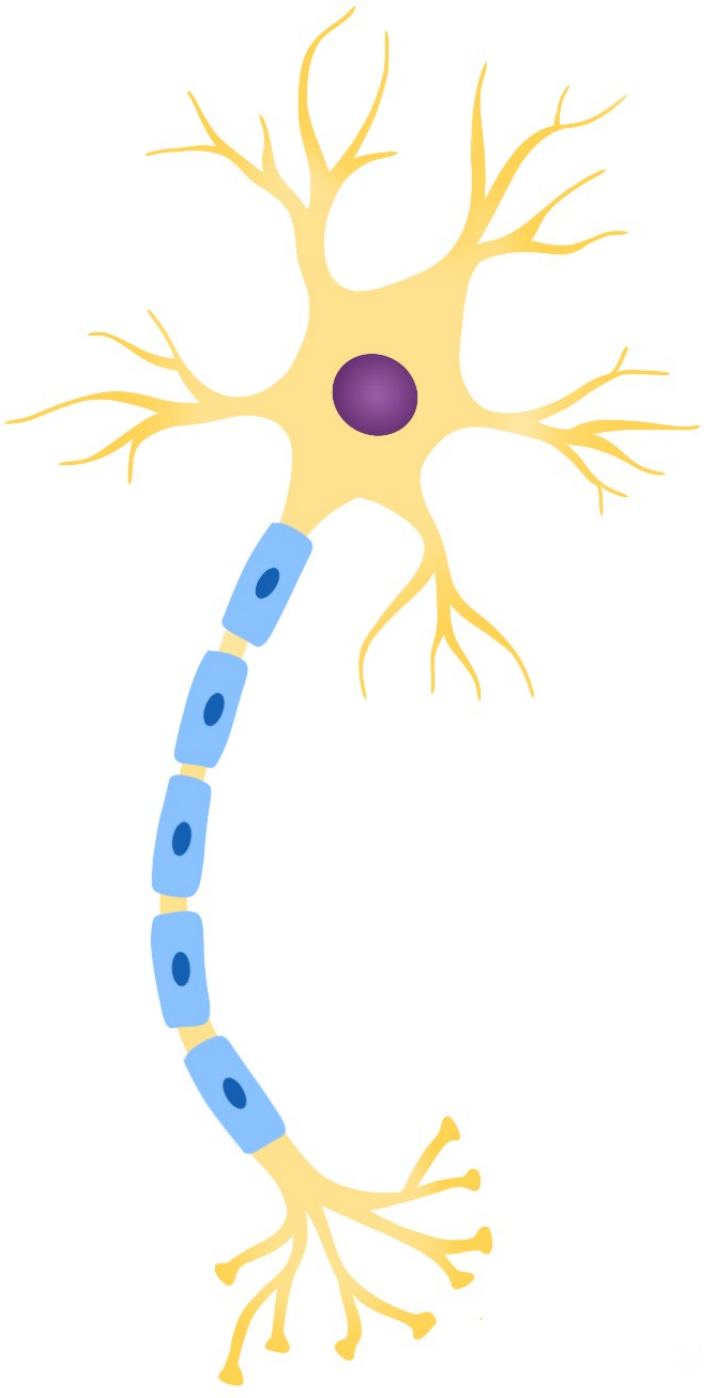

Neurophysiology

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Table of Contents

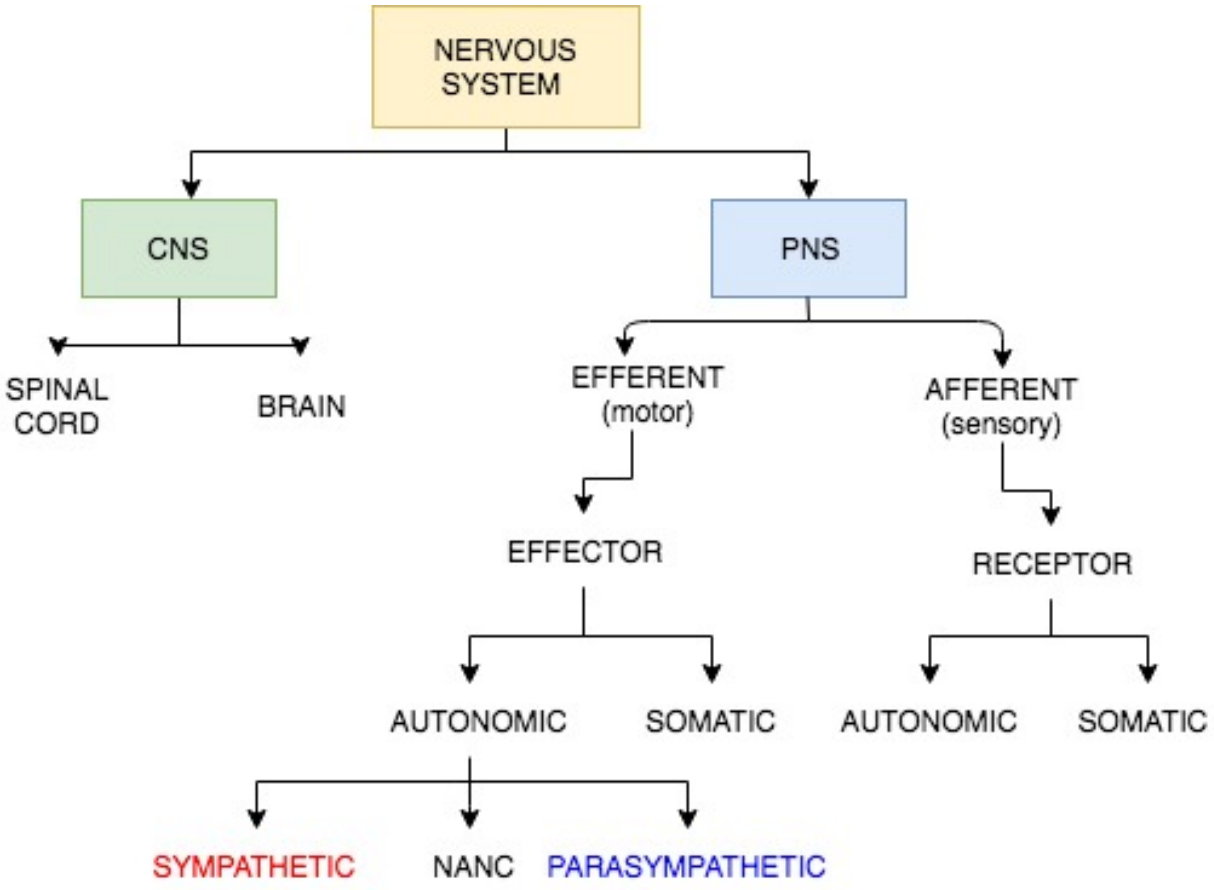
Introduction

There are 7 chapters in this booklet, and each contains what Studyaid considers high yield for the neurophysiology exam.
At the end of each chapter, you will find a couple of review questions so that you can check your own knowledge. There is not provided an answer sheet to these questions, but all the information needed is in the booklet. If in doubt, ask a tutor.

We wish you the best of luck on your exam, and happy studying!

Section 1 – General Neurophysiology

1.1 – Divisions of the Nervous System



1.2 – Important Components of the CNS

1.2.1 – Neurons

- Signal transmitting cells of the nervous system
    1. Dendrites: Receive input
    2. Axons: Send output
- Permanent cells – do not divide in adulthood

I. Mirror neurons

- Present in frontal an parietal lobe
- Neurons fire both when the person performs the activity itself, and also when the person observes the activity being done by others.
- They are responsible for empathy, recognition of emotions and also for learning skills by imitation.
    1. Important for social function
- It is hypothesized that dysfunction can lead to autism

1.2.2 – Glial Cells

- Non-neuronal cells that maintain homeostasis

<table>
<tr><td rowspan="4">Macroglial cells</td><td rowspan="3">CNS</td><td>Astrocytes
- Located all over the nervous system
- Make up 20-40% of all glial cells
- Physical Support, K+ and Ca2+ metabolism,
- Remove excess neurotransmitters
- Component in Blood-brain barrier
- Involved in scar formation/repair</td></tr>
<tr><td>Ependymal cells
- Present in cerebral ventricles, assist in CSF circulation and absorption
- Maintain homeostasis and ion flow
- Choroid plexus: Specialized ependymal cells that produce the cerebrospinal fluid (CSF)</td></tr>
<tr><td>Oligodendrocytes
- Myelinate the axons of neurons in the CNS
- Predominant type of glial cell in white matter
- Each oligodendrocyte can myelinate around 30 axons</td></tr>
<tr><td>PNS</td><td>Schwann cells
- Each Schwann cell myelinates only 1 PNS axon
- Promote axonal regeneration</td></tr>
<tr><td>Microglial cells</td><td>CNS</td><td>- Macrophage-like cells; phagocytic scavenger cells of the CNS
- Activated in response to damage of tissue and inflammation
- Present in the vicinity of blood vessels
- Hypothesized to produce Interleukins
- Can produce neurotrophins
- Hyperactive cells can damage other neurons</td></tr>
</table>

1.2.3 – Neurotrophins

- Small proteins that maintain the function and growth of neurons
- Secreted by target tissue (muscle cells, glial cells, etc)
- Capable of signaling particular cells to survive, differentiate, or grow
- Also induce differentiation of progenitor cells to form neurons
- Receptors for neurotrophins can be either p75 or TrK family

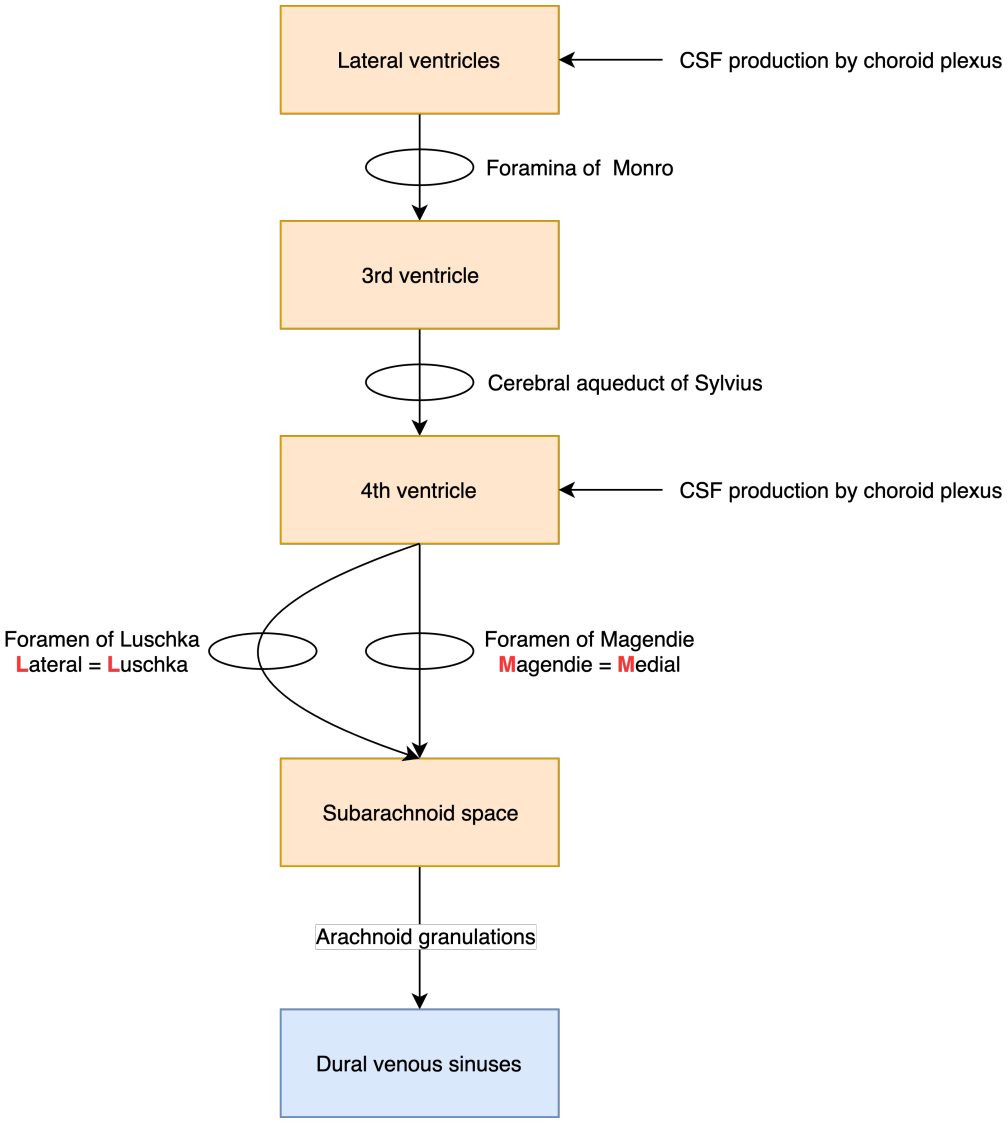
The four main neurotrophins

Nerve Growth Factor (NGF)	Brain Derived Neurotrophic Factor (BDNF)	NT-3	NT-4
Regulates the growth and up-keeping of sensory and sympathetic neurons Alpha, Beta, Gamma subunits	Located in the brain and the periphery Helps to support existing neurons Encourages the growth and differentiation of new neurons and formation of synapses	Closely related to NGF and BDNF Hypothesized to maintain cutaneous mechanoreceptors	Another neurotrophic factor

I. Other factors that can affect the nervous tissue

- Ciliary neurotrophic factor (CNF)
    1. Promotes the survival of neurons (for example, during inflammation) e.g. spinal cord
- Glial cell-line derived neurotrophic factor (GDNF)
    1. Promotes the survival of dopaminergic and motor neurons
- Leukemia Inhibitory Factor (LIF)
- Fibroblast Growth Factor (FGF)
- Transforming Growth Factor (TGF)
- Platelet Derived Growth Factor (PDGF)

1.2.4 – Cerebrospinal Fluid



- Approximately 500-600 mL of CSF is produced daily
    1. Only about 100-160 ml (avg. 150 ml) can be found in the ventricles at a time due to continuous reabsorption
- Intracranial pressure = 8-15 mmHg if patient is lying down, increases to around 18 mmHg when patient is standing

I. Composition

- A few lymphocytes (typically less than 5/microliter)
- No red blood cells
- pH of 7.33
- 60-65 mg/dL of Glucose
- 15-50 mg/dL of Proteins (avg. 35)

II. Significance

- Facilitates exchanges of nutrients, materials between different parts of Brain
- Protects nervous system against mechanical injury (trauma)
- Decreases the weight of the brain (neutral buoyancy)

III. CSF analysis

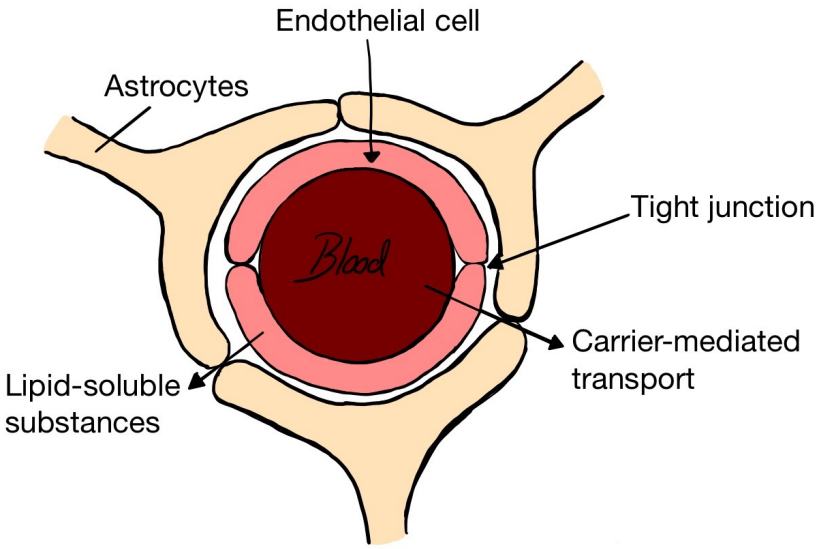
- Collected by performing a lumbar puncture
- Can give clues to causes of diseases
    1. Changes in white blood cells and proteins can be indicative of inflammation
    2. Along with glucose and differentiation of various WBC levels, etiology of infection may be deduced
    3. RBCs present may detect bleeding (e.g. a subarachnoid hemorrhage) or be a result of a traumatic spinal tap

1.2.5 – Blood Vessels

- Provide nutrients for all cells within the nervous tissue

I. Blood-brain barrier

- Formed by three structures
    1. Tight junctions between endothelial cells of blood capillaries
    2. Basement membrane
    3. Astrocyte processes
- Nonpolar/lipid soluble substances pass with ease via diffusion
    1. O2, lipids, steroid hormones, CO2 etc.
- Glucose and amino acids can cross through the membrane via carrier mediated transport
- Poorly permeable for protein and high molecular weight substances
- Hypothalamus influences blood-brain barrier permeability



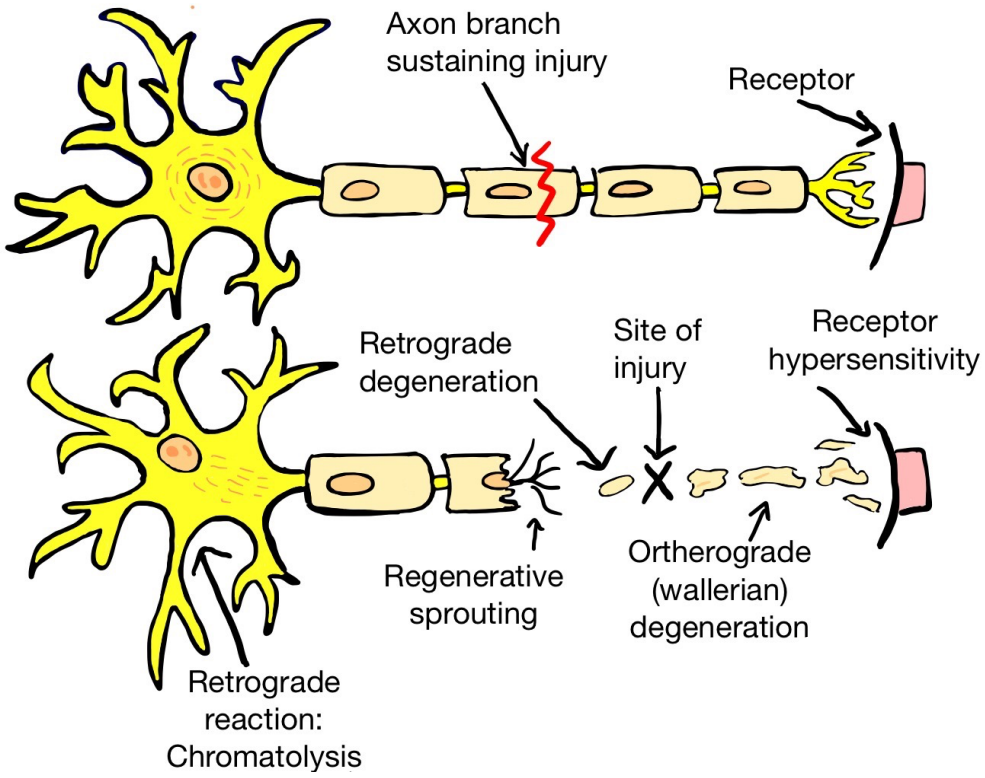
1.3 – Nerve Cell Degeneration

I. Chromatolysis

- Reaction of neuronal cell body to axonal injury
    1. Dissolution of the Nissl bodies in the cell body of a neuron
    2. Cellular edema
    3. Displacement of the nucleus towards the periphery
    4. Happening together with Wallerian degeneration

II. Wallerian degeneration

- Degeneration distal to the injury
- Axonal retraction proximally
- Allows for possible regeneration (if within the PNS)
    1. Macrophages remove debris and myelin



III. Trans-synaptic degeneration

- Occurs when a neuron is overstimulated by a neurotransmitter, causing synapsing neurons to be driven into metabolic deficit
- Degeneration of the neuron which synapses with the injured neuron

IV. Denervation hypersensitivity

- Interruption of innervation to an organ (denervation)
    1. As a result, the synaptic receptor becomes extremely sensitive to neurohumoral agents: Muscle denervated → Stronger response to ACh → Repetitive contractions
- Also called the Cannon-Rosenberg Law of Denervation

V. Regeneration

- Applies to PNS only
- Assuming less-extensive damage, the proximal axons are able to regrow as long as the cell body is intact
    1. Start with regeneration tube via Schwann Cells
    2. Secretion of NGF (nerve growth factor) by Schwann Cells
    3. Guidance of axon to destination
- Takes weeks to months

1.4 – Characteristics of the Autonomic Nervous System

Characteristic	Sympathetic	Parasympathetic
Origin of Preganglionic Nerve	Nuclei of Spinal Cord segs T1-T12, L1-L3	Nuclei of CNIII, VII, IX, X Spinal Cord S2-S4
Length of Preganglionic n. Axon	Short	Long
Receptor type in ganglion	Nicotinic	Nicotinic
Neurotransmitter in ganglion	Acetylcholine	Acetylcholine
Length of Postganglionic nerve axon	Long	Short
Effector Organs	Smooth + cardiac muscle, glands	Smooth + cardiac muscle, glands
Neurotransmitter in effector organs	Norepinephrine (ACh in glands)	Acetylcholine
Receptor types in effector organs	A1, A2, B1, B2, B3	M1, M2, M3

I. Non-adrenergic non-cholinergic (NANC) neurotransmitters

- The main neurotransmitters in of the autonomic nervous system: Acetylcholine, Epinephrine, and Norepinephrine
- Some neurons use other neurotransmitters called non-adrenergic non-cholinergic (NANC) neurotransmitters
- Examples:
    1. GABA and 5-HT (serotonin): Enteric nervous system (peristalsis)
    2. Dopamine: SNS of the kidney (vasodilation)
    3. Nitric Oxide: Pelvic nerve (erection)
    4. Substance P: Enteric nervous system and sympathetic ganglia

1.5 – Functional Levels of the CNS

I. Spinal cord level

- Automatic function
- Information entering the spinal cord produces an “automated” response
    1. Reflexes are based on this principle

II. Lower brain level

- Control of subconscious reactions
- Blood pressure, heart rate, breathing
- Appetite control

III. Higher brain level

- Processing and storing information
- Perception of information
- Voluntary actions
- Memory

1.6 – Test Yourself

1) What is the function of astrocytes?

2) Why are mirror neurons important?

3) Cerebrospinal fluid produced in _____ by the _____

4) What are the 4 main neurotrophins, and what is their function?

5) What does not need carrier mediated diffusion to pass through the blood brain barrier?

6) Explain when and how a neuron can regenerate

Section 2 – Spinal Cord

2.1 – Structure and Function

- Connecting nerve pathway segments
- Forming the pathway for reflexes
- Transmitting signals of voluntary movement
- Transmitting sensory information

Structure	Vertebral level it extends to
Spinal cord	L1-L2
Subarachnoid space	S2
Cauda equina	L3

I. Lumbar puncture

- To sample CSF we can perform a lumbar puncture
- Performed between L3 and L4 or L4 and L5, to avoid nervous tissue

II. Spinal roots

- Carry neurons to and from the spinal cord
- Bell-Magendie law states that sensory impulses enter the spinal cord via dorsal roots and motor impulses leave the cord via ventral roots → <u>Impulses are conducted in only one direction</u>

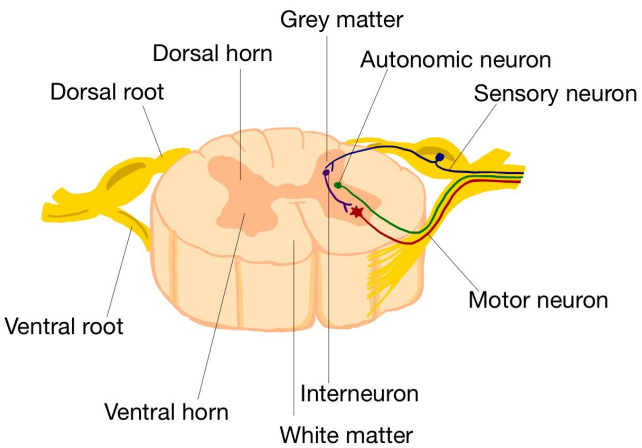
<u>CLINICAL CORRELATION</u>

Lumbar puncture

Lumbar puncture is a diagnostic or therapeutic procedure in which a needle is passed into the subarachnoid space. It enables collection or drainage of CSF as well as administration of intrathecal medications.

Indications for collection of CSF include suspicion of meningitis, subarachnoid hemorrhage, multiple sclerosis or Guillain-Barré syndrome. Drainage can also cause symptomatic relief in patients with idiopathic intracranial hypertension and normal pressure hydrocephalus.

Contraindications include bleeding disorders, infection at the puncture site or clinically suspected increased intracranial pressure (ICP). The contraindications are not absolute but increase the risk of complications.



2.1.1 – Grey and White Matter

- The grey matter = Cell bodies: Forms a butterfly-shaped area in the center of the spinal cord
- White matter = Axons: Contains fibers that make up the spinal tracts

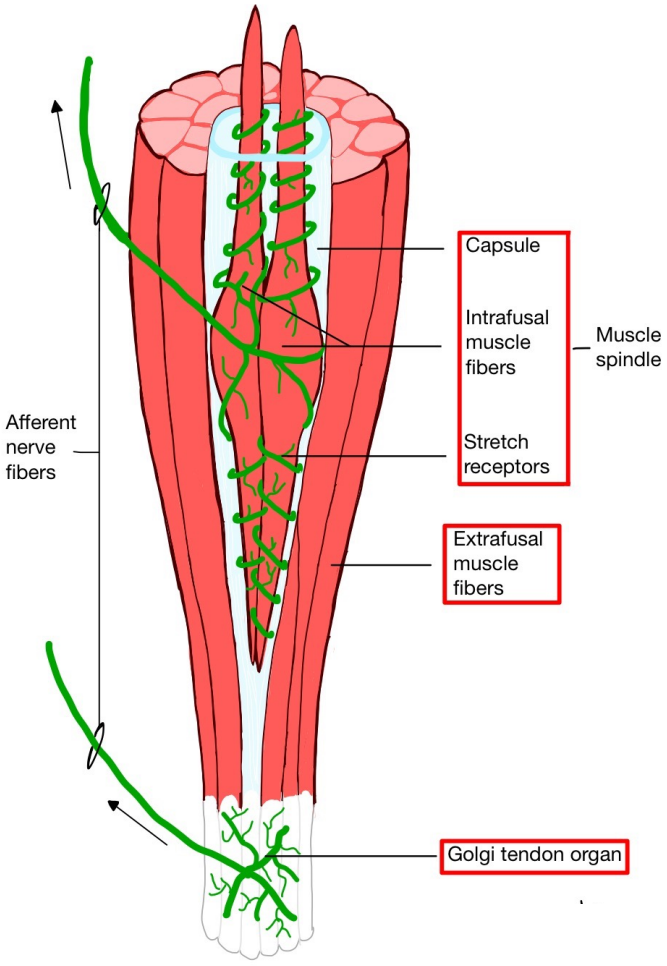
Grey matter can be divided into three sections

<table>
<tr><td rowspan="3">Ventral horn</td><td rowspan="3">Somatic motor neurons</td><td>Alpha neurons</td><td>Large diameter = High conduction velocity
Innervates extrafusal muscle fibers and cause muscle contractions</td></tr>
<tr><td>Beta neurons</td><td rowspan="2">Innervates intrafusal fibers</td></tr>
<tr><td>Gamma neurons</td></tr>
<tr><td>Intermediate horn</td><td colspan="3">Autonomic motor neurons</td></tr>
<tr><td>Dorsal horn</td><td colspan="3">Sensory neurons</td></tr>
</table>

- Motor unit: A single alpha motor neuron and all of the muscle fibers it innervates

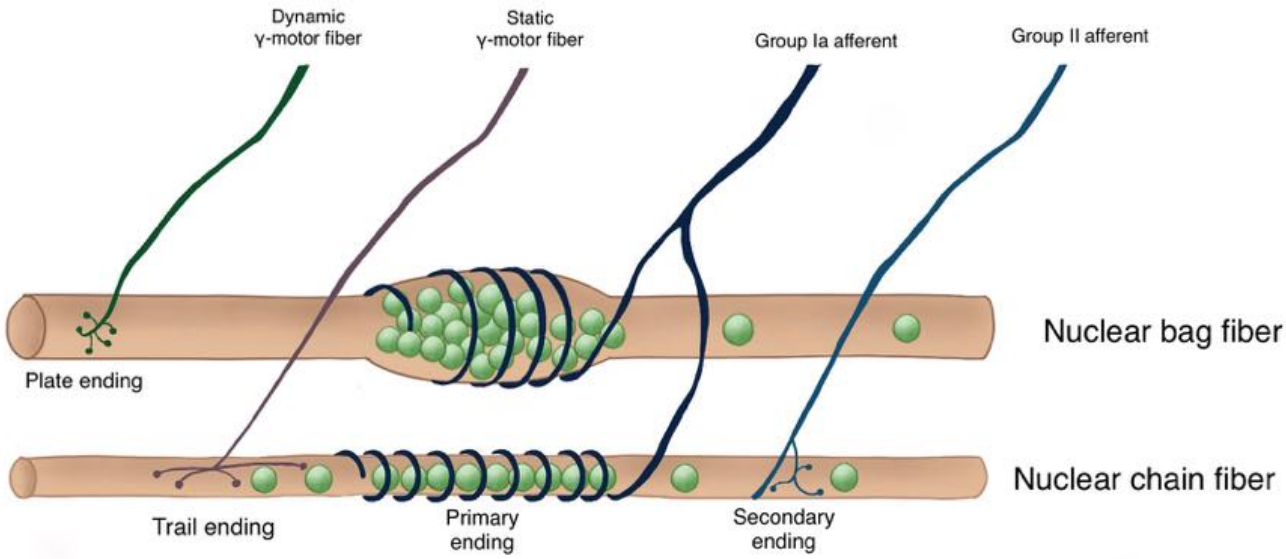
I. Intrafusal fibers

- Skeletal muscle fibers that serve as specialized sensory organs detecting the quantity and rate of change in length of a muscle
    1. Constitute the muscle spindle
- Consist of two axons - one sensory, one motor
- Walled off from other fibers with connective tissue (capsule)



Types of intrafusal fibers

Nuclear bag fibers	Nuclear chain fibers
Located in the center of a muscle spindle Contains a large number of nuclei concentrated in "bags"	Half the size of bag fibers Nuclei located in a chain



2.2 – Renshaw Inhibition

- Example of negative feedback
- Renshaw cells are inhibitory interneurons found in the spinal cord
    1. Releases GABA and glycine, the inhibitory neurotransmitters of the brain and spinal cord respectively
- Lateral inhibition - inhibits neighboring motor neurons
    1. If alpha-motor neuron is stimulated, Renshaw cells inhibit gamma and beta motor neurons
- "Sharpens" signal
- Receive an excitatory signal from the alpha neuron's axon
    1. Know how vigorously that neuron is firing

CLINICAL CORRELATION

Tetanus toxin

The Clostridium Tetani bacterium produces a toxin, tetanospasmin, which targets the Renshaw neurons.

The toxin enter the nervous system through neuromuscular junctions, travels retrogradely towards the spinal cord where it reaches the Renshaw neurons.

Tetanospasmin cleaves SNARE proteins necessary for exocytosis of GABA and glycine in the Renshaw neurons, resulting in failure of inhibitory neurotransmitter release.

The resulting loss of inhibitory signals to the muscles causes the classic tetanus symptoms (lock jaw, general spasticity etc.)

2.3 – Reflexes

- Subconscious, involuntary reaction produced in response to the stimulus applied to the receptor
- Most include some form of stretching/contraction
- Elements of a reflex
    1. Receptor (to detect stimuli)
    2. Afferent pathway of sensory neuron
    3. Integration (via interneurons, to motor neuron)
    4. Efferent pathway of motor neuron
    5. Effector

I. Clinical significance of reflexes

- Assessment of deep tendon reflexes (e.g. the knee-jerk reflex) can be helpful in determining lesions within the CNS
    1. Diminished reflexes can be a sign of a lower motor neuron lesion
    2. Hyperreflexia can be a sign of an upper motor neuron lesion
- Presence or absence of reflexes can also be helpful to determine viability of different spinal cord levels
- Presence of these reflexes indicates functional viability of transmission at this level of the spinal cord

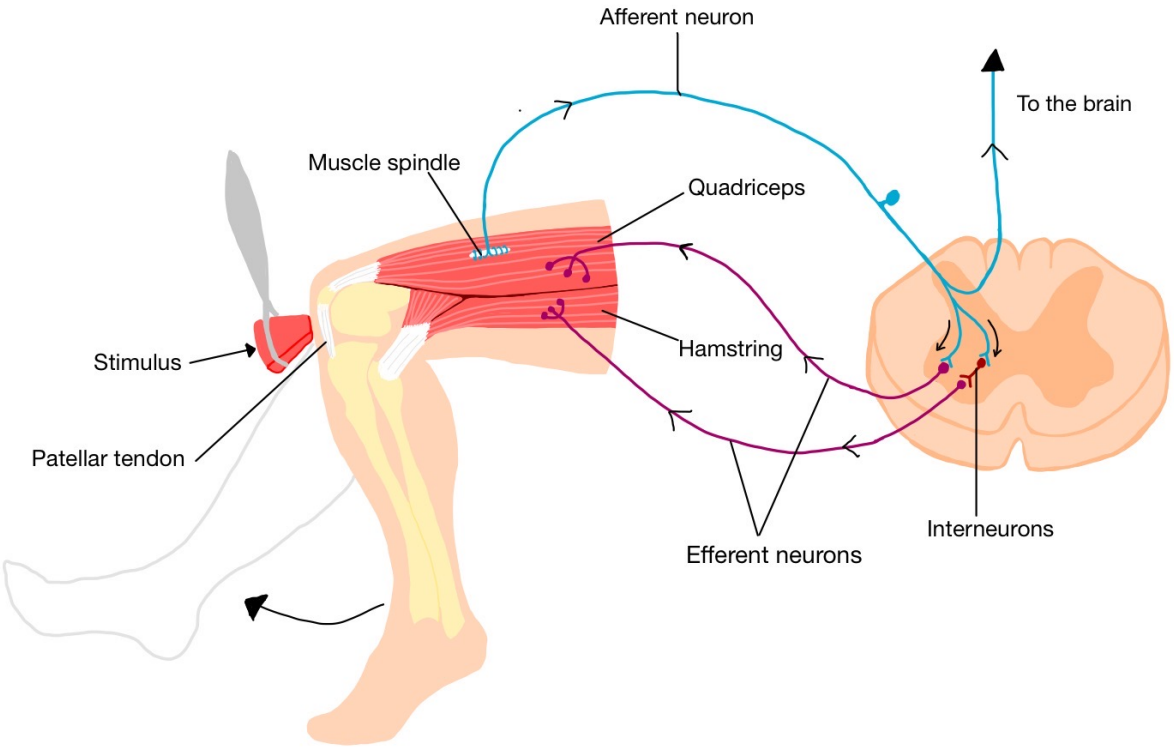
Reflex	Spinal roots involved
Biceps	C5 and C6
Triceps	C7 and C8
Abdominal	T8 - T12
Ankle jerk	S1 and S2

2.4.1 – Stretch Reflex

Stretch reflex arc		
1	Receptor	Muscle spindle – stretch of muscle spindle with intrafusal fibers
2	Afferent neuron	Ia myelinated fibrs (120 m/s)
3	Center (integration)	Monosynaptic – Single synapse to motor neuron
4	Efferent neuron	Motor axon (ventral root, via motor axon)
5	Effector	Extrafusal fibers of stretched muscle

I. Physiological significance

- Maintain muscle tone (static response)
- Adapting muscle tone to increased load
- Dynamic Response
    1. Receptor - primary endings on nuclear bag fibers
    2. Rapid discharge → rapid muscle contraction
- Static Response
    1. Receptor – primary endings on nuclear chain fibers
    2. Slow stretching → maintain the muscle tone



2.4.2 – Inverse Stretch Reflex

- Relaxation in response to strong stretch is called the inverse stretch reflex
- When the tension of muscle contraction becomes great enough, contraction suddenly ceases and the muscle relaxes

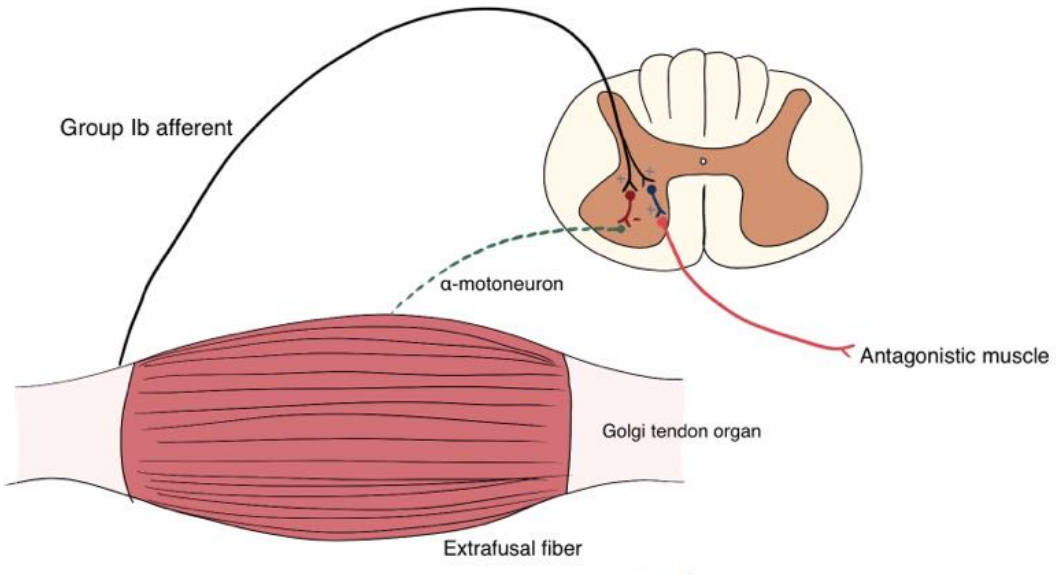
Inverse stretch reflex arc		
1	Receptor	Golgi tendon organ
2	Afferent neuron	Ib myelinated fibers – rapidly conducting
3	Center (integration)	Polysynaptic[1] Inhibition of motor neuron of contracted muscle Stimulation of antagonist muscle[2]
4	Efferent neuron	Motor axon – to antagonist muscle
5	Effector	Contracted muscle = relaxed Antagonist muscle = contracted

[1] Inhibitory interneurons = IPSP

[2] e.g. hamstring is inhibited, and quadriceps is stimulated

I. Physiological significance

- Prevention of direct muscle damage or separation of the tendon from the bone
- Maintaining the muscle tone
- Clasp-knife reflex
    1. Resistance during initial passive flexion, followed by a sudden release of tension (Like a pocket knife that is difficult to open at first, but gets easier towards the end)
    2. Suspect an upper motor neuron lesion



2.4.3 – Withdrawal Reflex

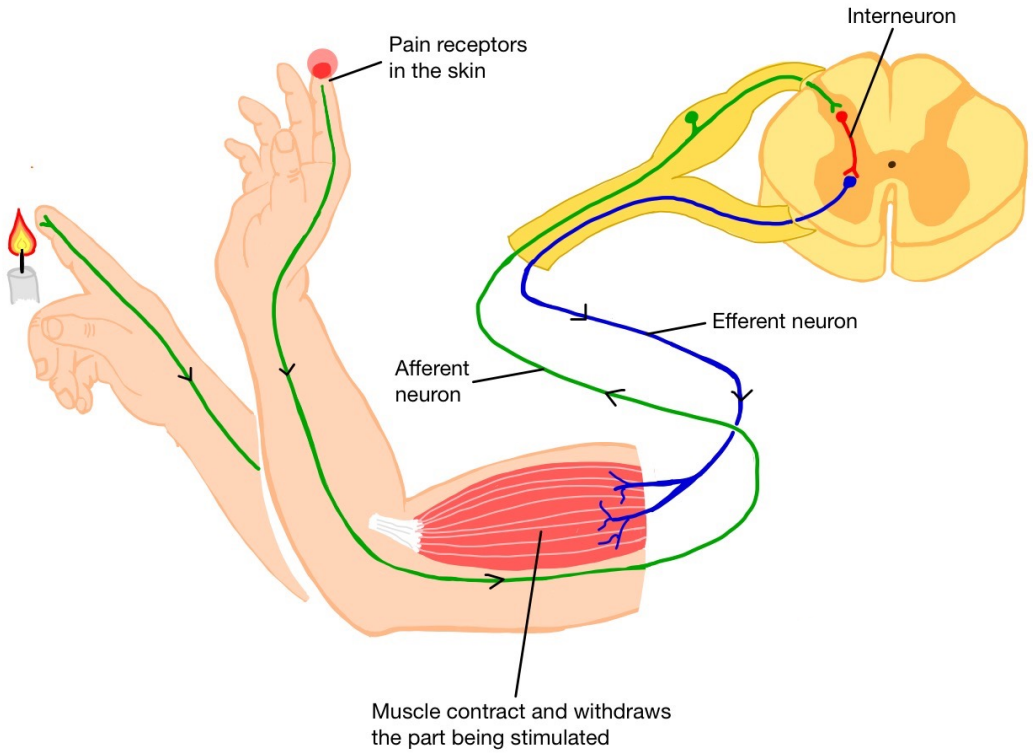
- Occurs in response to a noxious (painful) stimulus to the skin
- Response is flexor muscle contraction and extensor muscle inhibition
- Stimulated body part is withdrawn from dangerous stimuli

Withdrawal reflex arc		
1	Receptor	Naked (free) nerve endings
2	Afferent neuron	Type II, III nerve endings
3	Center (integration)	Polysynaptic[1] Inhibition of neurons of extensors Stimulation of neurons of flexors
4	Efferent neuron	Motor axon
5	Effector	Flexors = contracted Extensors = relaxed

[1] inhibitory interneurons, motor neurons

I. Physiological significance

- Protection of the body from danger
- Contribution to locomotion



2.4.3 – Crossed Extensor Reflex

- Is a withdrawal reflex
- Flexors in the withdrawing limb contract and the extensors relax
    1. The opposite occurs in the other limb
- E.g. Stepping on glass, the leg that is stepping on the glass pulls away, the other leg balances and maintains the weight of the whole body
- Also contributes to locomotion

2.5 – Spinal Shock

- During transection of the spinal cord, all functions below the point of transection are immediately blocked
- Possible effects are loss of
    1. BP
    2. Some thermoregulatory actions
    3. Spinal and sacral reflexes
    4. Sensation (depending on the level of transection)
    5. Voluntary movement (depending on the level of transection)
- After 2-5 weeks, some functions of the spinal cord may be restored
    1. Neurovegetative reflexes may return
    2. Muscle tone becomes spastic
    3. Spinal reflexes may return in hyperactive form
    4. Sacral reflexes may return (must be “trained” – e.g. urination, defecation)

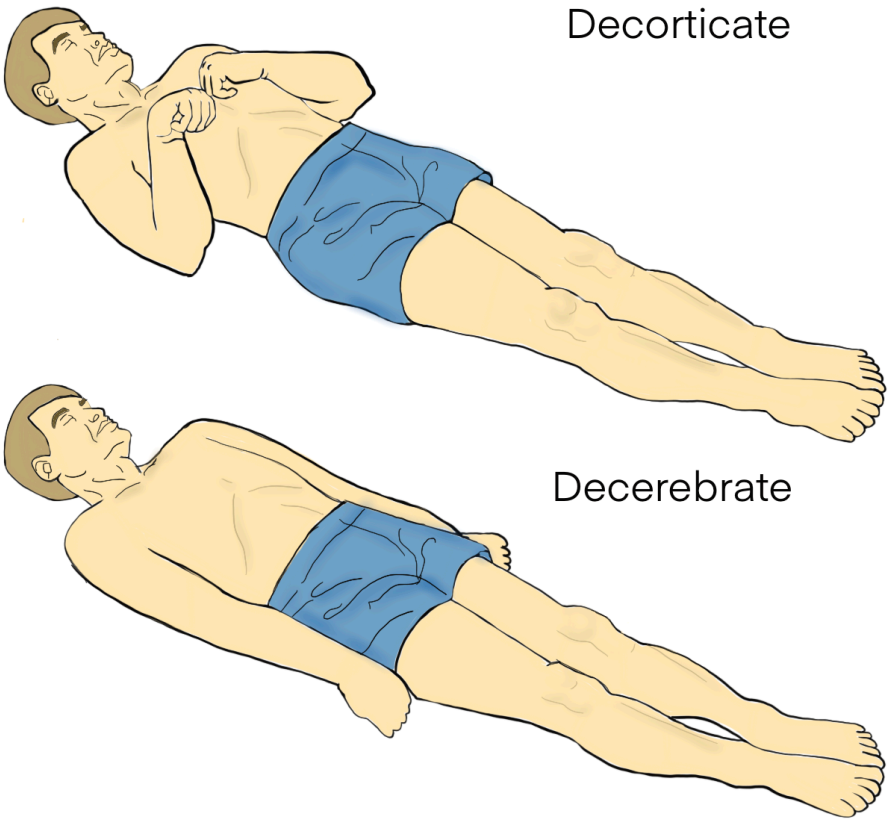
2.5.1 – Decerebrate Rigidity

- Complete transection of the brainstem between superior and inferior colliculus (aka at the superior border of the pons), causes decerebrate rigidity
    1. The transection permits the brainstem pathways to act without input from higher structures as this lesion stops all input from the cortex and red nucleus
    2. The reticulospinal tracts[1] remain intact, and dominance from ascending sensory tracts to the excitatory reticulospinal pathway leads to hyperactivity of extensor muscles in all four extremities.
- In other words the extensor muscles will stretch out the arms and legs, wrists will be pronated and feet will be plantarflexed due to the contraction of the extensor muscles.

[1] Reticulospinal tracts = Extrapyramidal motor tracts. Descend from the reticular formation in the brainstem and are involved in posture and locomotion control.

2.5.2 – Decorticate Rigidity

- Removal of the cortex (due to e.g. hemorrhage or infarction) causes decorticate rigidity
- Flexion of the upper extremities at the elbow and extensor hyperactivity in the lower extremities: The elbows are bent and legs are stretched



2.5 – Test Yourself

1) What different parts of the muscle does the alpha, beta and gamma motor neurons innervate?

2) What is the reflex arc of the inverse stretch reflex?

3) The Bell-Magendie law states that...

4) What is the function of intrafusal fibers?

5) What is the physiological role of the stretch reflex?

6) Decerebrate rigidity will occur when...

7) Explain the function of the Renshaw inhibition

Section 3 – Motor Axis

3.1 – Motor Cortex
3.2 – Corticospinal Tract
3.3 – Upper and Lower Motor Neurons
3.4 – Basal Ganglia
3.5 – Cerebellum
3.6 – Test Yourself

I. Elements needed for control of movement

- Cerebral cortex
- Basal Ganglia
- Cerebellum
- Reticular Formation
- Spinal Cord

II. Body Movement

- Voluntary movement: Pyramidal tracts (corticospinal + corticobulbar) + motor cortex
- Involuntary movement: Basal ganglia

3.1 – Motor Cortex

- Primary motor cortex (Brodmann area[1] 4)
    1. Sends impulses to the spinal cord and controls the execution of movement
- Premotor cortex
    1. Planning of coordinated, complex movements
- Supplementary motor area
    1. Planning of movement, series of movements

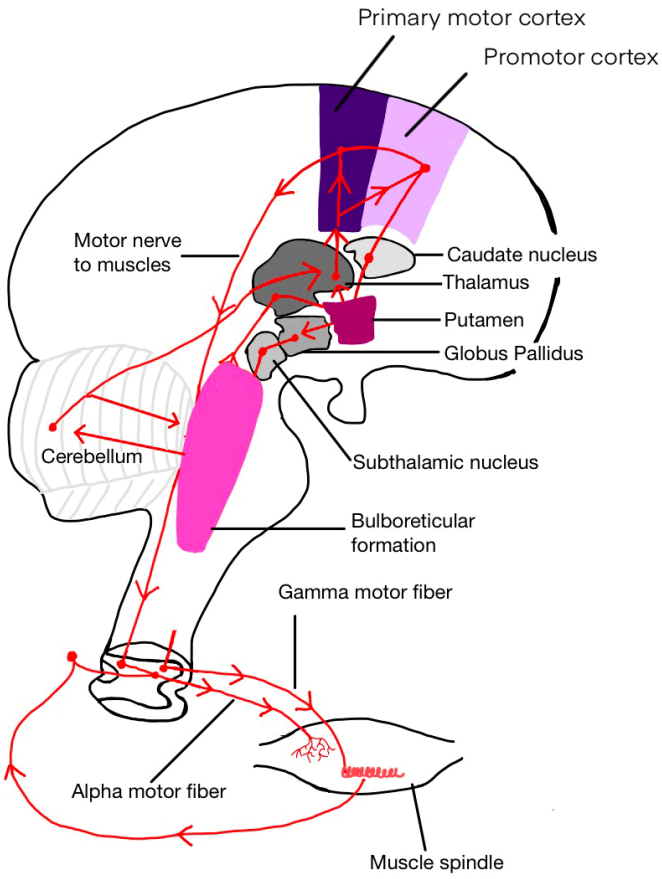
[1] Brodmann areas is a form of mapping out the brain based on the histological structure of neurons. It is a very theoretical way of organizing the brain structure.

I. Plasticity of motor cortex

- The motor cortex changes with experience
    1. E.g. Lesions can lead to rearrangement of "muscle representative areas"

II. Contralateral representation

- Motor area of the left hemisphere coordinates the movement of the muscles of the right side of the body
- Motor area of the right hemisphere coordinates the movement of the muscles of the left side of the body



3.2 – Corticospinal Tract

- Lateral corticospinal tract: Voluntary movement of contralateral limbs
- Anterior corticospinal tract: Voluntary movement of the trunk and neck
- Starts as one tract in the cortex, then divides into two, lateral and anterior tracts
- The first order neuron is an upper motor neuron (UMN)
    1. Begins in motor cortex, descends ipsilaterally through the internal capsule, most fibers undergo decussation[1] in the pyramids at the caudal medulla
    2. Continue descent on contralateral side
- The second order neuron is a lower motor neuron (LMN) with its cell body in the anterior horn of the spinal cord.
- Anterior corticospinal tract fibers do not decussate in the medulla, but at the level of the anterior horn in the spinal cord, where the LMN cell bodies are located
- Decussation is why the "left brain controls right side of the body" and "right brain controls the left side of the body"
- Destination is a neuromuscular junction

[1] Decussation = Crossing over to another side

Tract	1st and 2nd order neuron	Decussation	Function/transmission
Lateral corticospinal **80-90% of fibers**	1st - Giant cells of Betz in the precentral gyrus and anterior paracentral lobule 2nd - Motor nuclei of anterior horn of spinal cord	Pyramidal decussation Descend contralaterally	Motor function to distal musculature on the contralateral side
Anterior corticospinal **10-20% of fibers**		White anterior commissure of spinal cord at the level of the LMN they synapse with	Motor function to axial musculature of the contralateral side

3.3 – Upper and Lower Motor Neurons

- Since the corticospinal tract is transmitted via two successive neurons, we can divide the tract into upper motor neurons and lower motor neurons
- UMN have their cell bodies in the motor cortex
- LMN have their cell bodies in:
    1. Ventral horn in the spinal cord: Innervating muscles of the body
    2. Cranial nerve nuclei of the brainstem: Innervating muscles of head and neck
- Depending on whether the UMN or LMN is destroyed, muscles will present different signs of a lesion (e.g. spasticity, atrophy, hyperreflexia, fasciculations, etc.)
- Observation of these signs allow you to determine where the lesion lies, and clues you into what the disease process might be
- Some diseases, such as ALS, may have signs of both UMN and LMN lesions

CLINICAL CORRELATION

Amyotrophic lateral sclerosis (ALS)
(Lou Gehrig's disease)

ALS is a neurodegenerative disease with both upper and lower motor neuron dysfunction. The disease often begins with asymmetric weakness in the hands or feet, and eventually it spreads to the other side. Some patients present with atypical/non-specific symptoms such as subtle vocal changes.

As the disease progresses, most patients eventually develop one or both of the life-threatening symptoms: respiratory impairment and dysphagia. Most patients will die within 3–5 years, although about 20% have a chance of living longer

- **Up**per motor neuron lesions: Everything goes **up**
- **Lower** motor neuron lesions: Everything is **lower**ed

Sign	UMN lesion	LMN lesion
Weakness	Regional	Focal
Atrophy	No	Yes
Fasciculations	No	Yes
Reflexes	↑	↓
Tone	↑	↓
Babinski sign	+	-
Paralysis	Spastic	Flaccid
Clasp knife spasticity	Yes	No

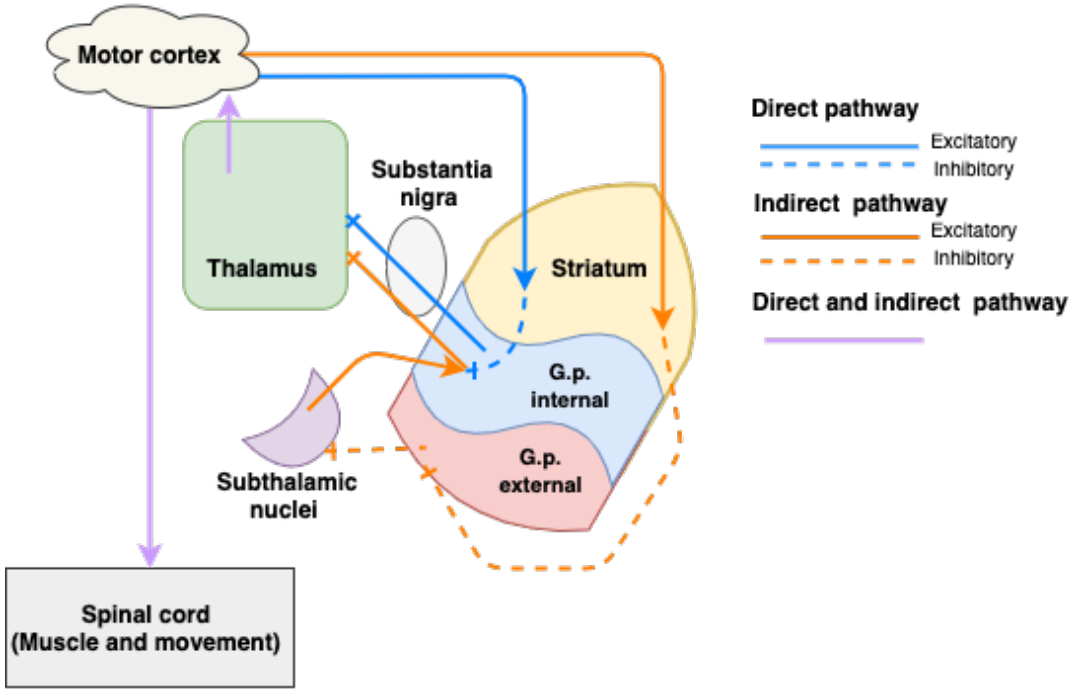
I. Tests with positive result in UMN lesions

- Babinski sign: Scratching the bottom of your foot normally causes all the toes to plantarflex[1]. In an UMN lesion, the big toe will extend (go the other way) while the other toes plantarflex – this is a positive Babinski sign.
- Rossolimo reflex: Stimulating the tips of the toes causes flexion of the toes
- Oppenheim sign: Extension of the toes induced by scratching inner side of leg

[1] Plantarflex = ankle and toes move "away" from the body

3.4 – Basal Ganglia

- Important in voluntary movements and making adjustments in posture
    1. Control scale of movement, combining planning with movement
- Receives cortical input, provides negative feedback to cortex for adjustments
- Five key components
    1. Caudate nucleus
    2. Putamen
    3. Globus pallidus (internal and external)
    4. Subthalamic nucleus
    5. Substantia Nigra
- The basal ganglia receive signals from all over the cortex, the thalamus and substantia nigra
- Striatum = putamen + caudate nucleus
- Lentiform = putamen + globus pallidus

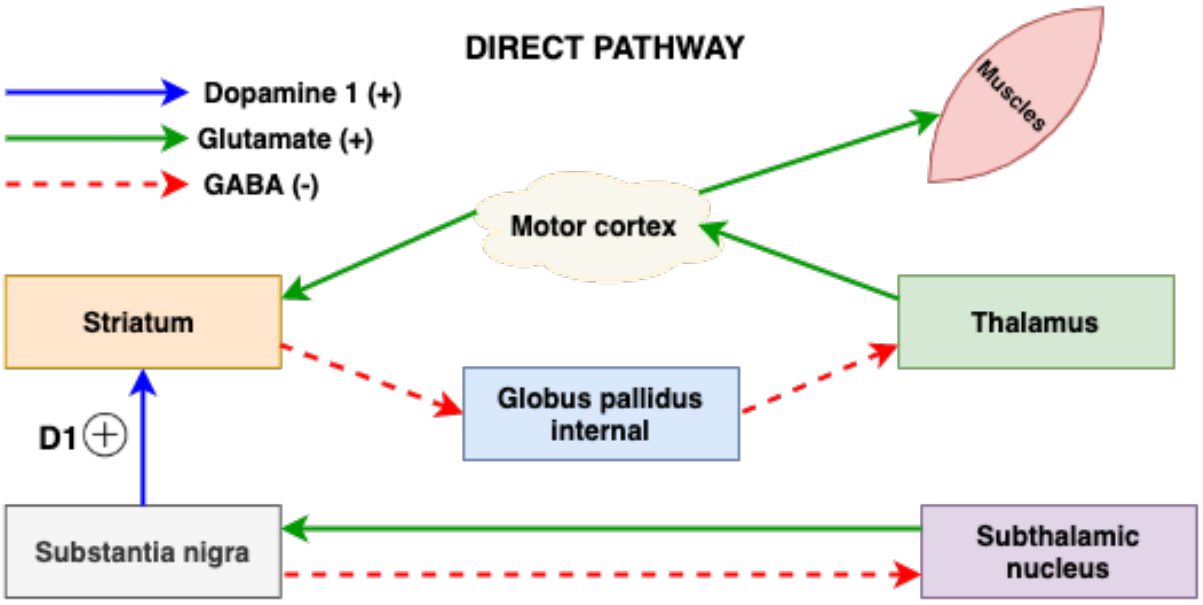


3.4.1. – Cortical-basal ganglia-thalamo-cortical loop (CBGTC)

- The basal ganglia aid in initiation of movement and control of skeletal muscles
- There are two main pathways (direct and indirect pathway), the balance between them is modulated by dopamine.

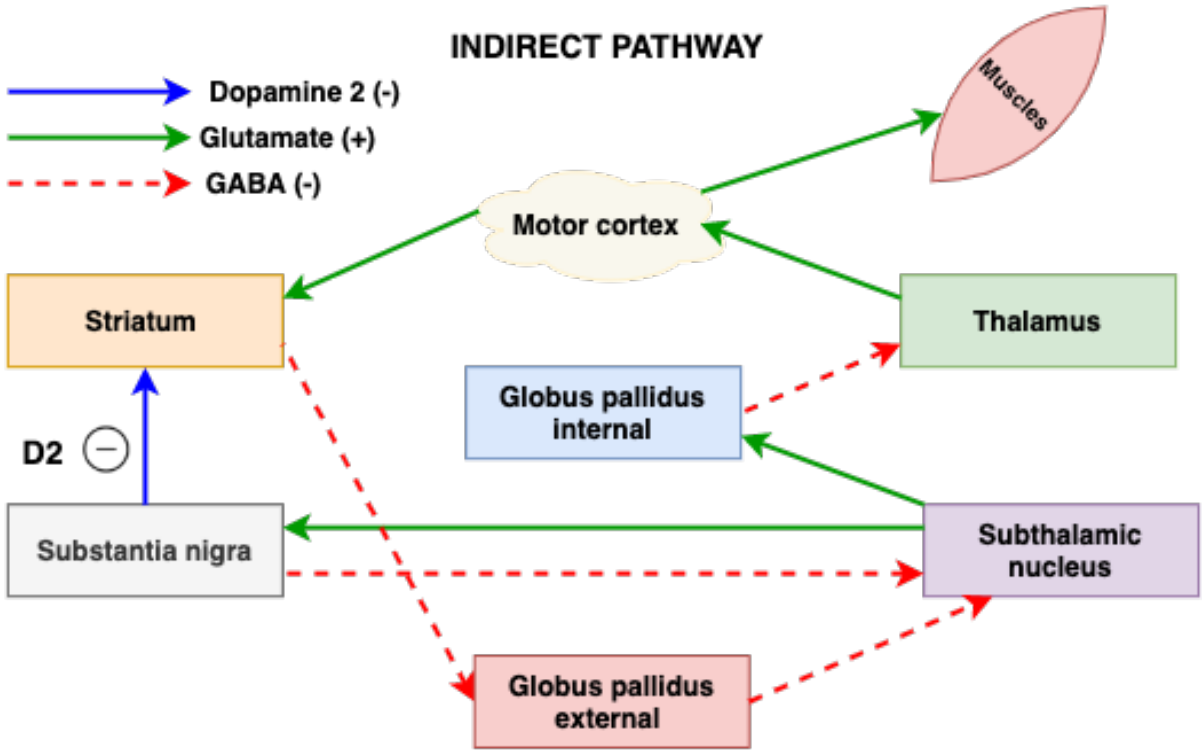
I. Direct pathway

- Function: Facilitates movement (increase in motor activity)
    1. Motor cortex stimulates striatum (**Glutamate**) → Inhibits GPi (**GABA**) → Less inhibition (disinhibition) of thalamus → Thalamus stimulates motor cortex → Activates muscles → Movement
    2. Simultaneously Subthalamic nucleus stimulates substantia nigra (Glutamate) → Substantia nigra stimulates D1 receptors in striatum Striatum (**Dopamine**) → Further inhibition of GPi (**GABA**) → see above



II. Indirect pathway

- Function: Inhibits movement (decrease in motor activity)
    1. Motor cortex stimulates striatum (**Glutamate**) → Inhibits GPe (**GABA**) → Less inhibition of Subthalamic Nucleus → More stimulation of GPi and Substantia nigra (**Glutamate**)→ More inhibition of Thalamus (**GABA**) → Less stimulation of cortex → Less stimulation of muscles → less movement
    2. Substantia nigra releases **dopamine** which stimulates D2 receptor in striatum and inhibits **GABA** release → less inhibition of GPe → inhibition of subthalamic nucleus (**GABA**)→ decreased stimulation of GPi → less inhibition of thalamus → Thalamus stimulates motor cortex → Activates muscles → movement



3.4.2 – Dysfunction of the Basal Ganglia

I. Parkinson disease

- Loss of dopaminergic neurons in the pars compacta region of the substantia nigra
- Symptoms: **TRAPS**
    1. **T**remor (at rest)
    2. **R**igidity (increased muscle tone)
    3. **A**kinesia (or bradykinesia – Difficulty initiating movements)
    4. **P**ostural instability
    5. **S**huffling gait

II. Huntington disease

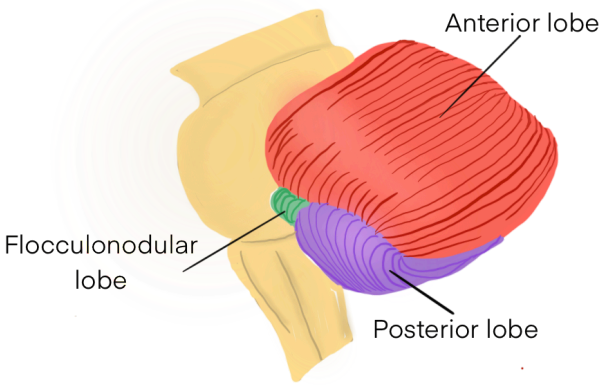
- Genetic defect on chromosome **4** (**4** letters in **hunt**)
- Trinucleotide repeat expansion (**CAG**), autosomal dominant inheritance
- Atrophy of caudate + putamen → Loss of acetylcholine and GABA
    1. Loss of GABA to external palladium releases inhibition, allowing for rapid/repetitive movements:
       Caudate loses **A**Ch and **G**ABA (**CAG**)
- Increased dopamine
- Symptoms:
    1. Chorea: repetitive/rapid movements
    2. Decreased muscle tone
    3. Aggression/depression/dementia

FUN FACT

Families who know they have the gene for Huntington disease tend to choose not to have biological children, to spare them from the disease.
Therefore, patients presenting with Huntington disease are often adopted and are unaware of the family history of the disease.

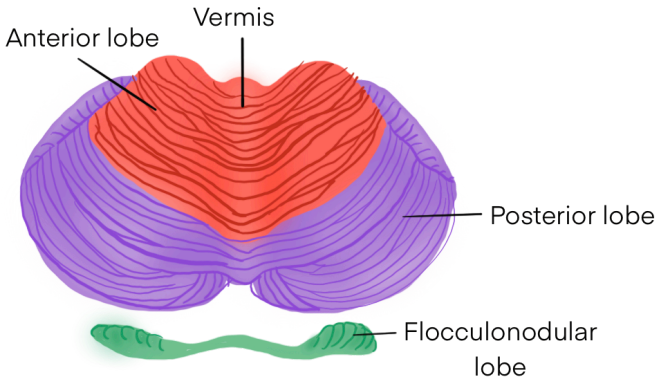
3.5 – Cerebellum

- The cerebellum is involved in the planning, coordination, and modification of motor activities



I. Anatomic division

- Anterior lobe
- Posterior lobe
- Flocculonodular lobe
- Vermis



II. Roles in movement

- Controls muscle tone
- Controls posture
- Controls muscle contraction
- Assists in planning/sequence of movement

III. Voluntary motor control

- The cortex and cerebellum are connected, and cooperate to modulate and plan voluntary movements
- Cerebellum compares intention of movement with what is actually occurring
    1. Cerebellum informs cortex about current muscle tone and body/limb position
    2. Cortex makes changes to the plan using information from the cerebellum

3.5.1 – Input to the Cerebellum

- The major input to the cerebellum is through the middle and inferior peduncles:
    1. Contralateral cortex through middle cerebellar peduncle
    2. Ipsilateral proprioceptive information from spinal cord through inferior peduncle

Afferent cerebellar tracts (information to the cerebellum)

Cerebellar peduncle	Tracts	Function
Superior Peduncle	Ventral spinocerebellar	Proprioceptive and exteroceptive impulses from the body Control of fine movement of the limbs
	Tectocerebellar	Hearing and visual from the inferior and superior colliculi, respectively
	Cuneocerebellar	Proprioceptive impulses (emphasis on head, neck)
Middle Peduncle	Pontocerebellar	Signals from motor and other parts of cerebral cortex
Inferior Peduncle	Dorsal spinocerebellar	Proprioceptive and exteroceptive reception Control of fine movement of the limbs
	Olivocerebellar	Proprioceptive input from the body
	Vestibulocerebellar	(vestibular input from labyrinths) Control of posture and equilibrium

3.5.2 – Output From the Cerebellum

- The major output from the cerebellum is through the superior peduncle
- Despite having afferent tracts, the superior peduncle contains mainly efferent tracts, providing information to the contralateral cortex about the position of the body.
- Path: Purkinje cells → deep nuclei of cerebellum → contralateral cortex through superior cerebellar peduncle
- Deep nuclei from lateral to medial: "**D**on't **E**at **G**reasy **F**oods"
    1. **D**entate
    2. **E**mboliform
    3. **G**lobose
    4. **F**astigial

I. Control of equilibrium

- Cerebellum controls balance between agonist and antagonist muscles
    1. E.g. when bicep flexes, triceps will extend
- Signals inform how rapid a movement is, and in what direction it is moving
- Signals from effectors (e.g. muscles) inform about their position and tone
- Signals from cortex relay planned sequences of movement. The cerebellum can determine where a body part will be a few milliseconds ahead

3.5.3 – Cerebellar Lesions

Symptom	Description	Physical examination
Dysmetria	Impaired coordination, overshoot or undershoot movements	Difficulty in performing finger to nose test
Ataxia	Lack of coordination due to errors in rate, force, direction of movement	Generalized difficulty in coordination: Shuffling or wide based gait, veering to one side etc.
Dysdiadochokinesia	Impaired ability to perform rapidly alternating, opposite movements	Patient is unable to quickly perform pronation, followed by supination
Dysarthria (ataxic)	Slurring of speech (Don't confuse with an aphasia!)	Slurring of speech, slow speech rate. Patient may seem "drunk"
Intention tremor	Tremor which worsens when reaching end of planned movement	During the finger-to-nose test, the patients finger will progressively "zig-zag" as it gets closer to the nose
Nystagmus	Rapid, involuntary movement of the eyes	Jerking of the eyes when patient look at your finger

3.6 – Test Yourself

1) What does "Plasticity of the motor cortex" mean?

2) What is the 1st order neuron in the corticospinal tracts?

3) At what level does the lateral corticospinal tract decussate?

a) Midbrain
b) Medulla
c) White anterior commissure in the spinal cord
d) Does not decussate

4) Babinski sign will be positive with a lesion in

a) Upper motor neuron
b) Lower motor neuron
c) Both

5) What are characteristic signs for a lower motor neuron lesion?

a) Positive Babinski sign, fasciculations, increased muscle tone and flaccid paralysis
b) Flaccid paralysis, hyporeflexia, muscle atrophy and negative Babinski sign
c) Clasp knife spasticity, hyperreflexia, negative Babinski sign and fasciculations
d) Muscle atrophy, muscle weakness, spastic paresis and hyporeflexia

6) What is the cause of Huntigton's disease?

7) What does the patient have difficulty with if he/she has ataxia?

8) Explain the pathway and function of the direct pathway of the Basal ganglia

Section 4 – Sensory Axis

4.1 – Functional Components of the Cranial Nerves

- A nerve can have different fibers depending on what type of information they process. Therefore the cranial nerve fibers can be categorized by 3 elements:

<table>
<tr><td rowspan="2">Type of sensation</td><td>Special</td><td colspan="2">Vision, taste, smell and hearing</td></tr>
<tr><td>General</td><td colspan="2">Pain, touch, pressure etc.</td></tr>
<tr><td rowspan="3">Intention</td><td>Visceral</td><td colspan="2">Nerve fibers with axonal endings in the viscera[1], glands and vessels
Transmits information about pain and distension of viscera Comparable to the autonomic motor fibers</td></tr>
<tr><td rowspan="2">Somatic</td><td rowspan="2">Information about body position, movement and contact with external factors
Comparable to the somatic motor fibers</td><td>Exteroceptive
Skin receptors
Info about external environment, perception of touch, superficial pain, temp</td></tr>
<tr><td>Proprioceptive
Joint receptors
Info about body position and movement</td></tr>
<tr><td rowspan="2">Direction of impulses</td><td>Afferent</td><td colspan="2">Impulses back to brain (Sensory)</td></tr>
<tr><td>Efferent</td><td colspan="2">Impulses from the brain to the tissues (Motor)</td></tr>
</table>

[1] Viscera = Internal organs in the main body cavities, e.g. intestines

- Combining these three words provides a lot of information about the fiber type in nerves
- Each cranial nerve can have more than one type of fibers, as they have more than one function

General somatic afferent (GSA)	Fibers from the skin and striated muscle
General visceral afferent (GVA)	Fibers convey impulses from the viscera and blood vessels
General visceral efferent (GVE)	Fibers innervate smooth muscle in viscera, intraocular muscles, heart, salivary gland etc.
General somatic efferent (GSE)	Fibers innervate striated muscle.
Special somatic afferent (SSA)	Fibers conduct from the retina and auditory and vestibular apparatus
Special visceral afferent (SVA)	Fibers conduct impulses from the taste buds of the tongue and from the olfactory mucosa
Special visceral efferent (SVE)	Fibers innervate muscle derived from the brachial arches (branchiogenic efferents and branchiogenic muscles.

4.1.1 – Classifying Receptors Based on Their Location

Receptor	Location	Function
Interoceptors or visceroceptors	Body cavities	Information about events in the viscera Blood pressure, glucose levels
Exteroceptors	Skin	Information about the external environment Touch, temperature, tickling, itching
Proprioceptors	joints, tendons, ligaments, muscles	Information about body position and movement Proprioception

4.2 – High Yield Receptors

Type	Responds to	Location	Adaption
Free Nerve Endings	Pain/Temperature	Skin/some viscera	Slow/Quick
Meissner Corpuscles	Fine/Light Touch	Hairless skin	Quick
Merkel Discs	Pressure	Fingertips/Superficial Skin	Slow
Pacinian Corpuscles	Vibration/Pressure	Deep Skin/Joints	Quick
Ruffini Corpuscles	Pressure/Skin Stretch/Joint Angle Change	Fingertips/Joints	Slow

I. Receptor specificity

- Receptors are able to respond to a form of energy different than typical stimulus but the threshold for such a sense is higher
    1. E.g. If you close your eyes and press them, you initiate mechanical stimulation and the colors change

II. Muller law

- Principle that each type of sensory nerve cell normally responds to only one specific stimulus and gives rise to one sensation
    1. A cell may be excited artificially by other forms of stimuli (eye rubbing above), but the sensation evoked will be the same
- In other words: the sensation triggered is dependent on the kind of stimulated receptor, not on the energy applied to the receptor

III. Law of projection

- The conscious sensation produced is referred to the location of the receptor
- Independent of where the pathway was stimulated
    1. E.g. phantom limb (patient feels pain in a limb that was amputated)

IV. Sensory transduction

- Stimulus finds itself at sensory receptor
    1. E.g. light hitting rod/cone, sodium receptor on the tongue
- Membrane conduction changes (allows current to flow, depolarization)
    1. Exception: Photoreceptor, hyperpolarization
- If these changes are large enough, and membrane potential exceeds the required threshold, action potential continues down sensory neuron
    1. Receptor potential is recorded from receptors: amplitude is directly proportional to the intensity of the stimulus
    2. Action potential is recorded from sensory nerves: frequency of action potential is proportional to the intensity of stimulus

4.3 - Sensory Adaptation

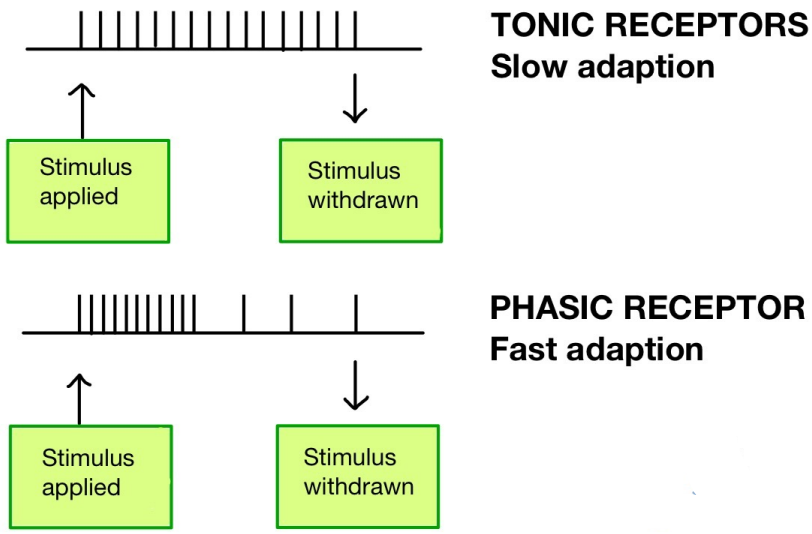
- Desensitization
- Continuous application of stimulus to a receptor leads to decreased frequency of action potentials in the sensory nerve
- The degree to which adaptation occurs depends on the type of sensory receptor

I. Tonic receptors

- E.g. Proprioceptors
- Adapt *slowly*
    1. Sometimes non-adaptive
    2. Continuous registration of receptor activation
    3. Plays active role in homeostasis due to constant update in registration

II. Phasic receptors

- E.g. touch receptors
- Adapt *rapidly*
    1. Registration of the start and of the end of stimulation
    2. Registration of the rate of change



4.4 – The Sensory Unit

- Sensory axon with all its peripheral branches
- Receptive field is the area innervated by a single sensory unit
- Recruitment of sensory units depends on the strength of the stimuli
    1. Weak stimulus → Activation of a receptor with the lowest threshold
    2. Stronger stimulus → Activation of receptors with higher threshold → Increased frequency from the unit
    3. Stronger stimulus → More units fire → More afferent pathways transmit the information to the brain → Brain interprets this as an increase in stimulus intensity

I. Two point discrimination

- How far apart do two separate points on the skin need to be before they are perceived as two points rather than one?
    1. Depends on the location on the body, directly relating to density of receptors
- E.g. Fingers are more receptor dense, skin on the back is less receptor dense → Stronger two point discrimination on the finger than on the back

4.5 – Processing of Information

I. Role of thalamus

- Information from different body parts is processed in the thalamus, which then relays the information to the appropriate parts of the sensory cortex
- Destruction of thalamic nuclei (e.g. a thalamic stroke) results in loss of sensation on the contralateral side of the body
- The thalamus typically contain the third-order neurons of the sensory tracts

High yield thalamic nuclei

Nuclei	Input	Sensation	Destination
Ventral **P**ostero**L**ateral	Spinothalamic + dorsal column/medial lemniscus	**V**ibration **P**ressure, **P**ain, **P**roprioception **L**ight touch Temperature	Somatosensory cortex
Ventral postero**M**edial	Trigeminal + gustatory[1] pathways	**Face** sensation "We put **M**akeup on the **face**"	
Lateral geniculate	CN II, optic chiasm + optic tract	Vision "**L**ateral = **L**ight"	Visual cortex
Medial geniculate	Superior olive + inferior colliculus	Hearing "**M**edial = **M**usic"	Auditory cortex
Ventral lateral	Cerebellum + basal ganglia	Motor	Motor cortex

[1] Gustatory = Taste

II. Somatic cortex

- "Decodes" the sensory signals
- Somatosensory area I - postcentral gyrus (parietal lobe 3, 1, 2)
- Somatic sensory cortex II – superior wall of sylvian fissure
- Plasticity of sensory cortex
    1. Ability to change the representative area of the cortex by experience: "rewiring" axons, dendrites of neurons
    2. In general, sensory unit connections to cerebral cortex became stronger with usage, weaker with a lack of usage

4.6 – High Yield Ascending Tracts

Tract	1st, 2nd + 3rd order neurons	Decussation	Sensation
Anterior spinothalamic Ascends in anterior white column	1: Dorsal root ganglion (no synapse here) 2: Nucleus in dorsal horn of spinal cord 3: Ventral Posterolateral nucleus (thalamus) Ends in primary sensory cortex	Anterior white commissure Ascends *contralaterally* in spinal cord	Crude touch and pressure
Lateral spinothalamic Ascends in lateral white column	1: Dorsal root ganglion (no synapse here) 2: Nucleus Proprius and/or Substantia Gelatinosa of dorsal horn of spinal cord 3: Ventral Posterolateral nucleus or reticular formation (thalamus) Ends in primary sensory cortex		Pain Itching Temperature
Dorsal Column-Medial Lemniscus (Spinobulbothalomocortical) *"C comes before G in the alphabet, therefore Cuneate have the fibers from above T4"*	1: Dorsal root ganglion (no synapse here) 2: Cuneate (from above T4) + Gracile nuclei (from below T4) 3: Ventral posterolateral nucleus Ends in primary sensory cortex and posterior paracentral lobule	Medulla Ascends ipsilaterally in spinal cord Decussate as internal arcuate fibers in the medulla then becomes medial lemniscus	Fine touch (2 point discrimination) Pressure Vibration Proprioception

4.7 – Pain

- Protective mechanism for the body to remove dangerous stimuli
- Receptors for pain are *free nerve endings*
    1. Detect thermal, chemical, and mechanical noxious stimuli
- Pain can be arbitrarily (for the purposes of this course) divided into two types

	Fast pain	**Slow pain**
Type of fiber	A delta fibers (6 - 36 m/s) Myelinated	C fibers (0,5 - 2 m/s) Non-myelinated
Neurotransmitter	Glutamate	Substance P
Type of pain sensation	Fast, sharp	Weak burning pain
Stimuli	Acute mechanical or thermal stimuli	Prolonged mechanical or thermal stimuli
Localization of pain	Very exact when stimulated together with tactile receptors	Poor localization
Destination of signals	Thalamus (ventrobasal complex)	75 – 90 % of fibers terminated in Reticular Formation (RF)

4.7.1 – Analgesic System

- Refers to the system which <u>reduces</u> pain
- Gate Control Theory
    1. When fibers larger than the pain fibers fire, the “pain gate” close, preventing the pain transmission from reaching the CNS
- Analgesic nerve fibers produce endogenous painkillers: the opioid substances (e.g. enkephalins, endorphins, dynorphin). These inhibit pain transmission
    1. Signals from raphe nuclei → interneurons release endogenous opioids → pain gate closes
- Neuromodulators of pain
    1. Serotonin (of the raphe nuclei)
    2. Enkephalins, endorphins, dynorphins

4.7.2 – Other Types of Pain

I. Visceral pain

- Poorly localized and frequently are accompanied by sweating and changes in BP
- Associated with autonomic sensations (nausea, vomiting)
- Receptors for pain in the viscera are similar to those in skin
    1. No proprioceptors in the viscera
    2. Few temperature and touch receptors
    3. Nociceptors are present, although not very well distributed

II. Referred pain

- Discomfort of a visceral organ frequently produces pain that is felt in a structure that can be distant from the actual location of pain
- There are multiple theories of this phenomenon, two of which are described here.
- Dermatome theory: When pain is referred, it is usually to a structure that developed from the same embryonic segment (dermatome) as the structure in which the pain originates
    1. E.g. heart and arm came from the same segment, during a myocardial infarction, pain is often felt in the left arm
- Theory of convergence: Convergence of somatic/visceral pain fibers to the same neurons in the dorsal horn that project to the thalamus and then to the sensory cortex

III. Parietal pain

- Typically occur as a result of irritation of visceral membranes
- Described as sharp, strong pain
- Typically well localized

4.8 – Thermal Sensation

I. Heat receptors

- React between 30 - 50 ℃
- Pain receptors stimulated by heat > 45 ℃
- Heat receptors typically begin to fail around 45 ℃, at which point nociceptors (pain receptors) begin to kick in
- Overlap exists at midrange temperatures
- Transduction of warm temperatures involves transient receptor potential (TRP) channels
    1. There are many - e.g. vanilloid receptor 1 (VR1) and VRL-1
    2. These channels are also activated by substances from the vanilloid class (e.g. capsaicin found in hot peppers)
- Transmission of thermal sensation via the anterolateral pathway
    1. Through reticular formation → thalamus → sensory cortex

II. Cold receptors

- React between 5 - 40 ℃
- Pain fibers stimulated by cold at <10 ℃
- Transduction of cold temperatures involves a different class of TRP channels (e.g. TRPM8)
    1. Also sensitive to menthol

4.9 – Test Yourself

1) Meissner corpuscles are found in _____and responds to _____

2) The Muller law states that...

_____

_____

_____

3) Phasic receptors adapts _____, while tonic receptors adapts_____ (slow or fast)

4) Anterior spinothalamic tract decussates in

a) Spinal cord
b) Medulla
c) Midbrain
d) Thalamus
e) Does not decussate

5) What sensations are transmitted by the lateral spinothalamic tract?

_____

_____

_____

6) _____ fibers transmits the slow pain, while _____ fibers transmits fast pain

7) Which tract is responsible for the transmission of proprioception?

a) Anterior spinothalamic
b) Lateral spinothalamic
c) Dorsal column/medial lemniscus
d) A and B

8) Describe the pathway and sensory information transmitted by the Dorsal Column Medial Leminiscus

1st order neuron:

2nd order neuron:

3rd order neuron:

Decussation:

Sensory information:

Section 5 – Activation of the Brain and Sleep

5.1 – Electroencephalogram
5.2 – Brain Waves
5.3 – Sleep
5.4 – Circadian Rhythm

I. Awareness

- Relaxed awareness
- Awareness with concentrated attention

II. Reticular formation

- Located in the central portion of the medulla and midbrain
- Contains the cell bodies and fibers of many systems:
    1. Basic life functions: Regulation of heart rate, blood pressure, respiration
    2. Sensory systems: Connections from ascending sensory tracts, trigeminal, auditory, olfactory, visual systems, descending motor tracts
- Ascending reticular activating system: Regulates brain wakefulness
- Descending reticulospinal tracts: Regulation of muscle tone and spinal reflexes
    1. Facilitatory area: Increases muscle tone, controls reflexes. Spontaneous neuron discharge.
    2. Inhibitory area: Reduces tonic signals, decreases muscle tone. Driven by higher neural centers.

III. Reticular activating system

- Controls level of consciousness
    1. E.g. if you are sleeping, the reticular activating system (RAS) determines whether stimulus around you is important enough that you wake up
- Pathway arises from the brain stem reticular formation and hypothalamus
- Connections to the intralaminar and reticular nuclei of the thalamus
- Non-specific system
- Anesthetics decrease conduction in RAS by blocking parts of synaptic connections → loss of consciousness

CLINICAL CORRELATION

Anesthesia

Anesthesia is a state of controlled, temporary loss of sensation or awareness that is induced for medical purposes. It may include some or all of analgesia, paralysis, amnesia and unconsciousness.

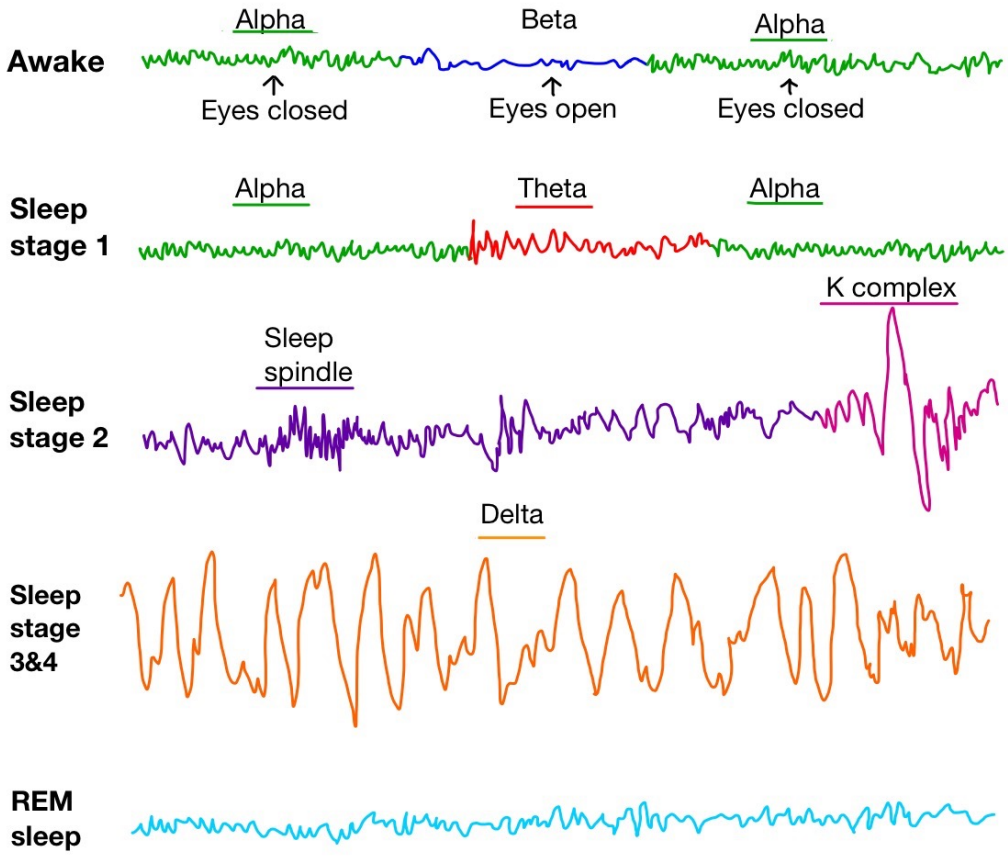
Anesthesia enables the painless performance of medical procedures that would otherwise be intolerable for the patient.

5.1 – Electroencephalogram (EEG)

- Non-invasive method used to measure the electrical activity of the brain via electrodes attached to the skull
- Alternating excitatory and inhibitory signals at synapses produces an extracellular current flow large enough for the electrodes on the skull to detect
- These signals are not action potentials, as they would be too weak for the electrodes to detect.
- EEG activity always reflects the sum of the synchronous activity of thousands or millions of neurons that have similar spatial orientation
- Synchronization: Produces a wave with larger amplitude on EEG
    1. Observed when large groups of neurons fire at the same time
    2. Example of spatial summation
- Desynchronization: Produces a wave with smaller amplitude on EEG
    1. Decreases in oscillatory activity are referred to as event-related desynchronization
    2. Simultaneous unrelated neuron events lead to cancelling each other out

5.2 – Brain Waves

Alpha Rhythm	Observed at rest, awake, eyes closed Most observed in the parietal and occipital lobes Associated with decreased levels of attention
Beta Rhythm	Alert, active mental concentration, eyes open Highest frequency, lowest amplitude Mostly observed in the frontal leads Also occurs during REM sleep (see below)
Theta Rhythm	Light sleep, occurs during stage N1 Hypothesized for memory consolidation
Delta Rhythm	Low Frequency, high amplitude Seen during stage N3 of sleep Deepest non REM sleep Associated with sleepwalking, night terrors
Seizure	Occurs when there is a sudden abnormal discharge of electrical activity in the brain Characterized by synchronized, high frequency neuronal firing EEG is useful in finding the defective area of the cortex



5.3 – Sleep

- Sleep is regulated by circadian rhythms
- Controlled through Suprachiasmatic Nucleus (SCN) of hypothalamus
    1. Regulated by levels of light
- Two stages of sleep
    1. Rapid eye movement (REM) - also called paradoxical sleep
    2. Non rapid eye movement (NREM)
- The entire sleep cycle takes between 90-120 min in the average adult
- REM = Rapid eye movement
- At night **BATS** **D**rink **B**lood:

MNEMONIC

Supra**C**hiasmatic **N**ucleus
=
Sun **C**ensing **N**ucleus

Awake	
Eyes open	**B**eta Waves
Eyes closed	**A**lpha Waves
Non REM sleep	
Stage N1 (shortest)	**T**heta waves Light sleep, hypnic jerks
Stage N2 (longest)	**S**leep spindles and K complexes Sleeper easily awakened
Stage **N3**	**D**elta waves Deepest Non REM sleep Bedwetting + sleepwalking: wee and flee in **N3** Right before REM sleep, **PGO** spikes can be observed: Waves begin as electrical pulses from the **P**ons Move to the lateral **G**eniculate nucleus residing in the thalamus Finally end in the visual cortex of the **O**ccipital lobe
REM sleep – occurs every 90 minutes, duration increases through the night	
Beta waves Paradoxical sleep: Brain waves most similar to awake state, but the person is most difficult to wake Loss of motor tone Increased brain oxygen consumption Increased and variable pulse and blood pressure Dreams from this state can be recalled As age increases, amount of REM sleep decreases Sleep, especially REM sleep, is necessary for learning and memory consolidation	

5.4 – Circadian Rhythm

- Controls night release of ACTH, prolactin, melatonin, norepinephrine
- Mediated via the Suprachiasmatic nucleus
- SCN → norepinephrine release → pineal gland → melatonin
- Regulated by light hitting vs. not hitting the retina
- Light inhibits the pathway of production of melatonin (not produced during the day whilst exposed to sunlight)

5.6 – Test Yourself

1) The longest phase of NREM sleep is:

a) N1
b) N2
c) N3

2) Suprachiasmatic nucleus is responsible for regulating...

3) Which sleep phase is characterized by sleep spindles and K complexes?

a) N1
b) N2
c) N3
d) REM

4) What is the function of RAS (Reticular Activating System)?

5) What does the EEG show us?

6) Describe the different characteristics of the 4 types of brain rhythms:

1:
2:
3:
4:

7) Explain what happens with the body during REM sleep and why is it important

Section 6 – Hypothalamus and the Limbic System

6.1 – Hypothalamus

- Center of complex mechanisms that maintain the homeostasis of the body

Structures	Anterior Hypothalamus Tuberal Hypothalamus Posterior Hypothalamus Lateral area Ventromedial area
Afferent connections from	Limbic system Brain stem Thalamus
Efferent connections to	Thalamus Brain stem Pituitary gland

I. Role of the hypothalamus

TAN HATS

- **T**hirst and water balance (osmolarity control)
- **A**denohypophysis control (adenohypophysis = anterior pituitary)
- **N**eurohypophysis releases hormones produced in the hypothalamus
- **H**unger regulation
- **A**utonomic regulation
- **T**emperature regulation
- **S**exual urges

II. Relationship with the pituitary gland

- The posterior pituitary[1] is a collection of axonal projections from the hypothalamus that terminate behind the anterior pituitary
- Serves as a site for the secretion of posterior pituitary hormones oxytocin and ADH[2]
- Hypothalamic–posterior pituitary system consists of:
    1. Hypothalamus (specifically the paraventricular nucleus and supraoptic nucleus)
    2. Posterior pituitary
    3. Axonal projections

[1] Posterior pituitary = Neurohypophysis

[2] ADH = Vasopressin

III. Regulation of food intake

	Lateral	**VentroMedial**
Feeling	Hunger Chronically active, only temporarily inhibited by the ventromedial area (satiety)	Satiety (feeling full)
Result of lesion	Anorexia "**L**ateral injury makes you **L**ean"	Increased appetite (hyperphagia) "**V**entro**M**edial injury makes you **V**ery **M**assive"
Stimulated by	β-endorphins Neuropeptide Y Orexins A and B Ghrelin Melanin-concentrating hormone	Leptin CCK CRH Bombesin Glucagon GLP-1,GLP-2 Oxytocin Somatostatin PYY

IV. Regulation of ECF osmolarity and volume

- Hypertonicity occurs → osmoreceptors activated → signal to hypothalamus → increased thirst
- Hypovolemia occurs → baroreceptors activated → Release of Angiotensin II (pathway) → ADH
    1. Water retention by renal system

See Section 9.0.1 – Water Balance in the Studyaid Renal Physiology booklet for further explanation.

V. Hypothalamus and stress

- Regulation of hormone release
- Control over autonomic system
    1. Heart rate, BP, respiration etc.

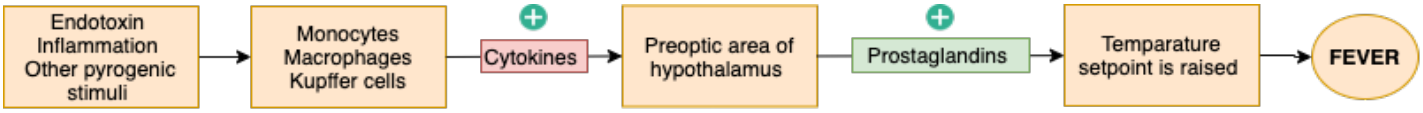
6.2 – Temperature Regulation

Hypothalamus	Anterior	Posterior
Responsibility	Cooling the body	Heating the body
Part of nervous system involved	Parasympathetic	Sympathetic
Mechanism of action	Sweat Increased rate of respiration Cutaneous vasodilation Decreased rate of physical activity, muscle relaxation Decrease in appetite Increased thirst	Shivering Cutaneous vasoconstriction Increased muscle movement (e.g. shivering) Horripilation response (“goose bumps”) In babies, brown adipose tissue activation

I. Regulated changes of body temperature

- Lowest levels around 4 a.m. and the highest in the late afternoon
- Menstrual cycle mildly increases the body temperature due to the effect of progesterone
- Physical activity increases body temperature

6.2.1 – Fever



- Endotoxins stimulates monocytes, macrophages and kupffer cells[1] to produce cytokines[2] , which reaches the OVLT[3] of the hypothalamus which then activates the Preoptic area.
- Via release of prostaglandins (e.g. PGE2) the temperature set point is raised, and you have fever in the body.

[1] Subset of macrophages in the liver
[2] e.g. IL-1, IL-6, TNF-a
[3] Organum vasculosum of the lamina terminalis

I. Benefits of fever

- Inhibition of bacterial growth
- Stimulation of antibody production
- Decrease of tumor growth

6.3 – Limbic System

- Collection of neural structures involved in emotion, long term memory, behavior modulation (e.g. motivation, addiction), ANS function, sexual behavior, olfaction
- Structures include
    1. Allocortex
    2. Hippocampus
    3. Parahippocampal gyrus
    4. Cingulate gyrus
    5. Olfactory bulb
    6. Orbitofrontal part of frontal lobe
    7. Amygdala
    8. Septal Nuclei
    9. Hypothalamic Nuclei

I. Hypothesis of emotional states

- Two systems related to hypothalamus and limbic system
    1. System promoting rage
    2. System promoting placidity
- Emotional state depends on the balance between rage and placidity

Disclaimer: The remaining part of the limbic system chapter is still highly theorized and under research, but there will most definitely be questions about it so here is what is presented during the lectures

II. Amygdala

- Important structure of the limbic system
- Believed to be responsible for strong (negative) emotions such as rage and fear
- Stimulation of amygdala for example causes
    1. Rage reaction
    2. Pain
    3. Punishment

CLINICAL CORRELATION

Klüver-Bucy syndrome
Caused by destruction of amygdala.
Symptoms:
Loss of fear
Extreme curiosity
Increased sex drive
Tendency to put everything into the mouth

6.4 – Reward and Punishment System

- Reward involves dopaminergic system
    1. Nucleus accumbens
    2. Ventral tegmentum
    3. Dorsal brain stem
- Punishment involves cholinergic system
    1. Posterior hypothalamus
    2. Dorsal midbrain
    3. Entorhinal cortex

I. Addiction

- Repeated compulsive use of a substance despite of its negative effects (opiates, drugs, alcohol, nicotine etc.)
- Each system affects the brain in different ways, but all increase the quantity of dopamine available to bind with D3 receptors in the nucleus accumbens.

Dopaminergic systems (noted associations)	Serotonergic System
Nigrostriatal system Mesocortical system (n. Accumbens) Tubero-infundibular system (PRL secretion) Interohypothalamic system Dopaminergic receptors overstimulation: D2 – Role in schizophrenia D3 – Role in addiction	Key neurotransmitter of the body: Decreased [serotonin] can lead to anxiety and depression Produced in the Raphe nuclei (pons, midbrain, medulla) Receptors for serotonin are called 5-HT 5-HT receptors bind a broad range of pharmaceutical and hallucinogenic drugs Drugs that primarily affect 5HT2 receptors: LSD, Psilocin, Mescaline

6.5 – Test Yourself

1) Name the functions of the hypothalamus:

2) The area of the hypothalamus responsible for hunger is the _____, and the are area responsible for satiety is the _____.

3) Which structure is responsible for cooling of the body, and what is the mechanisms of action?

4) The addiction center of the brain is located in the _____

5) What are the cause and symptoms of Kluver Bucy syndrome?

6) Explain the mechanism of fever

Section 7 – Higher Function of the Brain

- Learning – The ability to replicate, change, or modify behavior as a result of experience
- Memory – The retention and storage of information

7.1 – Types of Memory

I. Declarative (explicit)

- Associated with consciousness (or awareness)
- Dependent on hippocampus
- Two types
    1. Episodic - memory of events, facts
    2. Semantic - memory of words, rules of language, etc

II. Non-declarative (implicit)

- Does not involve awareness, or processing in the hippocampus
- Skills and habits
- Associative learning
    1. Classical
    2. Operant
    3. Imprinting
- Non-associative learning
    1. Habituation, sensitization

III. Brain structures associated with memory

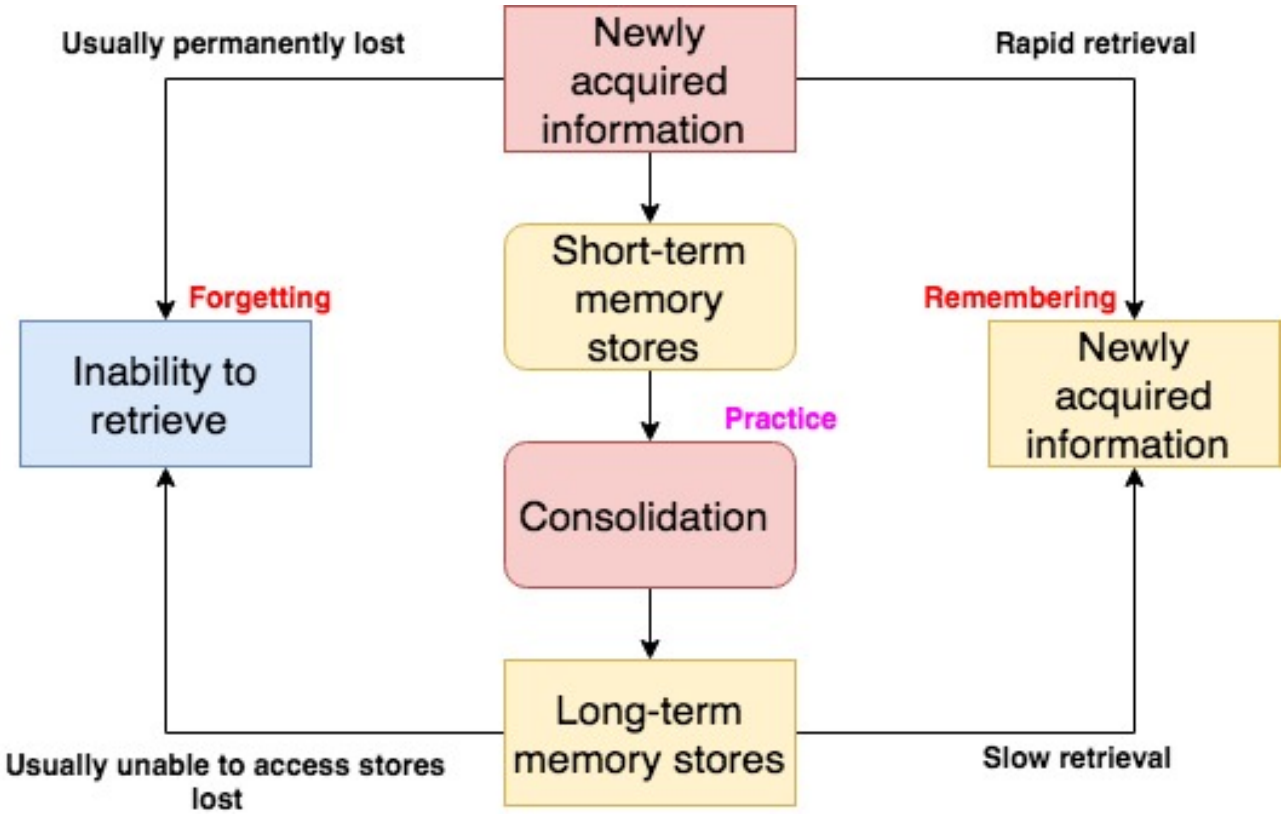
Declarative memory	Temporal lobe, diencephalon
Skills and habits	Striatum
Priming	Priming
Non-associative learning	Reflex pathways (spinal cord)

IV. Working memory

- Keeps information available for short period of time (decision on what to do with it)
- Involves hippocampus

V. Long term memory

- Persists for years
- Information is stored in neocortex
    1. Visual, auditory or olfactory areas
- Can be recalled by different associations
- Associations are proportional to quantity and strength of neural connections



VI. Reflexive memory

- Associative learning (skills, habits, conditioned reflexes)
    1. Person learns about the relation of one stimulus to another
- Non-associative learning
    2. Person learns about a single stimulus

VII. Habituation

- Single stimulus is repeated many times
- Decrease in responsiveness to stimulus
- Organism is “habituated” and begins to ignore stimulus

VIII. Sensitization

- Enhancement of a behavioral response to a stimulus
- Occurs when coupled to a novel stimulus

IX. Conditioned reflexes

- Unconditioned stimulus (US) is a stimulus that normally evokes a specific response
- Conditioned stimulus (CS) is a neutral stimulus that did not previously produce a response
    1. The CS and US have to be paired countless times until eventually the (now) conditioned stimulus is evoked during propagation of the unconditioned stimulus
    2. If the CS is presented without the US enough, there is extinction, which means that the conditioned reflex disappears
- External inhibition - in the presence of external stimuli the organism is disturbed, and the reflex may not occur

7.2 – Mechanisms of Learning and Memory

- Short term sensitization
    - Involvement of facilitatory (5HT) interneurons
    - Greater influx of calcium → more neurotransmitters releases
- Long term sensitization
    - Activation of RNA transcription and protein synthesis
    - Movement of axons → new neuronal connections, strengthen memory, make new associations

7.3 – Amnesia

I. Retrograde amnesia

- Inability to recall former events
- Typically resulting from brain damage

II. Anterograde amnesia

- Inability to form new long-term memory
- Typically resulting from neurodegenerative disease, senile dementia

7.4 – Language Disorders

- Dysarthria – Inability to produce words (motor problem, e.g. due to cerebellum lesions)
- Dysphonia – Inability to produce sounds
- Dysphasia/Aphasia – Higher-order inability to speak

Dysphasia/Aphasia	Lesion
Broca	Non-fluent with intact comprehension Patient understands what you're asking, but can't express themself
Wernicke	Fluent with impaired comprehension and repetition "word salad" – there are words, but they're not in the right order or don't make sense
Conduction	Poor repetition but fluent speech, comprehension intact
Anomia	Consistent inability to produce words for things desired to talk about

7.5 – Prefrontal Association Area

- Planning for voluntary movement, the future
- Consideration of consequences of actions before following through
- Predictions
- Solving logical/math problems
- Self-control in regards to social, moral, ethical laws and norms

7.6 – Parieto-Occipito-Temporal Area

- Work between the somatosensory, auditory, and visual cortex
- Analysis of spatial coordination
- Area for language comprehension
- Area for visual language (reading)
- Area for associating vision with memory

7.7 – Categorical Hemispheres

- For the typical (right handed) human, each of the two hemispheres is divided into specific ranges of processes

I. Left hemisphere

- Dominant side
- Analytical processes
    1. Sensation/movement of the contralateral side of the body
    2. Mathematical/logical problem solving
    3. Analysis and Conclusions
    4. Language
- Lesions: language disorders, depression

II. Right hemisphere

- Non-dominant side
- Spatio-temporal relations
    1. Sensation/movement of the contralateral side of the body
    2. Creativity/Artistic qualities
    3. Identification of form of objects, emotions

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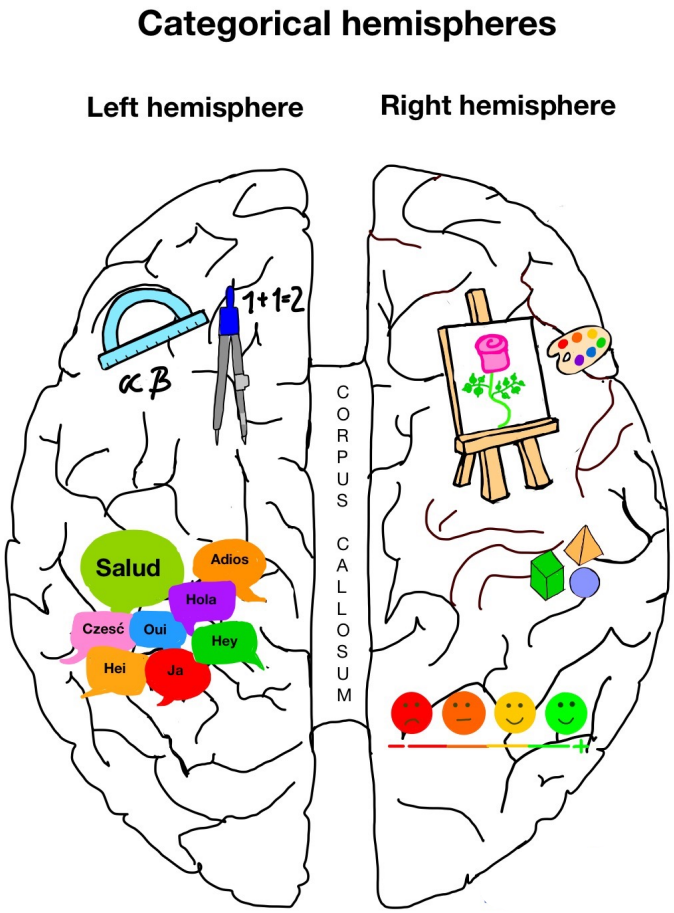

7.8 – Test Yourself

1) What is the difference of declarative and non-declarative memory?

2) Long-term memory is stored in _____

3) Explain the term "habituation"

4) Define retrograde and anterograde amnesia

5) A lesions to the Wernicke area will result in

6) Explain what a conditioned reflex is

7) A lesion in the left hemisphere will most likely impair abilities tied to

8) Prefrontal association area is responsible for


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