventional NTs, and are hydrophobic. The endocannabinoids (endogenous cannabinoids such as anandamide) are derived from membrane lipids and bind to their receptors (G protein coupled receptors) located on the presynaptic or postsynaptic membrane. Gasotransmitters are soluble gases and include nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H2S). Since they are hydrophobic, gasotransmitters can diffuse directly into and across the plasma membrane and regulate protein activities in the membrane and the cytoplasm. In some cases, gasotransmitters can act as retrograde messages, messengers that are synthesized by the postsynaptic neuron in response to NTs, diffuse across the synapse and act on the presynaptic neuron. Other unconventional messengers will probably be discovered as we learn more about how neurons work. As these new chemical messengers are discovered, we may need to further modify and update our idea of what it means to be a neurotransmitter.

1. *What are endocannabinoids and how are they proposed to function? From Wikipedia:*

The endocannabinoid system (ECS) is a biological system composed of endocannabinoids, which are endogenous lipid-based unconventional neurotransmitters that bind to cannabinoid receptors (CBRs), and cannabinoid receptor proteins that are expressed throughout the vertebrate CNS (including the brain) and PNS. The endocannabinoid system remains under preliminary research, but may be involved in regulating physiological and cognitive processes, including and in mediating the pharmacological effects of cannabis (the psychoactive component of the marijuana plant). Two primary cannabinoid receptors have been identified: CB1 receptors and CB2 receptors, which are G protein coupled receptors. CB1 receptors are found predominantly in the brain and nervous system, as well as in peripheral organs and tissues, and are the main molecular target of the endogenous partial agonist, anandamide (AEA), as well as exogenous THC, the psychoactive component of cannabis. Endocannabinoid 2-arachidonoylglycerol (2-AG), which is 170-fold more abundant in the brain than AEA, acts as a full agonist at both CB receptors. CBD is a phytocannabinoid that acts as a rather weak antagonist at both CBRs and a more potent agonist at TRPV1 and antagonist at TRPM8. It can be a negative allosteric modulator at CB1. CBD has been found to counteract some of the negative side effects of THC.

Once of the endogenous cannabinoids, anandamide (ANA), also known as N-arachidonoylethanolamine (AEA), is a fatty acid neurotransmitter derived from the non-oxidative metabolism of eicosatetraenoic acid (arachidonic acid), an essential omega-6 fatty acid. In rats, anandamide has been shown to impair working memory, and has also been shown to play a role in the regulation of feeding behavior, and the neural generation of motivation and pleasure. Moreover, the acute beneficial effects of exercise (termed as runner's high) may be mediated by anandamide in mice. 2-Arachidonoylglycerol (2-AG) is an endocannabinoid, an endogenous agonist of the CB1 receptor and the primary endogenous ligand for the CB2 receptor. 2-AG, unlike anandamide, is present at relatively high levels in the central nervous system.

Tetrahydrocannabinol (THC) is one of at least 113 cannabinoids identified in the cannabis (marijuana) plant. THC is the principal psychoactive constituent of cannabis. It produces the effects of euphoria, the “high.” The psychoactive effects of THC are primarily mediated by the activation of cannabinoid receptors, which are G protein coupled receptors that result in a decrease in the concentration of the second messenger cAMP through inhibition of adenylate/adenylyl cyclase. The actions of THC result from its partial agonist activity at the cannabinoid receptor CB1, located mainly in the central nervous system, and the CB2 receptor, mainly expressed in cells of the immune system. The presence of these specialized cannabinoid receptors in the brain led researchers to the discovery of endocannabinoids, such as anandamide and 2-AG. Medical marijuana is used to treat nausea, especially for patients undergoing cancer chemotherapy, to improve appetite in cancer and AIDS patients, and to decrease spasticity. It is also used to treat anorexia, Crohn’s disease, multiple sclerosis, glaucoma, schizophrenia and PTSD. The non-psychoactive component of cannabis, cannabidiol CBD), is used to treat epilepsy and anxiety.

1. *What are gasotransmitters and how are they proposed to function? From Wikipedia:*

The gasotransmitters is a subfamily of endogenous molecules of gases or gaseous signaling molecules, including NO, CO, H2S. The gasotransmitters are proposed to play essential roles in the brain and body under normal physiological and under pathological conditions. These particular gases share many common features in their production and function but carry on their tasks in unique ways, which differ from classical signaling molecules, in the human body. For a gas molecule to be categorized as a gasotransmitter, all of the following criteria should be met:

It is a small molecule of gas; It is freely permeable to membranes. As such, its effects do not rely on a typical membrane receptor (though it can act on membrane proteins). It can have endocrine, paracrine, and autocrine effects. In their endocrine mode of action, for example, gasotransmitters can enter the blood stream; be carried to remote targets by scavengers and released there, and modulate functions of remote target cells; It is endogenously and enzymatically generated and its production is regulated; It has well defined and specific functions at physiologically relevant concentrations. Thus, manipulating the endogenous levels of the gas evokes specific physiological changes; Functions of the endogenous gas can be mimicked by its exogenously applied counterpart; Its cellular effects may or may not be mediated by second messengers, but should have specific cellular and molecular targets.

H2S is a member of the gasotransmitter family that is associated with the maintenance of neuronal plasticity and excitability. NMDA receptors ( ) are targets of H2S in the brain; H2S potentiates the activity of NMDARs and facilitates the induction of hippocampal LTP. H2S modulates NMDAR-mediated currents in pyramidal neurons of neonatal hippocampal slices. NO is a ubiquitous signaling molecule in the brain as well as in other organs in the body, with neural roles in retrograde signaling, cellular function, synaptic plasticity, development, excitotoxicity, blood flow, and mental health. NO inhibits the activity of NMDARs and reduces effects of glutamate and induces changes in neuronal transmission. A reduction in NMDAR expression is associated with the change in synaptic plasticity driven by the age-related conditions in sensory input, demonstrating age-related impairment in the function of the NMDAR/NO signaling pathway in the CNS. Physiologically, CO is generated by two heme oxygenases (HO), which catalyze the catabolism of heme groups. HO-2 is concentrated in hippocampal pyramidal cells; therefore, CO might be a candidate retrograde messenger for LTP as an HO inhibitor blocks the induction of LTP in hippocampal slices.

1. *Describe the cerebral cortex, including the different regions and layers of neocortex and their functions.*

The cerebral cortex is a thin layer of gray matter between 2 and 4 mm thick and overlying the cerebral white matter. In humans, the largest part of the cerebral cortex (~90%) is the neocortex, which has 6 neuronal layers and is present only in mammals. A few small regions of human cerebral cortex (~10%) are allocortex, which has only 3 or 4 layers and is evolutionarily older, evolving in vertebrates. Note that the hippocampus and olfactory cortex are allocortex. Thus the hippocampus is part of the cerebral cortex. Although the cerebral cortex is only a few millimeters thick, it occupies a sizeable area in humans; it is estimated that the human neocortex represents approximately 75% of the total brain gray matter. It has been proposed that, in humans, gyri and sulci result from the expansion of the surface area of the cerebral cortex during fetal development, allowing a greater area of cerebral cortex to fit into the confines of the skull. The increased cortical areas have been proposed to underlie the evolution of higher cognitive functions in humans.

Although the neocortex displays a consistent 6-layer organization, different regions of the cerebral cortex are composed of distinguishably different neuronal morphologies and connections. Brodmann, Ramon y Cajal, and others predicted that cortical areas that look different perform different functions. Through numerous types of analyses in the past century, we now know this to be true. Because there is little difference in the thickness of the neocortex in different mammals, Brodmann also predicted that the neocortex expanded (for example the increase in prefrontal cortex) by the insertion of new areas. The neocortex contains approximately 80% excitatory glutamatergic neurons and approximately 20% inhibitory GABAergic neurons and receives inputs from neurons in all the major neurotransmitter systems, but from only other cortical areas and a few specific regions (see below). Recent studies have suggested that there are a very small number (less than 1%) of cholinergic neuron cell bodies in the neocortex as well.

Many neuroscientists propose that the smallest functional unit of the neocortex is a cylinder of neurons approximately 2 to 3 mm in height (the distance from the white matter to the pial surface) and approximately 0.5 mm in diameter. Called a “cortical column,” this cylinder is estimated to contain approximately 10,000 neurons and 100 million synapses (~10,000 synapses per neuron). The neurons in cortical columns are proposed to receive and integrate information from other neurons within the same column and may represent a computational unit. Cortical columns have been characterized in primary visual and somatosensory cortex where neurons have similar sensory receptive fields. It has been proposed that each cortical column is composed of about 100 “minicolumns” that contain approximately 80-100 neurons each.

The neocortex is formed of six cortical layers, numbered I (one) to VI (six) from the outermost (adjacent to the pia mater) to the innermost (adjacent to the white matter). Each layer has a characteristic distribution of different neurons and their connections with other cortical and subcortical regions. There are direct connections between different cortical areas and indirect connections via the thalamus. Staining cross-sections of the cortex to reveal the position of neuronal cell bodies and the intracortical axon tracts produced detailed descriptions of the laminar structure of the cortex.

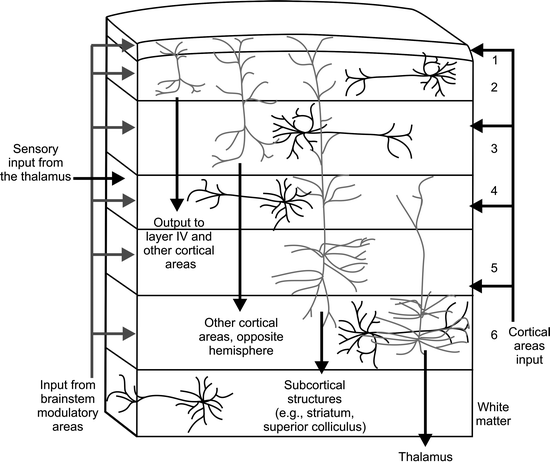
Layer I: molecular layer, input from thalamus/ axons from contralateral

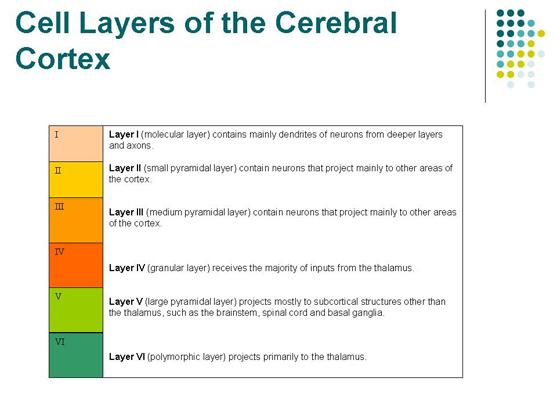
Layer II: external granular layer, input from contralateral, output to other cortical areas

Layer III: external pyramidal layer, input from contralateral, output to other cortical areas

Layer IV: internal granular layer, input from intra-hemispheric/ thalamus

Layer V: internal pyramidal layer, output to BG, SC, brainstem, voluntary motor control

Layer VI: multiform layer, output to thalamus



Note that the cerebral cortex sends direct outputs to both ipsilateral and contralateral cerebral cortical areas. The axons that connect the cerebral cortical regions on the same side are the association tracts. The axons that connect the cortex on the opposite sides form the commissural tracts, with the corpus callosum being the largest one. The axons that emerge from the cerebral cortex and connect to subcortical or other CNS regions are the projection tracts. The cerebral cortex sends direct outputs to the majority of other brain areas: the thalamus, hypothalamus, basal ganglia, brainstem, spinal cord and amygdala. The cerebral cortex transmits information to the cerebellum by connections to the pons (see below). In contrast, the cerebral cortex directly receives input from only a few brain regions. The thalamus is the main subcortical input to the cortex. It provides sensory input, as well as motor input from the basal ganglia and cerebellum. The other brain regions that provide direct input to the cerebral cortex are the basal forebrain, amygdala and brain stem. Cholinergic and monoaminergic neurons provide inputs to the cerebral cortex. (Cholinergic neuron cell bodies are located in the basal forebrain and brainstem, and monoaminergic neuron cell bodies are located in the brainstem.) Above are two nice summary slides. As shown, note that all cortical layers receive inputs from other cortical regions and from the brainstem. Note the main inputs and outputs are shown some layers involve additional inputs and outputs. Also note that since different regions of cortex have different functions (sensory, motor or association), the relative size of each layer is different for each region of cortex. For example, primary sensory cortices have larger layer IV since they receive many sensory inputs from the thalamus. Primary motor cortex has a larger layer V since it sends many motor outputs to the brainstem and spinal cord.

The cerebral cortex is typically described as comprising three parts or types: sensory, motor, and association areas. The sensory areas are the cortical areas that receive and process information from the sensory receptor tracts. Parts of the cortex that receive sensory inputs from the thalamus are called primary sensory areas. The senses of vision, hearing, and touch are served by the primary visual cortex, primary auditory cortex and primary somatosensory cortex respectively. In general, the two hemispheres receive information from the opposite (contralateral) side of the body. Organization of sensory maps in the cortex is in what is known as a topographic map.

The motor areas are located in both hemispheres of the cortex. The motor areas are very closely related to the control of voluntary movements, including fine fragmented movements performed by the hand. The right half of the motor area controls the left side of the body, and vice versa. The primary motor cortex contains upper motor neurons and executes voluntary movements. The supplementary motor area and premotor cortex, are involved in the selection and control of voluntary movements and also contain upper motor neurons. The posterior parietal cortex guides voluntary movements in space. The dorsolateral prefrontal cortex helps determine which voluntary movements to make according to higher-order instructions, rules, and self-generated thoughts.

The cortical association areas are the parts of the cerebral cortex that do not belong to the primary sensory or primary motor areas. There is a motor association area, and several sensory association areas and several cognitive association areas. They function to produce a meaningful perceptual experience of the world, enable us to interact effectively, and support abstract thinking and language. The parietal, temporal, and occipital lobes - all located in the posterior part of the cortex - integrate sensory information and information stored in memory. The frontal lobe prefrontal association complex is involved in planning actions and movement, as well as abstract thought. Globally, the association areas are organized as distributed networks. Each network connects areas distributed across widely spaced regions of the cortex. Distinct networks are positioned adjacent to one another yielding a complex series of interwoven networks. The specific organization of the association networks is debated with evidence for interactions, hierarchical relationships, and competition between networks.

1. *The great majority of sensory neurons and sensory relay neurons are glutamatergic. Provide an overview describing how information is transmitted in sensory systems.*

Organisms need information to solve at least three kinds of problems: (a) to maintain an appropriate environment, i.e., homeostasis; (b) to time activities (e.g., seasonal changes in behavior) or synchronize activities with those of other individuals; and (c) to locate and respond to resources or threats (e.g., by moving towards resources or evading or attacking threats). Organisms also need to transmit information in order to influence another's behavior: to identify themselves, warn others of danger, and coordinate activities of survival and reproduction.

The sensory nervous system is a part of the nervous system responsible for processing sensory information. A sensory system is responsible for detecting, transmitting and processing sensory information. A sensory system refers to the pathway and nervous system regions that transduce a stimulus input into electrical signal that is ultimately received and interpreted in the brain. A sensory system consists of sensory neurons (including the sensory receptor cells), neural (axonal) pathways, and parts of the brain involved in transmitting sensory information and sensory perception. Commonly recognized sensory systems are those for vision, hearing, touch, taste, smell, and balance. In short, senses are transducers from the physical world to the realm of the mind where we interpret the information, creating our perception of the world around us.

The stimulus is the energy source or chemical signal, it can be external or internal. Cellular sensory receptors are specialized cells or cellular process that detect and monitor specific conditions and/or changes. Primary somatosensory receptors can detect touch and pressure, temperature, and chemicals. In addition, sensory receptors are present in special sense organs, which are structures specialized to respond to stimuli. The molecular receptors and transducers respond to the stimulus energy or chemical and convert that into synaptic signals to other neurons that are eventually transduced into action potentials. Sensory pathways and conduction include the axons (afferent pathways) and neurons involved in relaying sensory information and transmitting it to the brain. Nerve impulses (which are action potentials) are transmitted to the CNS. For 5/7 senses, information is relayed through the thalamus. For most senses, sensory information is relayed/transmitted from the thalamus to the primary sensory cortex for each modality. Then, the sensory information is integrated and processed by the sensory association cortex for each modality and eventually combined with other sensory information. The sensory information that is detected and arrives at the primary sensory cortex is a sensation. Awareness of a sensation is perception – reality. In summary, sensory receptor cells detect specific stimuli, neural pathways including axons in nerves and tracts transmit the action potentials to the thalamus, which relays the information to the primary sensory cortices; the sensory association cortices process and integrate that information to produce perception.

1. *Upper motor neurons are glutamatergic, and the majority of local circuit neurons involved in control of lower motor neurons are either glutamatergic or GABAergic/glycinergic. Provide an overview describing how information is transmitted in motor systems.*

The motor system is the set of central and peripheral structures in the nervous system that support motor functions, i.e. movement. Peripheral structures include skeletal muscles and neural connections with muscle tissues. Central structures include cerebral cortex, basal ganglia, brainstem, spinal cord, pyramidal system for voluntary muscle control, extrapyramidal system for involuntary muscle control in posture and balance, cerebellum, and the lower motor neurons in the brainstem and the spinal cord. The pyramidal motor system involved in voluntary movement, involves the corticospinal and corticobulbar tracts, which originate in the motor cortex.

The motor cortex controls voluntary movements. The motor cortex receives inputs from and is controlled by numerous parts of the brain. The motor cortex receives input information directly from the prefrontal cortex, parietal association cortex, and somatosensory cortex. The motor cortex also receives information indirectly from the cerebellum and basal ganglia, by the relay from the thalamus. The great majority of the inputs to the motor cortex are excitatory from glutamatergic neurons, from either other cortical regions or from the thalamus. (The majority of inputs to the cerebral cortex from subcortical structures occur through the thalamus, hence the thalamus is called the “gateway to the cerebral cortex.”)

The upper motor neurons in the motor cortex extend their axons to either the brainstem (for the control of movements of the face, head, mouth and tongue), or to the spinal cord (for the control of the movements of the rest of the body). Upper motor neurons are glutamatergic projection neurons and their myelinated axons form several white matter regions in the brain. Upper motor neuron axons synapse on lower motor neurons and local circuit neurons in the brainstem or spinal cord. The lower motor neurons are cholinergic neurons that extend their axons out of the brainstem or spinal cord, the axons form parts of cranial nerves or spinal nerves, and the axons innervate skeletal muscle cells at the neuromuscular junction. Local circuit neurons are sometimes called brainstem or spinal interneurons, and there are two types: excitatory glutamatergic interneurons and GABA/glycinergic inhibitory interneurons. These interneurons also send inputs to the lower motor neurons and control their activity. In fact, only about 20% of the inputs to lower motor neurons are from upper motor neurons. The other 80% of inputs (and control) of lower motor neurons are from the local interneurons in the nearby regions of the brainstem or spinal cord.

The somatic motor nervous system innervates skeletal muscle for the voluntary/conscious control of movement, and also the involuntary/unconscious control of several automatic reflexes such as breathing and muscle contractions involved in balance and posture. The autonomic nervous system is involved in the involuntary/unconscious control of smooth muscles, cardiac muscles and glands. The autonomic and somatic motor systems are similar in that they both include cholinergic motor neurons located in either the spinal cord or brainstem, that extend their axons out of those regions. In the somatic system, those axons directly innervate the target skeletal muscle where they produce muscle contraction. In the autonomic system, those motor axons innervate the post-ganglionic neurons (PGNs) found in autonomic ganglia, which then extend their axons and innervate the target tissues. PGNs use different neurotransmitters (acetylcholine, norepinephrine or dopamine) depending on whether they are sympathetic or parasympathetic and the tissue they control.

1. *Describe the basic anatomy and functions of the basal ganglia.*

Just underneath the cerebral cortex are interconnected subcortical masses of grey matter called the basal ganglia (or nuclei). The basal ganglia, also called the basal nuclei, include a set of six major subcortical structures located deep within the cerebral hemispheres. The main components of the basal ganglia are the caudate nucleus, the putamen, the globus pallidus, the substantia nigra in the midbrain, the nucleus accumbens, and the subthalamic nucleus. Several regions of the basal ganglia are grouped together to form the structure called the striatum, defined below. Functionally, the basal ganglia are involved in the control and coordination of voluntary motor movements, decisions about which motor actions to select (action selection), eye movements, procedural learning, some behaviors and habits, cognition, and emotions such as motivation and reward. The basal ganglia are strongly interconnected with areas of the cerebral cortex, thalamus, and brainstem, as well as several other brain areas.

The striatum is the largest structure of the basal ganglia. The striatum is divided into a dorsal and ventral subdivision, based upon function and connections. The dorsal striatum is formed from the caudate nucleus and putamen and the ventral striatum is formed by the nucleus accumbens and olfactory tubercle. The striatum is the main recipient of inputs to the basal ganglia. Inputs to the striatum are excitatory afferents from the entire cerebral cortex and intralaminar nuclei of the thalamus. The nucleus accumbens receives a large input from the limbic cortex. The dorsal striatum contributes directly to decision making, especially to action selection and initiation, through the integration of sensorimotor, cognitive, and motivational/emotional information. The dorsal striatum primarily mediates cognition involving motor function, certain executive functions such as inhibitory control, and stimulus-response learning. It is associated with the acquisition of habits and is the main region linked to procedural memory. The ventral striatum is associated with the limbic system and has been implicated as an essential component of the circuitry for decision making and reward-related behavior. As part of the reward system, the nucleus accumbens plays an important role in processing rewarding stimuli, reinforcing stimuli, and stimuli that are both rewarding and reinforcing such as addictive drugs.

Located just below the thalamus is the subthalamic nucleus. The substantial nigra is a brainstem structure composed of the pars compacta (SNc) and pars reticulata (SNr). The SNc (pars compacta) contains the cell bodies of dopaminergic neurons that innervate the neostriatum. A functionally analogous midbrain area is the ventral tegmental area (VTA), which contains dopaminergic neurons that project to the nucleus accumbens.

The striatum contains GABAergic inhibitory neurons and sends its axons to the globus pallidus. The globus pallidus is divided into 2 segments: the internal globus pallidus (GPi) and the external globus pallidus (GPe). The main output structures of the basal ganglia are the GPi of the globus pallidus and the substantia nigra pars reticulata (SNr). The GPe and GPi neurons are also GABAergic inhibitory neurons and the output from the GPi to the thalamus is inhibitory. The GPi projects to a number of thalamic structures by way of 2 tracts. The SNr projects to the superior colliculus, an area involved in eye movements, as well as to thalamic nuclei. Thus note that while the majority of projection/principal neurons from the cerebral cortex to the striatum are excitatory, the majority of projection/principal neurons within and from the basal ganglia are inhibitory. The two exceptions are the SNc neurons which are dopaminergic and STN neurons which are excitatory.

Two distinct pathways process signals through (within) the basal ganglia. Called the direct pathway and the indirect pathway, they have opposite net effects on thalamic target structures. Excitation of the direct pathway has the net effect of exciting thalamic neurons (which in turn make excitatory connections onto cortical neurons). Excitation of the indirect pathway has the net effect of inhibiting thalamic neurons (rendering them unable to excite motor cortex neurons). The normal functioning of the basal ganglia involves a balance between the activity of these 2 pathways.

1. *Describe the basic anatomy and functions of the thalamus.*

Considered the gateway to the cerebral cortex, the thalamus is positioned in the center of the brain, located between the cerebral cortex and midbrain, adjacent to the basal ganglia and dorsal to the cerebellum, and has extensive connections to all 4 regions. One of the main functions of the thalamus is to transmit sensory and motor information to the cerebral cortex. However, not merely a “relay station,” the thalamus is also engaged in integration and sorting of sensory and motor information that will reach the cerebral cortex and impacts cognitive functions.

The thalamus is a midline symmetrical structure of 2 halves. The medial surface of the thalamus constitutes the upper part of the lateral wall of the third ventricle and is connected to the opposite thalamus by the interthalamic adhesion. The thalamus is an organized group of approximately 50-60 specific nuclei, each with defined connections and roles in sensory, motor, and some cognitive functions. (You do not need to memorize the names of any thalamic nuclei for the quiz or final exam.) Every sensory system (with the exception of the olfactory system and unconscious proprioception) involves a specific thalamic nucleus in the dorsal/sensory thalamus that receives sensory signals from ascending tracts or cranial nerves and transmits sensory information to the specific primary sensory cortex. The thalamus also processes sensory information and receives reciprocal connections from the sensory cortex (layer IV neurons) it innervates. A current concept about the sensory thalamus is that inputs can be divided into “drivers,” which provide the primary excitatory drive for the relay of information to cortex, and “modulators,” which are neurons that alter the gain of signal transmission (and can be inhibitory, excitatory or modulatory neurons). Thalamic relay neurons that project to layer IV of the cerebral cortex are glutamatergic excitatory neurons.

The thalamus plays a critical role in regulation of motor function. A region of the ventral thalamus called the motor thalamus (Mthal) encompasses thalamic nuclei that are functionally positioned between cerebral cortical motor areas and 2 subcortical networks, the basal ganglia and cerebellum. Consequently, the thalamus provides specific channels from the basal ganglia and cerebellum to the cortical motor areas and receives reciprocal connections from those motor areas. Mthal is also proposed to have a role in motor learning.

The thalamus also receives inputs from the reticular thalamic nucleus, the superior colliculus, the pedunculopontine nucleus, and the somatosensory spinal cord, and has been implicated in wakefulness and sleep, awareness and alertness, and consciousness. Connections with the prefrontal cortex, hippocampus, and other cortical association areas also likely underlie the contribution of the thalamus to cognitive functions, including language processing, attention, short-term working memory, long-term memory, and decision making.

1. *Describe the basic anatomy and functions of the cerebellum.*

Lying underneath the forebrain and adjacent to the brainstem is the cerebellum. The cerebellum receives substantial motor and sensory inputs directly from the brainstem and spinal cord, and indirectly from the cerebral cortex. Primarily a movement control center, cerebellar functions include control of posture and balance, coordination of voluntary movements that result in smooth and balanced muscular activity of parts of the body, and learning motor behaviors. The cerebellum has also been implicated in cognitive functions including language, attention, and mental imagery and emotional control. Receiving extensive inputs, the cerebellar intrinsic circuits are thought to have substantial computational capacity in producing their outputs.The cerebellum has 3 functional subdivisions and is involved in control of both conscious and unconscious movement. The flocculonodular lobe and adjacent vermis is called the vestibulocerebellum and is involved in balance and eye movements. The spinocerebellum includes the vermis and other small regions and functions in posture and proprioception. The cerebrocerebellum makes up the lateral hemispheres of the anterior and posterior lobes and functions in control of voluntary movement. Each of the 3 lobes has a left and right half, and each lobe consists of an inner medulla of white matter and a richly folded thin outer layer of cortical gray matter.

The cerebral cortex provides the largest source of inputs to the cerebellum, although indirectly via the pons. Corticopontine fibers originate in the frontal lobe motor cortex and the parietal lobe somatosensory cortex and visual association areas, which project to the pontine nuclei in the pons. Neurons in the pons send outputs to the cerebellum by the middle cerebellar peduncles. The target of the pontine output is the cerebrocerebellum, which functions in coordination and smoothing of complex motor movements, evaluation of sensory information for action, and some cognitive functions.

Although it represents only 10% of the brain mass, the cerebellum contains as many neurons as the entire cerebrum, but many fewer types of neurons. The outer cortical layer consists of a regular 3-layer arrangement that contains Purkinje neurons and granule neurons. The majority of inputs to cerebellum are to the cerebellar cortex. Inputs from pons (pontine nuclei) and other sources are called mossy fibers which synapse on granule cells. The granule cells then for parallel fibers which synapse on Purkinje neurons. The other inputs to Purkinje neurons is from climbing fibers that originate in a region of the brainstem called the inferior olive. The inputs from granule neurons/parallel fibers and climbing fibers are glutamatergic/excitatory. The Purkinje neurons are themselves GABAergic inhibitory projection/principal neurons. The Purkinje neurons integrate incoming signals and send outputs to the deep cerebellar nuclei located in the white matter interior and back to the vestibular nuclei. The majority of outputs from the cerebellum to the brainstem and thalamus occur via the deep cerebellar nuclei. About 2/3 of the output neurons in the deep cerebellar nuclei are glutamatergic excitatory projection neurons and about 1/3 are inhibitory projection neurons. The cerebrocerebellum sends output to the brainstem and the thalamus, which provides the feedback to the motor cortex for the adjustment of movement. The vestibulocerebellum is involved in maintenance of balance and coordinating eye movements and speech. The spinocerebellum regulates body and limb movements involved in proprioception and posture. Numerous studies support the conclusion that the cerebellum also plays an important role in some types of motor learning, in particular those voluntary motor actions that require fine adjustments for performance, and some cognitive functions and emotional control.