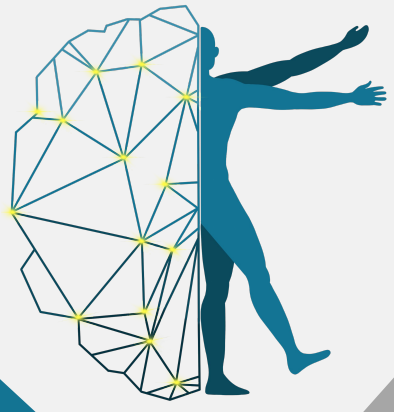
Physiology Team 439

MED439
KING SAUD UNIVERSITY



Dr.Shahid's Final Exam Revision

Homoud Algadheb

DISCLAIMER!

- We **DONT** recommend studying from this file, Only revising.
- You might want to listen to the recording just in case some parts haven't made it to the file

Good luck

Pain and its modulation

R

Questions from this lecture are almost guaranteed to come in the SAQs

Make sure you can compare them and know their examples

Nociception Pain	Neuropathic Pain (non-Nociception)
It is caused by the presence of a painful stimulus on nociceptors	**Occurs as a result of damage to the nerve fibers with the pain impulse emanating from the nerve itself** (Pain caused by a primary lesion or dysfunction in the nervous system)*
Nociceptive pain is detected by specialized transducers connected to A-delta and C-fibers (stimuli from somatic and visceral structures)*	Neuropathic pain damage to nerves (trigeminal neuralgia, postherpetic pain, diabetic neuropathy and after chemotherapy. Hyperalgesia, allodynia and spontaneous pain.*
Sustained primarily by the nociceptive system	Sustained by aberrant processes in PNC or CNS
Proportionate to stimulation of the nociceptors when acute	Disproportionate to stimulation of the nociceptors
Serve as a protective function, normal pain when acute	Serve no protective function
Pathological when chronic	Pathological pain
Respond to common analgesics	Resistant to common analgesics. Can persist for years.
E.g.: acute burn, bone fracture and other similar somatic & visceral pain	E.g.: painful diabetic & peripheral neuropathies, sympathetic-mediated pain, nerve inflammation, compression, post herpetic neuralgia, diabetic neuropathy and after chemotherapy.

Idiopathic Pain : No underlying lesion found yet, disproportionate to the degree of clinically discernible tissue injury. *

Mixed Pain: Eg; Failed low back surgery syndrome and complex regional pain syndrome. *

Pain and its modulation

R

Types of Nociceptors

Many of these are part of a family of nonselective cation channels called transient receptor potential (TRP) channels.

- **TRPV1:** receptors (the V refers to a group of chemicals called **vanilloids**) that are activated by **intense heat, acids, and chemicals** such as capsaicin (the active principle of hot peppers is an example of a vanilloid).
- **TRPA1: Noxious mechanical, cold, and chemical** stimuli may activate TRPA1 receptors (A, for **ankyrin**) on sensory nerve terminals.
- **ASIC:** Sensory nerve endings also have **acid sensing ion channel (ASIC)** receptors that are activated by **pH changes** within a physiological range and may be the dominant receptors mediating acid-induced pain.
- **P2X & P2Y:** For example, nociceptive mechanical stimuli cause the release of ATP that acts on **purinergic receptors** (eg, P2X, an ionotropic receptor and P2Y, a G protein coupled receptor).
- The receptor that is activated by moderate cold is **TRPM8**. The M refers to methanol, the ingredient in mint that gives it its "cool" taste.
- **TRPV4** receptors are activated by by warm temperatures up to 34C; **TRPV3** receptors respond to slightly higher temperature 35-39C

"This will be easy because in MCQs you will be able to recognize the answer"

Chemical Substances Released During Tissue Damage

Substance	Source
Potassium	Damaged cells
Prostaglandins	Damaged cells
Leukotrienes	Damaged cells
Bradykinin	Plasma, mast cells and basophils
Histamine	Mast cell
Serotonin	Platelets
Substance P main pain sensitizer	Primary nerve afferents

Pain is perceived at both the **cortical** & **thalamic** levels. Thalamic level: you can not localize it, grade it, specify it. **The quality of pain cannot be specified in the thalamic level**

Pain and its modulation

R

Fast/immediate (1st) pain epicritic Pain	slow/delayed (2nd) pain
Sharp, intense, pricking, well localized e.g. pricking, cut with knife	Burning, aching, throbbing "unbearable" diffuse, dull, chronic pain, poorly localized
Felt within 0.1 sec on stimulation of Mechanical & Thermal nociceptors skin or superficial stimuli	Felt after 1 sec or more on stimulation of Polymodal receptors
Associated with reflex withdrawal*	Associated with destruction of tissue*
Usually somatic not visceral*	Can occur in skin or internal organ/tissue*
Transmitted by **Aδ- fibers** in the peripheral nerves & centrally by **Neospinothalamic Tract**	Transmitted by **C fibers** peripherally & centrally by **paleospinothalamic Tract**
Terminate at I and V laminas lamina marginalis	Terminate at II and III laminas (substantia gelatinous)
Neurotransmitter – Glutamate	Neurotransmitter – Substance-P
20% pain conduction	80% of pain conduction

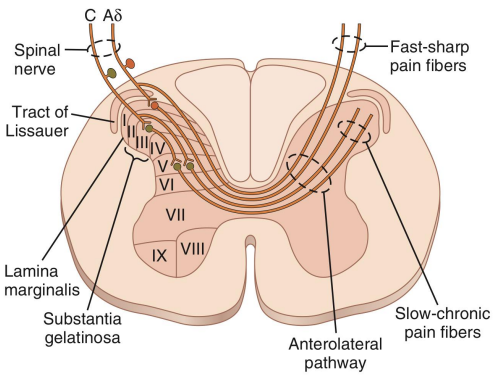


Figure 49-2. Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain. Aδ fibers transmit fast-sharp pain, and C fibers transmit slow-chronic pain.

Pain and its modulation

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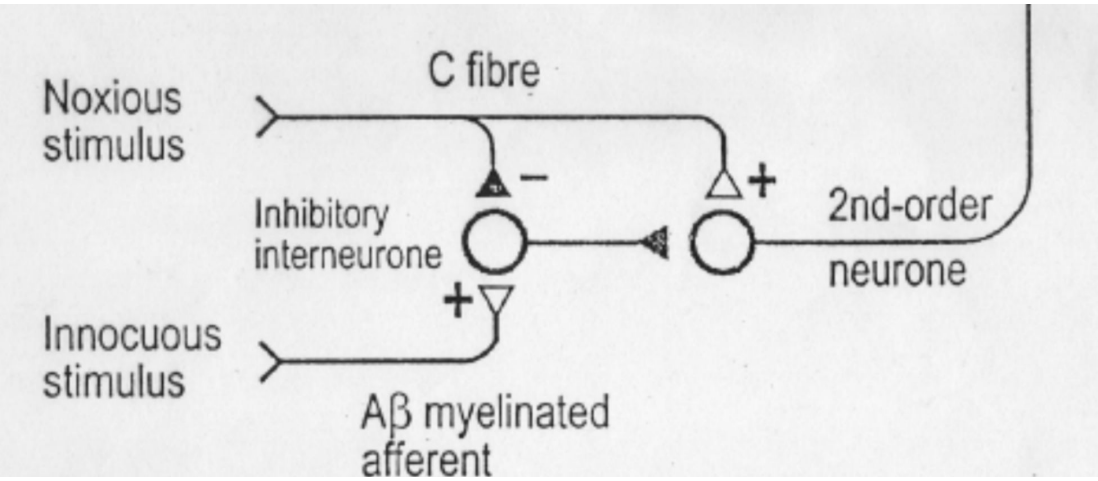
Gate Control Theory of Pain:



- Implies a non-painful stimulus can block the transmission of a noxious stimulus.
- Is based on the premise that the gate, located in the dorsal horn of the spinal cord, modulates the afferent nerve impulses

	Conditions that open the gate	Conditions that close the gate
Physical Conditions	• Extent of the injury. • Inappropriate activity level.	• Medication. • Counterstimulation, e.g. massage.
Emotional Conditions	• Anxiety or worry. • Tension. • Depression.	• Positive emotions. • Relaxation. • Rest.
Mental Conditions	• Focusing on the pain. • Boredom.	• Intense concentration or distraction. • Involvement and interest in life activities.

Pain and its modulation

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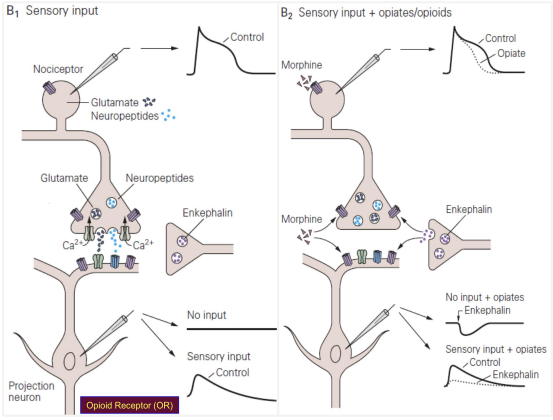
Visceral Pain

Characteristics:

1	Gradual onset (always slow), poorly localized.
2	associated with nausea and autonomic disturbances
3	Pain is caused by distension, ischemia and inflammation
4	Cutting and crushing are not painful when applied to viscera.

Cellular Actions Of Opioid Peptides: know the general mechanism and the 3 sites of action

- Activation of the **presynaptic (#1)** opioid receptor leads to a decrease in Ca++ influx, resulting in a decrease in release of glutamate and substance P.
- Activation of the **postsynaptic(#2)** opioid receptor hyperpolarizes the dorsal horn interneuron by causing an increase in K+ conductance.
- Decrease duration of the EPSP in the dorsal horn neuron.and Activation of opioid receptor on dorsal root ganglia cell bodies also contributes to reduced transmission from nociceptive afferents. **(#3: sensory pathways)**



Placebo Effect: know the definition

Used to describe pain reduction obtained from a mechanism other than those related to the physiological effects of the treatment. Linked to **psychological mechanisms**.

Pain and its modulation

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Special pain control analgesic system

The doctor explained this system briefly in the revision but he wasn't specific.
It's better that you watch his explanation which starts at minute 22:00

This is a specific system that blocks pain transmission in CNS. Its major constituents are:

The Periventricular & Periaqueductal Gray Areas:	- Enkephalin Neurons In the mesencephalon and upper pons. - It send signals to Raphe magnus nucleus. - These neurons surround portions of the third and fourth ventricles and the aqueduct of Sylvius.
Raphe Magnus Nucleus (RMN):	- A thin midline nucleus located in the lower pons and upper medulla. - From these nuclei, second-order neurons go down the dorsolateral columns in the spinal cord & secrete Serotonin which act on local neurons to secrete Enkephalin.
Pain inhibitory complex:	- In dorsal horn of spinal cord. - It consists of: multiple short enkephalinergic neurons that terminate on central endings of pain conducting afferent fibers. - When stimulated the release enkephalin cause pre & postsynaptic inhibition of pain transmission. presynaptic: inhibit release of NT by substance p. postsynaptic: by hyperpolarization.

Analgesia system of the brain and spinal cord, showing:*

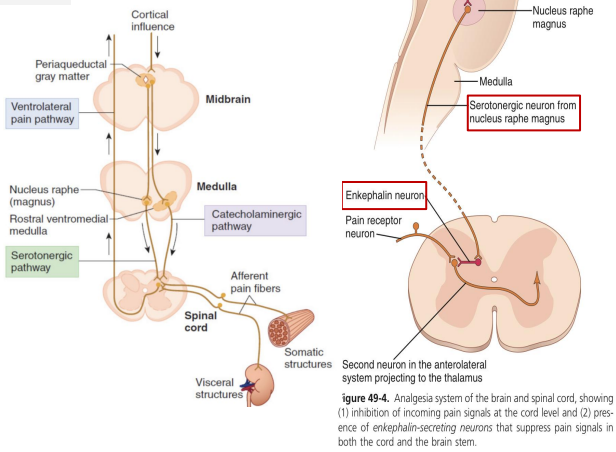
(1) inhibition of incoming pain signals at the cord level.

(2) presence of enkephalin-secreting neurons that suppress pain signals in both the cord and the brain stem.

Analgesia Occurs As Follows:*

1. Enkephalin neurons from PAG (periaqueductal gray) and periventricular areas send signals to RMN.
2. RMN projects serotonin- ergic neurons to dorsal horn.
3. Serotonin- ergic neurons act on local neurons (PIC) at dorsal horn to release encephalin.

At this point, the analgesia signals can block the pain before it is relayed to the brain.



igure 49-4. Analgesia system of the brain and spinal cord, showing (1) inhibition of incoming pain signals at the cord level and (2) presence of *enkephalin-secreting neurons* that suppress pain signals in both the cord and the brain stem.

Pain and its modulation

R

Questions from the doctor (answered by doctor):

1) **In which type of pain will you have a strong autonomic reaction?**
   a) Visceral pain

2) **At which levels in the nervous system is pain perceived?**
   a) Thalamic and cortical levels. In the thalamic level, you can't specify the quality of pain

3) What is the equivalent of blood vessels in the brain?
   a) sinuses

4) **Mention two receptors located at the ending of nociceptive sensory nerves** (answers are examples by the doctor, you can choose any others)
   a) TRPV1, V for Vanilloids, Activated by heat or acids,
   b) ASIC, Acid sensing ion channels, Activated by pH changes

5) **What is the primary source of substance P** (any substance could be asked)
   a) Primary afferent nerves

6) **Where does the referred pain of appendix start?** (next few questions are related)
   a) periumbulical region

7) **from previous Q. If it shifts to Right iliac fossa in later stages, what will be the cause of that pain ?**
   a) Irritation of the peritoneum

8) **From previous Q. Is the new pain somatic or visceral?**
   a) Somatic, Because parietal peritoneum has somatic nerve supply

9) **From previous Q. If he feels pain in both referred and localized areas (pain started at umbilicus but now is moving to right iliac fossa), that type of pain is known as?**
   a) Radiating pain

10) **What is the dermatomal theory of referred pain?**
    a) the pain location is where thee organ originated from in the embryo

11) **What causes pain in the viscera?**
    a) Ischemia, distension, Inflammation

12) **Which type of pain is trigeminal neuralgia? (MCQ)**
    a) Mixed **b) Neuropathic** c) Idiopathic d) Nociceptive

Pain and its modulation

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<u>Questions from the doctor</u> (not answered):

1) What is the significance of Innocuous stimulus.
    a) Understand the figure from gate control theory
2) How does visceral pain differ from somatic pain?
    a) Mention characteristics of visceral pain
3) Somebody had an injury and you started massaging that area, which type of receptors were stimulated? What is the mechanism
    a) talk about brain analgesia system

Basal Ganglia

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Make sure you know 4 points:

1. The 4 circuits and their functions
2. Putamen and caudate circuit (input/output and functions)
3. Direct and indirect pathways (In detail)
4. Basal ganglia disorders (locations especially)

Basic circuits of movement control

1-Motor loop (putamen circuit):	Concerned with learned movement. (Not planned movement)
2-Cognitive loop (Caudate circuit):	concerned with cognitive control of sequences of motor pattern. Basically it is concerned with motor intention. (planned movement) Note: Cognition means thinking process using sensory input with information already stored in memory.
3-Limbic loop:	involved in giving motor expression to emotions like, smiling, aggressive or submissive posture (Via nucleus accumbens reward circuit) *
4-Occulomotor loop:	concerned with voluntary eye movement (saccadic movement)

Basal Ganglia

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The Putamen Circuit

Inputs	Outputs
Somatosensory Cortex	Premotor
Premotor	Supplementary Motor
Supplementary Motor Areas	Primary Motor Cortex

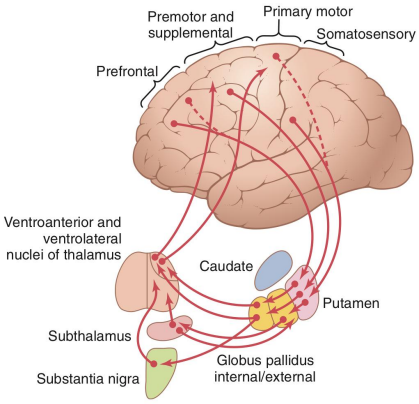


Figure 57-11. Putamen circuit through the basal ganglia for subconscious execution of learned patterns of movement.

Functions of Putamen Circuit:

- Associated with Learned patterns of motor activity **(Subconsciously and without a plan)**
  - -Examples:
    - Shooting a basketball
    - Passing a football
    - Hammering nails

The Caudate Circuit

Input	Outputs
Association areas	Prefrontal
	Premotor
	Supplementary Motor

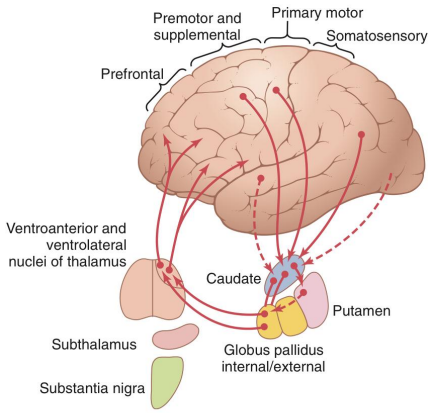


Figure 57-12. Caudate circuit through the basal ganglia for cognitive planning of sequential and parallel motor patterns to achieve specific conscious goals.

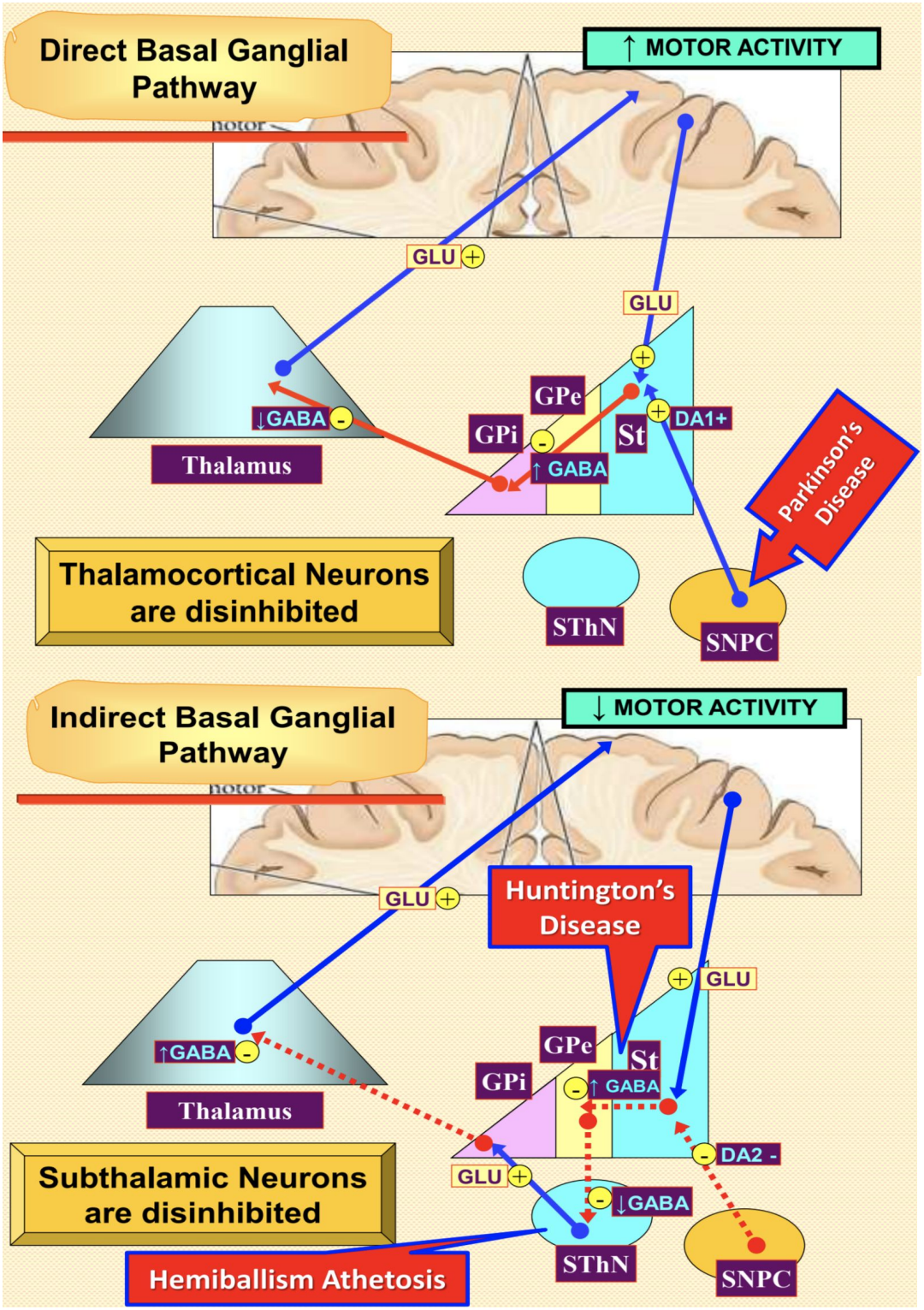
Functions of Caudate Circuit:

- **Cognitive control of sequence of motor patterns**
  - **Example: Seeing a lion approach**
    1. **Turning away from the lion**
    2. **Beginning to run**
    3. **Attempting to climb a tree**
- Timing and scaling the intensity of movements(how rapid and how large a movement would be)
  - Example: writing the letter "a" slowly or rapidly

Basal Ganglia

R

Memorize everything in these slide (NTs and what happens in each neuron). You can find a very excellent video explanation **HERE**



Basal Ganglia

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Movement disorder	Lesion	Features
Chorea	Atrophy of the striatum. Ex: Huntington's Chorea ,St vitus (post streptococcal infection)	Multiple quick, random movements, usually most prominent in the appendicular muscles
Athetosis	Diffuse hyper myelination of corpus striatum and thalamus	Slow writhing movements,which are usually more severe in the appendicular muscles
Hemiballismus	Hemorrhagic destruction of contralateral subthalamic n. Ex: Hypertensive patients	Wild flinging movements of half of the body
Parkinsonism	Degeneration of Substantia Nigra	Pill rolling tremor(كأن المريض يسبح بالمسبحة) of the fingers at rest, lead pipe rigidity and akinesia
* Tardive Dyskinesia *	Neuroleptic drugs blocking dopaminergic transmission	Either temporary or permanent uncontrolled involuntary movements of the face and tongue and cogwheel rigidity

UMN & LMN

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	Upper Motor Neuron Lesion	Lower Motor Neuron Lesion
Pattern	paralysis affect movements affects limbs	individual muscle or group of muscles are affected
Wasting	not pronounced (about 20 -30% wasting)	pronounced (about 70-80% wasting)
Tone	spasticity muscles hypertonic (clasp knife)	tendon reflexes diminished or absent
Tendon reflexes	brisk/increased	diminished or absent
Superficial reflexes	Absent	Absent
NCV	normal	decreased
Denervation potentials (Fibrillations) from fibrils, so can't be seen with eye only on EEG	Absent	Present
Fasciculations can be seen with eyes	Absent	Present
Trophic changes	Less	Pronounced in skin and nails
Clonus	present	Absent
Babinski's sign *Normal physiological Babinski's sign : in neonates	Extensor plantar response (positive)	Flexor or absent plantar responses

UMN & LMN

R

Brown Sequard Syndrome

Hemisection of Spinal Cord

"This is our favorite condition"

Symptom causes are found in the original team file

Ipsilateral Loss

- Fine touch, vibration, proprioception (dorsal column)
- leg ataxia (dorsal spinocerebellar)
- spastic paresis below lesion (lateral corticospinal)
- Flaccid paralysis (ventral horn destruction)
- Dermatomal anesthesia (dorsal horn destruction)

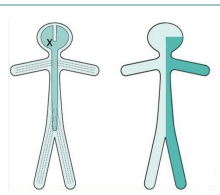
Contralateral Loss

- Loss of pain and temperature (lateral spinothalamic)
- Loss of crude touch and pressure (ventral spinothalamic)
- Minor contralat muscle weakness (ventral corticospinal)
- Leg ataxia (ventral spinocerebellar)

Contralateral Hemiparesis

Internal capsule

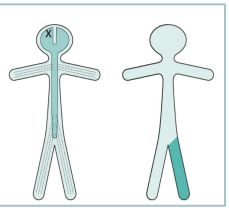
Lesions situated deep in the cerebral hemisphere, in the region of the internal capsule, are much more likely to produce weakness of **the whole of the contralateral side of the body**, face, arm and leg. Because of the funnelling of fibre pathways in the region of the internal capsule, such lesions commonly produce significant contralateral sensory loss (hemianesthesia) and visual loss (homonymous hemianopia), in addition to hemiparesis

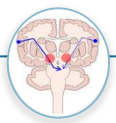


Contralateral Monoparesis

Lesion situated peripherally in the cerebral hemispheres

i.e. involving part of the motor homunculus only, produces weakness of **part of the contralateral side of the body,** e.g.the contralateral leg. If the lesion also involves the adjacent sensory homunculus in the postcentral gyrus, there may be some sensory loss in the same part of the body

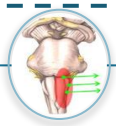




Extra Picture

Bulbar Palsy

- Bilateral affection of **LMN**
- defect of IX-XII cranial nerves or their nuclei in Medulla Oblongata
- LMN lesion Peripheral Palsy
- Dysphagia (liquid>solid), nasal regurgitation, slurred speech.
- Nasal speech, **wasted tongue** with fasciculation, absent gag reflex.
- Cause: polyradiculoneuritis (GBS): brainstem lesions, tumors, meningoencephalitis, MND



Extra Picture

Pseudobulbar Palsy (supranuclear)

- Bilateral lesion of corticobulbar tract
- **UMN** defect of central palsy IX-XII cranial nerves.
- Dysphagia, dysarthria, emotional lability (unprovoked crying or laughing).
- Slow indistinct speech, **spastic tongue**, brisk jaw jerk (masseter reflex).
- Frontal release signs.
- Cause: CVA, arteriosclerosis

Inner ear and balance

R

Maintaining equilibrium	
SemiCircular Canals	**Saccule and utricle (vestibule)**
Crista ampullaris	Macula
Hair cells in each crista are oriented in the **same direction**	Hair cells in each macula are oriented in **all direction**
No Otoliths	Otoliths (calcium carbonate crystals)
Dynamic Equilibrium and angular motion	Static equilibrium and Linear Acceleration
Predictive function	No predictive function

Utricle detect balance in horizontal direction and saccule detect balance in horizontal and vertical directions
stereocilia bend toward kinocilium = depolarization
stereocilia bend away from kinocilium = hyperpolarization

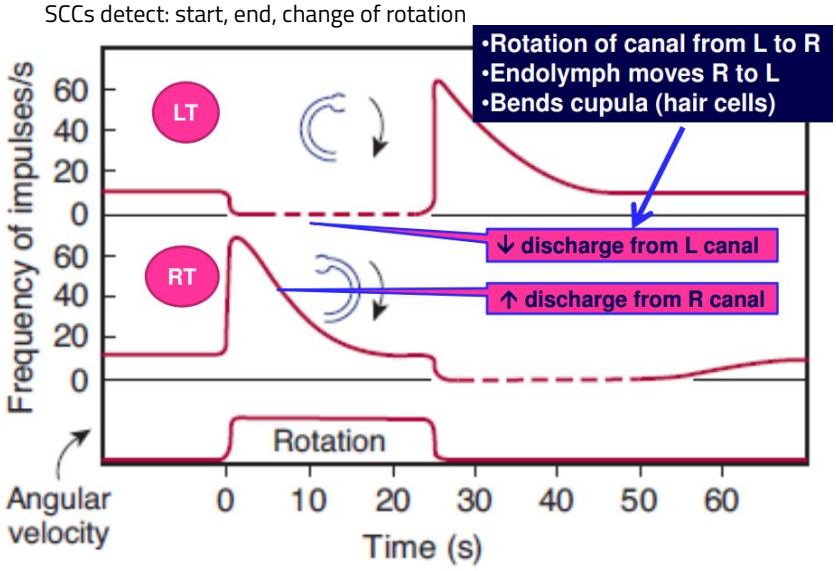
Detection of linear acceleration:

Sudden acceleration* ⇒ at beginning of movement statoconia lag behind movement by its inertia* ⇒ Falling backwards* ⇒ Otoliths falls back on hairs* ⇒ cilia moves backward* ⇒ sensation of mal-equilibrium (falling backwards)* ⇒ Correction by leaning forward to shift statoconia & cillia anteriorly.

at deceleration (runner try to stop) ⇒ statoconia move forwards by its momentum ⇒ person feels falling anteriorly. *

Detection of angular acceleration:

SCCs detect: start, end, change of rotation



-If you move your head from left to righ "important for MCQs"

1. Movement of endolymph in SCC
2. Bending of hairs (Opposite on two sides)
3. Opposite discharge from two sides
4. Sensation of rotation in CNS
5. As rotation continues endolymph will soon rotate in the same direction (& speed) as the SCC
6. Cupula being elastic returns to resting position
7. Discharge from both sides returns to resting level

Aging

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Nervous System changes

"every sentence is an MCQ"

1	Neuronal loss is normal in the aging brain but the ability to learn remains generally unchanged
2	There is loss of dendritic arborization so less communication between neurons
3	Recall memory is affected more than cognitive function in normal aging
4	Lowered seizure threshold
5	Reduced Neurotransmitter levels (Dopamine, Serotonin, Glutamate)
6	changes in sleep patterns **(Decreased quality sleep)**
7	increased risk of stroke

Dementia and Delirium

Dementia

Dementia is a syndrome of **progressive decline** in which multiple intellectual abilities deteriorate, causing both cognitive and functional impairment.

Delirium

Delirium is an **acute state** of confusion.
Delirium may be the only manifestation of a life threatening illness in the older adult.

Aging

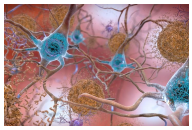
R

You should know the details about the two changes in alzheimer's:

Amyloid Plaques **Found outside the neuron**

Plaques have not been found to be a consistent feature of normal aging. It is hallmark of Alzheimer's disease.

There is accumulation of amyloid plaques between nerve cells (neurons) in the brain.



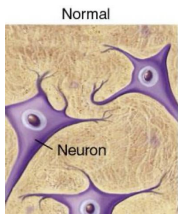
Amyloid is a general term for protein fragments that the body produces normally. Beta amyloid is a protein fragment snipped from an amyloid precursor protein (APP).

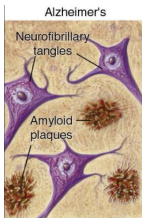
In a healthy brain, these protein fragments are broken down and eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques.

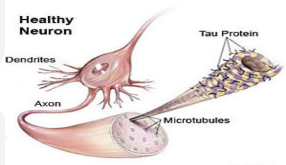
Amyloid plaques are seen in very old age 80 but if we find it in a person who is 40 this is due to Alzheimer's disease

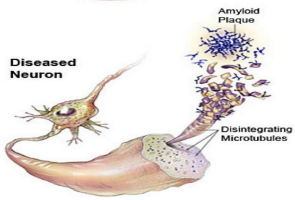
Neurofibrillary Tangles **Found inside the neuron**

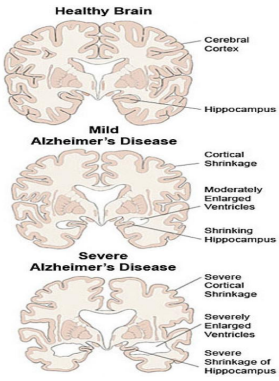
- These are insoluble twisted fibers found inside the brain's cells.
- Consist primarily of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another.
- In normal, non-demented aging, the number of tangles in each affected cell body is relatively low
- In Alzheimer's disease, however, the tau protein is abnormal and the microtubule structures collapse.











Thank you