MOTOR SYSTEM

TYPES OF NEUROTRANSMITTERS

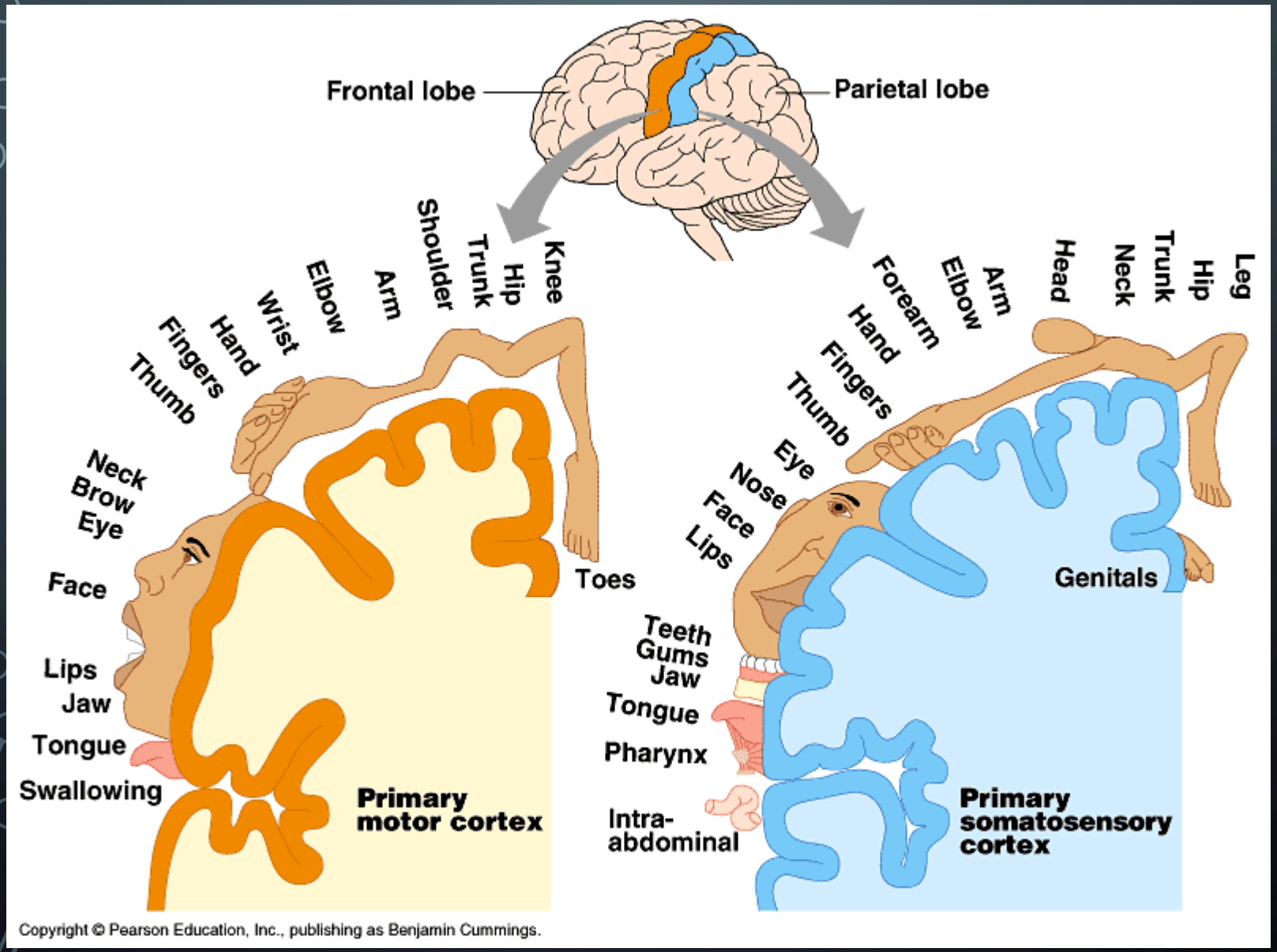
- There are many different ways to classify neurotransmitters. Dividing them into amino acids, peptides, and monoamines is sufficient for many purposes.
- Some more precise divisions are as follows:
- Around 10 "small-molecule neurotransmitters" are known:
  - acetylcholine (Ach)
  - monoamines (epinephrine (E), norepinephrine (NE), dopamine (DA), serotonin (5-HT) and melatonin)
  - 3 or 4 amino acids, depending on exact definition used: (primarily glutamic acid, gamma aminobutyric acid (GABA), aspartic acid & glycine)
  - Purines, (Adenosine, ATP, GTP and their derivatives)
  - Fatty acids are also receiving attention as the potential endogenous cannabinoid.
- Over 50 neuroactive peptides (vasopressin, somatostatin, neurotensin, etc.) have been found, among them hormones such as Luteinizing hormone (LH) or insulin that have specific local actions in addition to their long-range signalling properties.
- Histamine
- Single ions, such as synaptically released zinc, are also considered neurotransmitters by some.
- Gaseous, including nitric oxide (NO) and carbon monoxide (CO)
- The major "workhorse" neurotransmitters of the brain are glutamic acid and GABA.

WHAT'S THE MOTOR SYSTEM?

- Parts of CNS and PNS specialized for control of limb, trunk, and eye movements
- Also holds us together

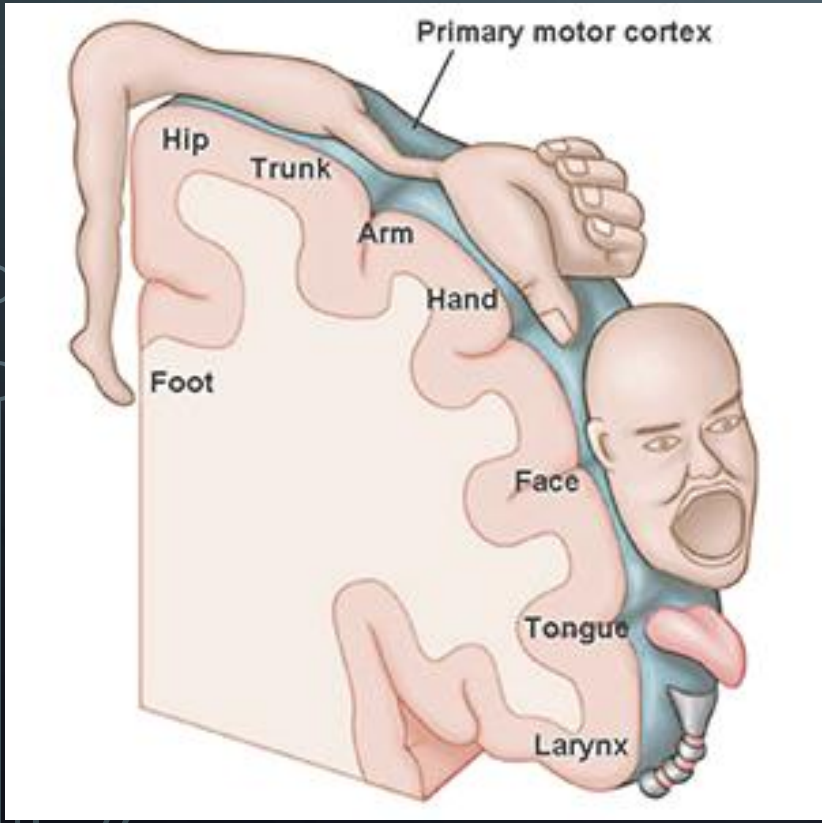
- From simple reflexes (knee jerk) to voluntary movements (96mph fast ball)

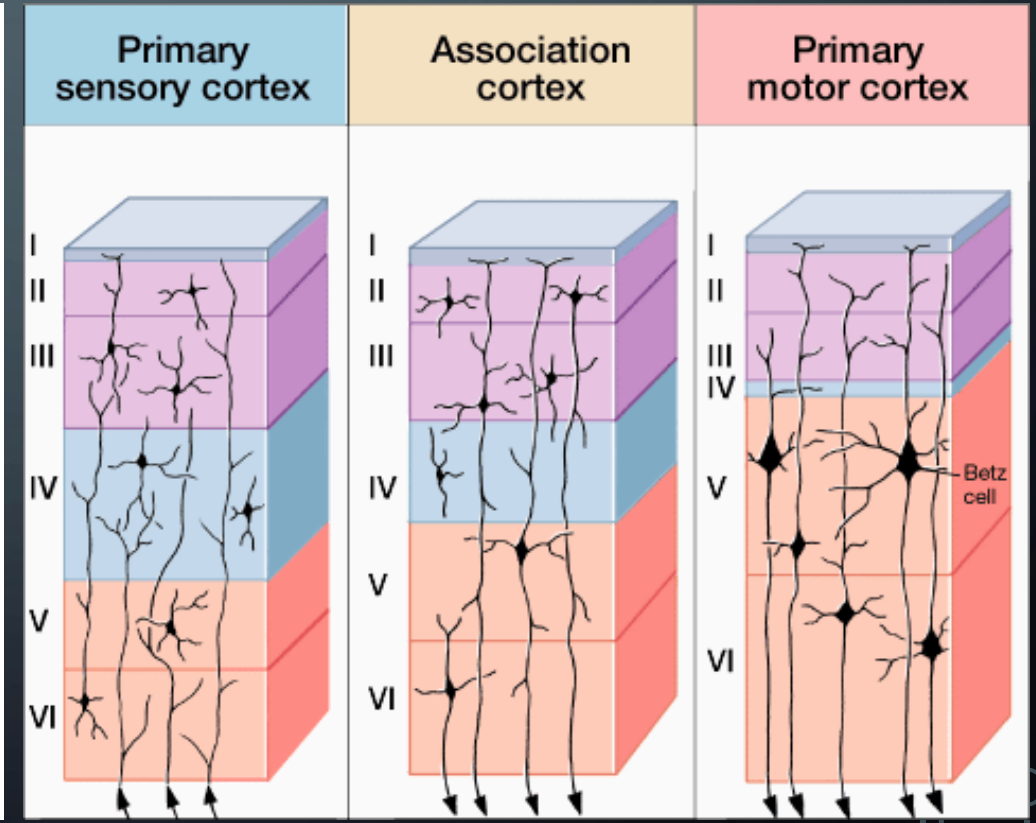
PRIMARY MOTOR CORTEX



Primary somatomotor cortex

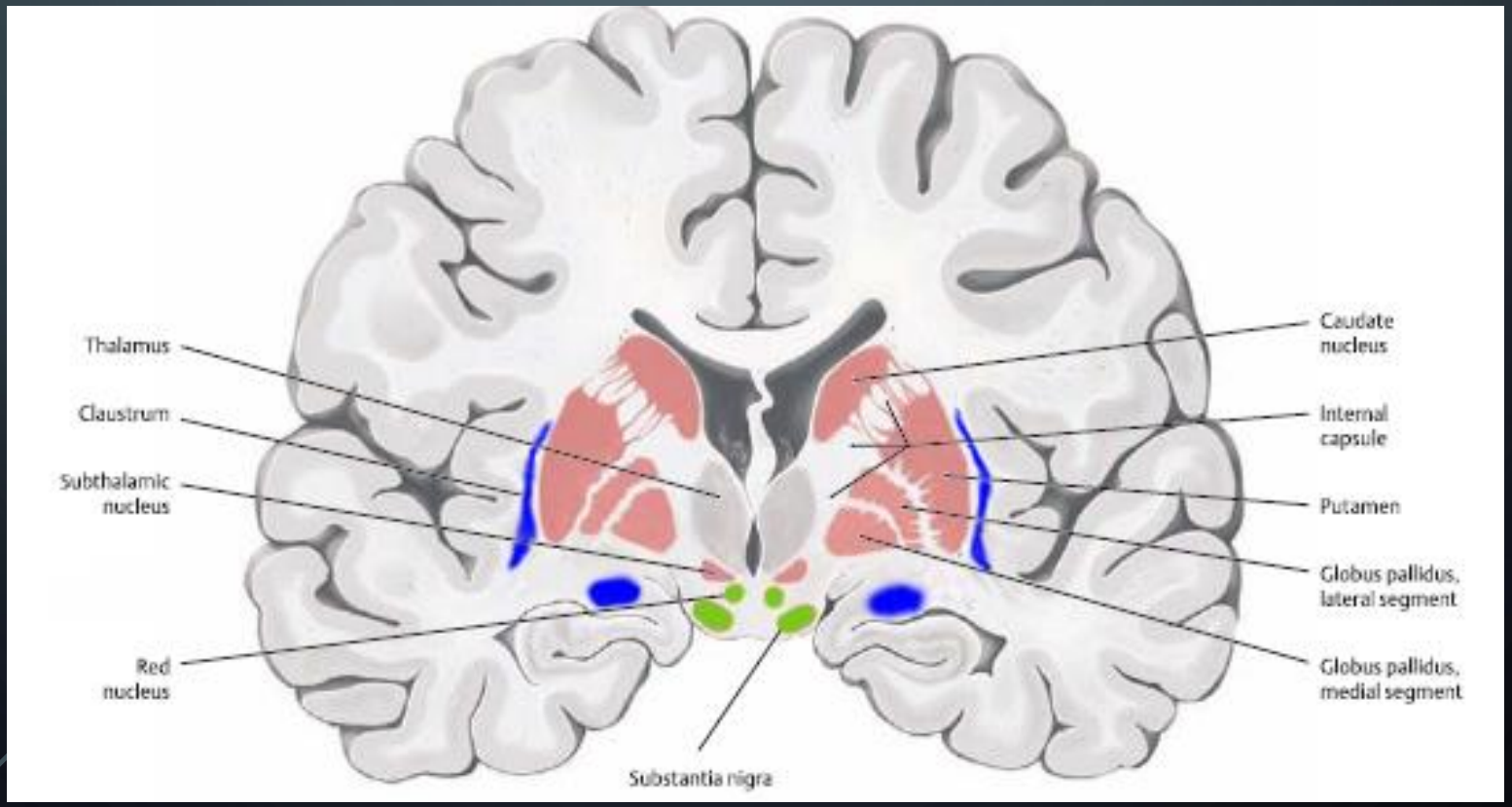
- precentral gyrus, (Brodmann 4 area)
- somatotopic arrangement
- agranular cortex (layer 2 and 4 are thin, giant pyramidal cells - Betz cells in layer 5)



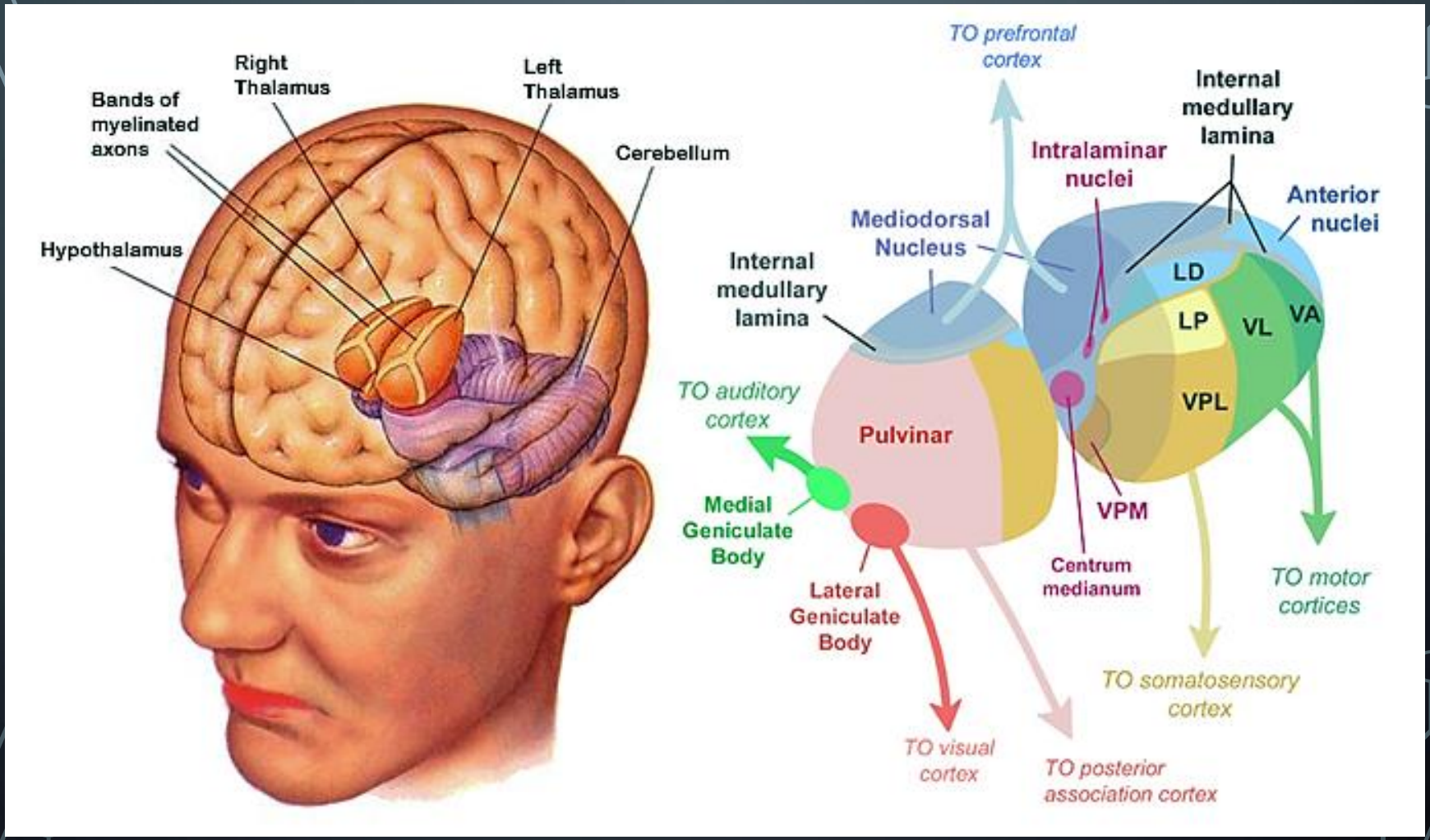


Motor systems – basal ganglia

- Subcortical groups of neuronal cell bodies developing from the prosencephalic wall (**dorsal striatum** constituted by the caudate nucleus and putamen, the **ventral striatum** formed by the nucl. accumbens and the olfactory tubercle, the **globus pallidus**, the **subthalamic nucleus**, **claustrum, amygdaloid body** (red and blue)…
- *It is not correct anatomically, but in clinical practice red nucleus and substantia nigra are also considered as basal ganglia (green)*

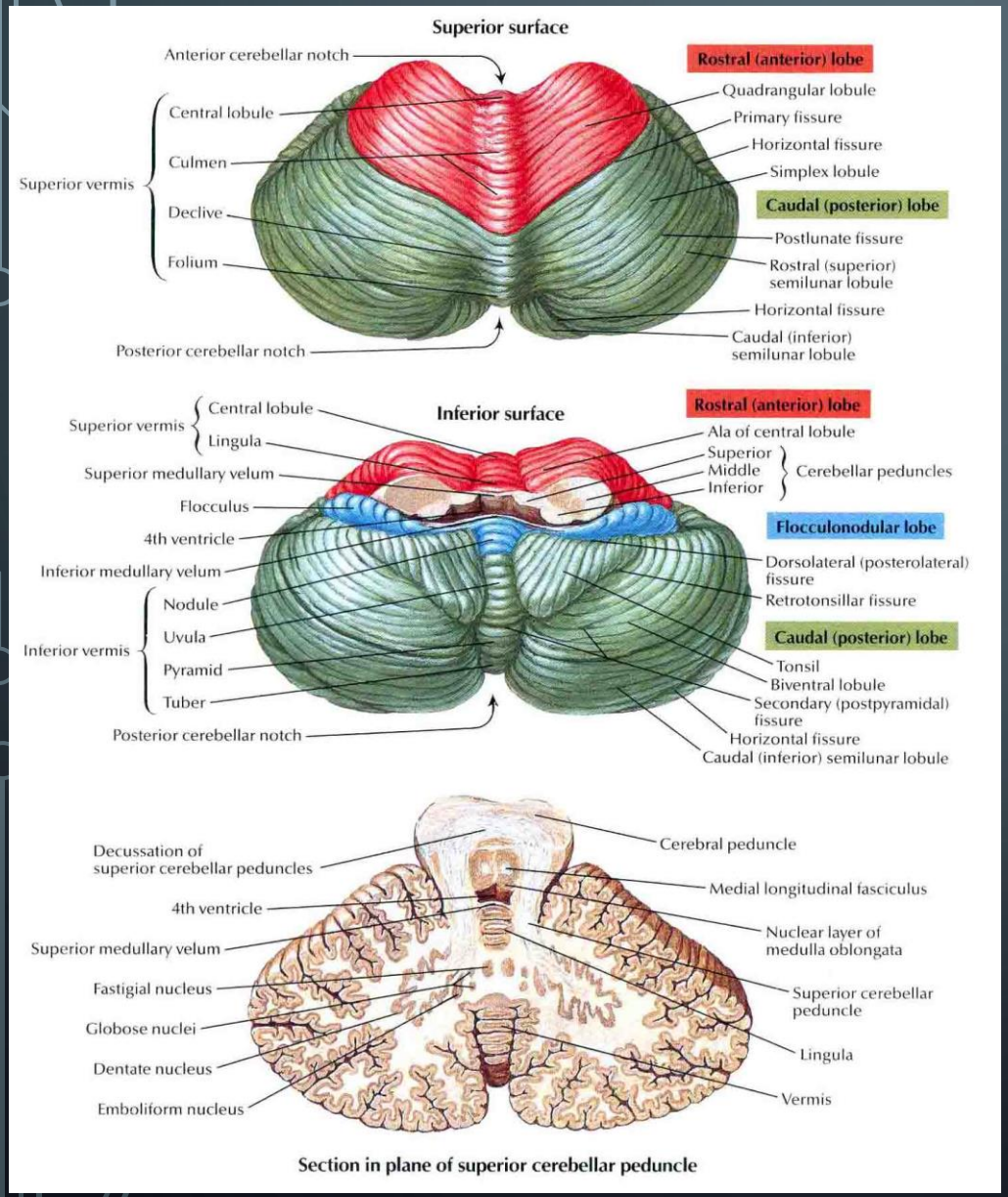


Motor systems – thalamus



Ventral-anterior (VA) and ventrolateral (VL) nuclei of the thalamus are considered as motor nuclei and they are connected to different motor cortical areas.

Motor systems – cerebellum

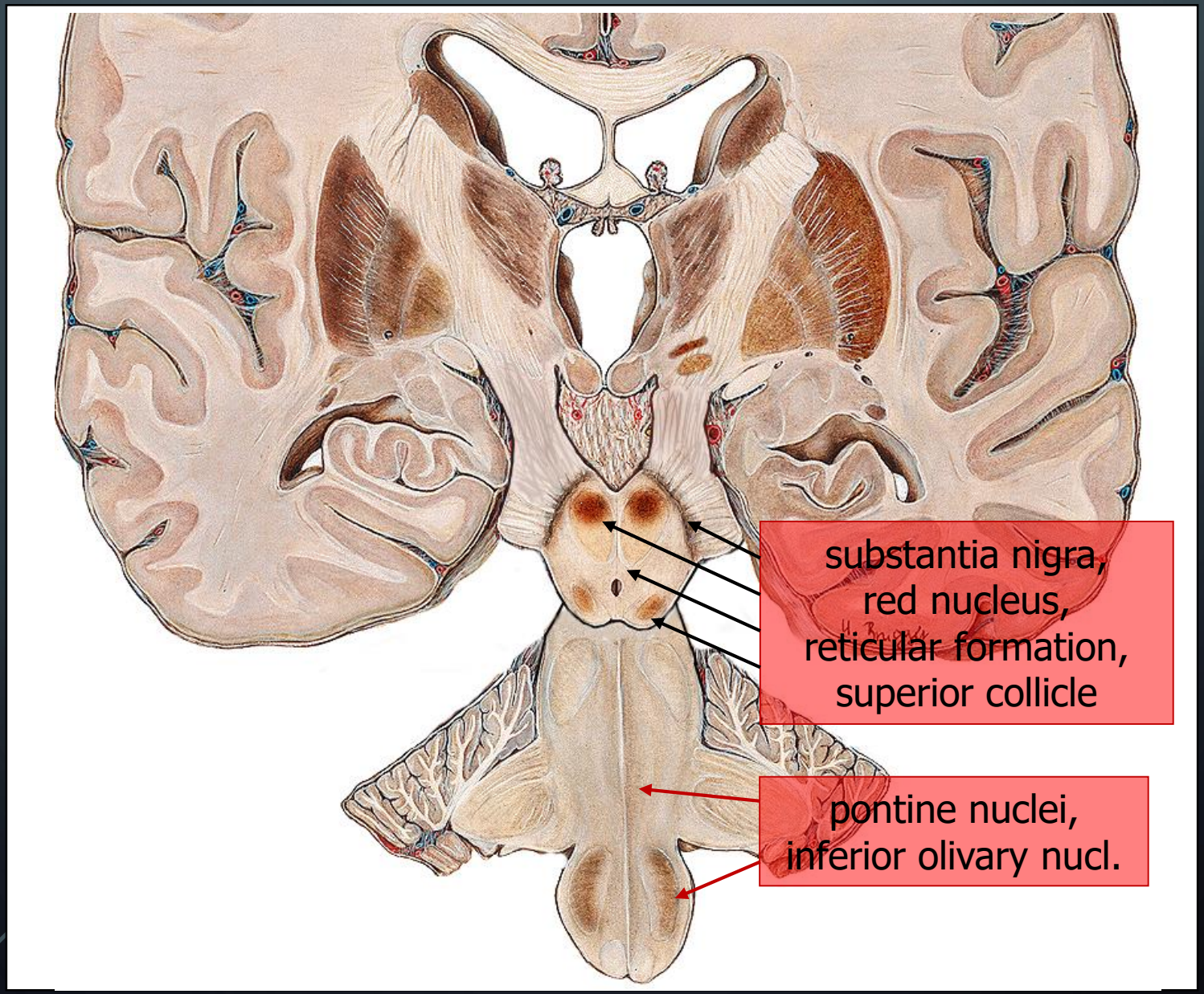


archicerebellum
reciprocal connection with the vestibular nuclei (body balance posture)

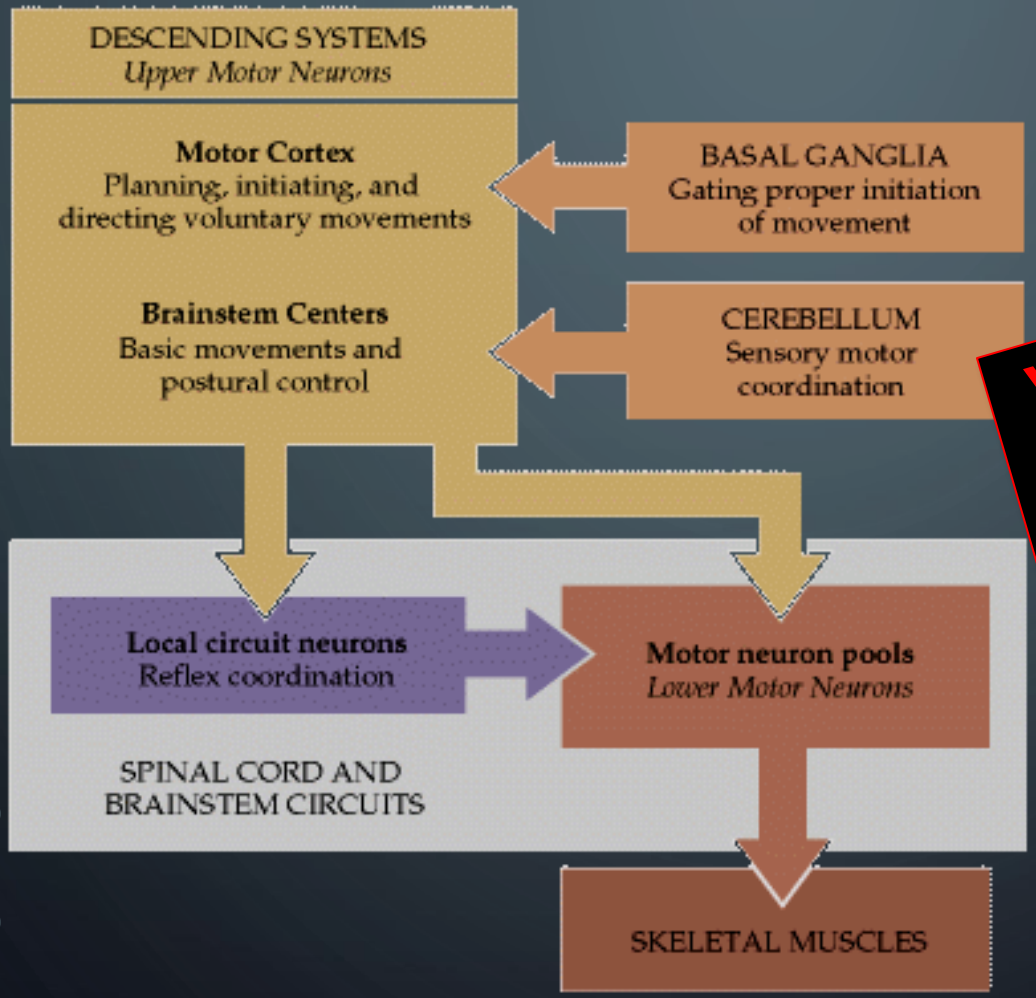
paleocerebellum
epicritic and proprioceptive sensory feed-back (spinocerebellar and cuneocerebellar tracts)

neocerebellum
descending information from the motor cortical areas (corticopontine-pontocerebellar indirect pathways)

Motor systems – brainstem nuclei



HIERARCHIC ORGANIZATION OF MOTOR SYSTEM



Voluntary movement

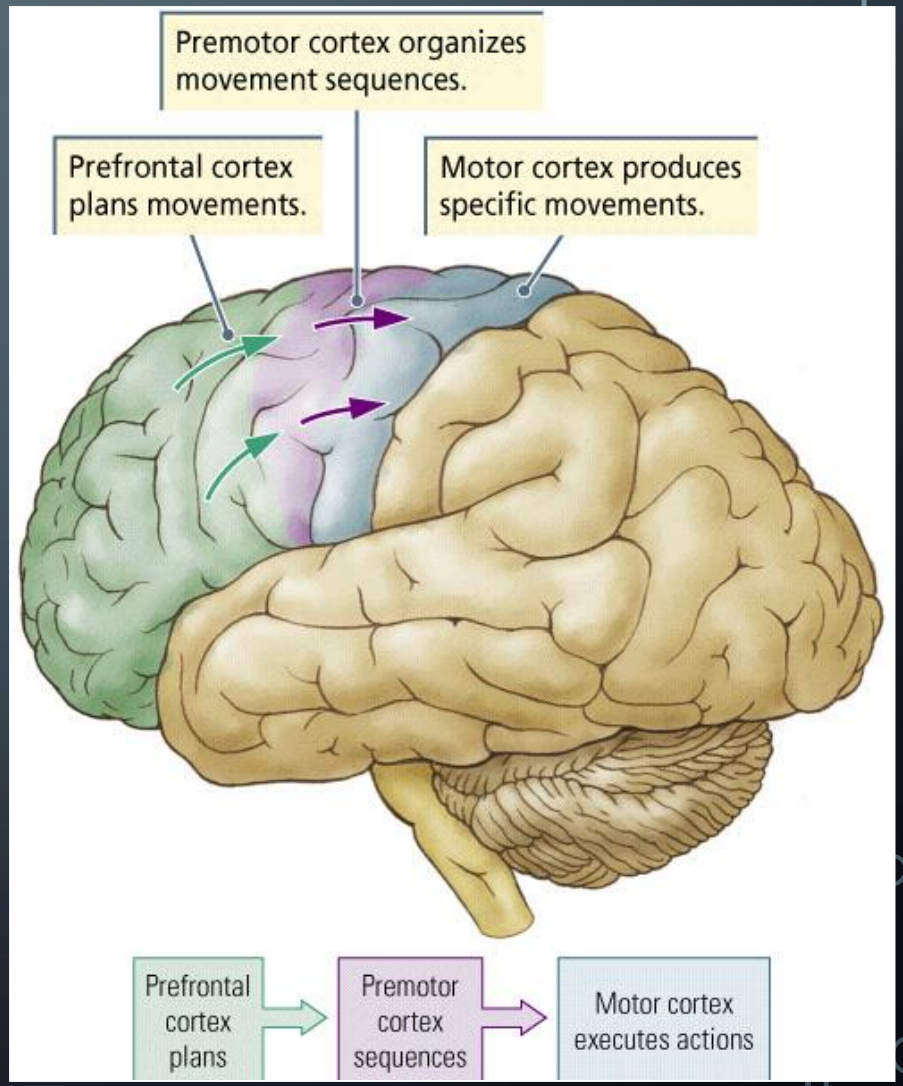
Reflex movement

Rhythmic movement

http://www.slideshare.net/drpsdeb/presentations

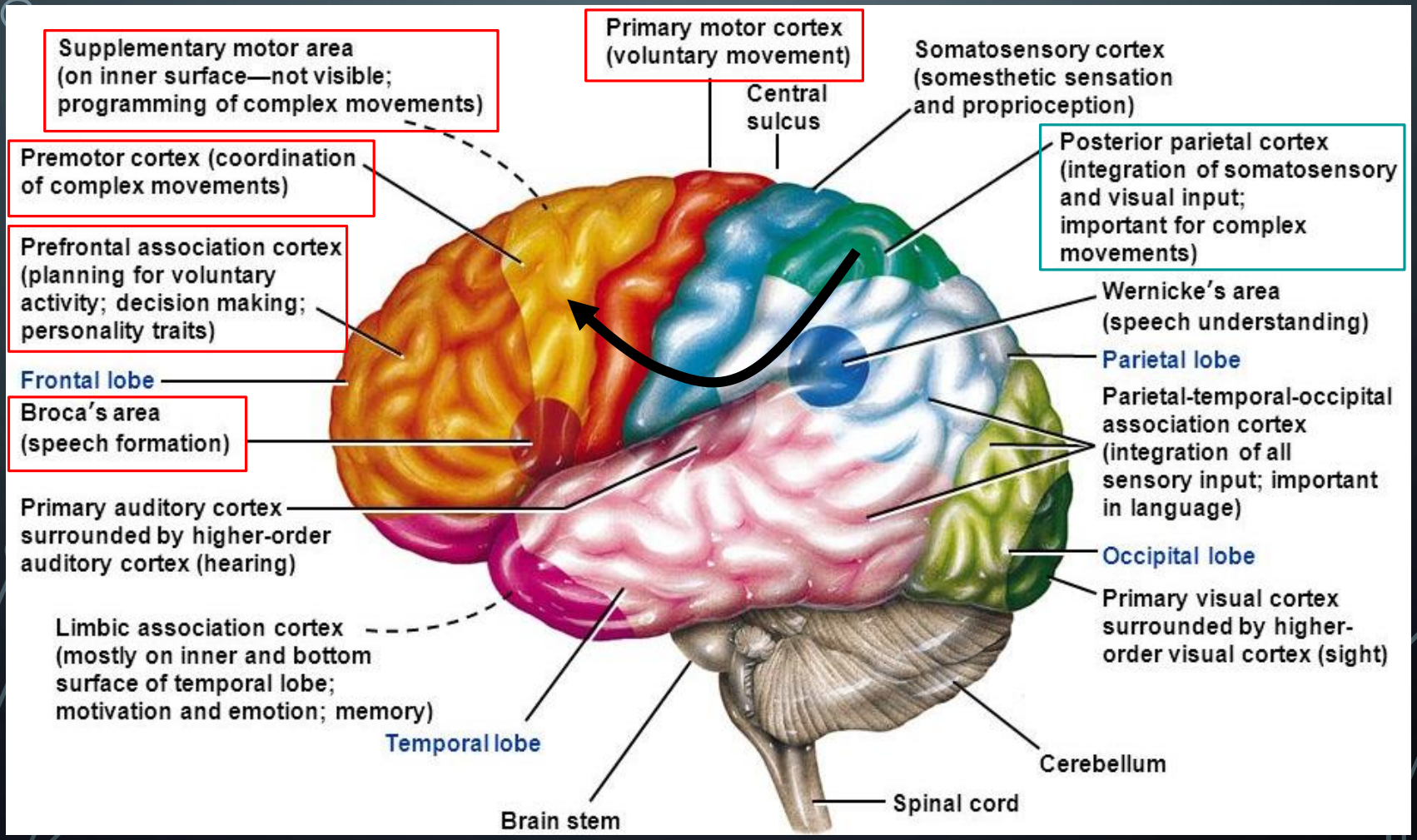
CORTEX

- Externally guided movements – those requiring sensory inputs
- Picking up objects, using tools, moving eyes to explore faces, making gestures etc.



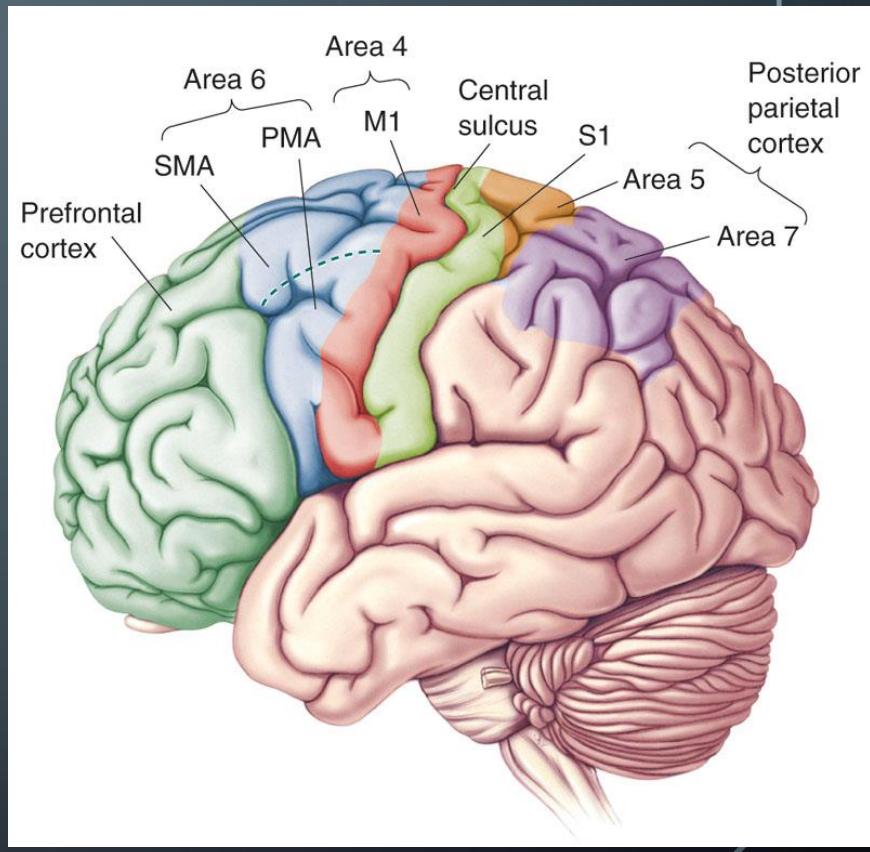
Motor systems – cortical areas

- Many different cortical areas: mainly within the frontal lobe



MOTOR CORTEX

- Primary motor cortex (area 4)
  - Somatotopic organization
  - Control of lower motor neuron
- Premotor cortex (area 6 laterally)
  - Preparation of strategy of movement
    - Sensor motor transformation
    - Movement patterns selection
- Supplementary motor cortex (area 6 medially)
  - Involved in planning of complex movements
    - Movement of both limbs
    - Complex motion sequences
  - Activated also by complex movement rehearsal



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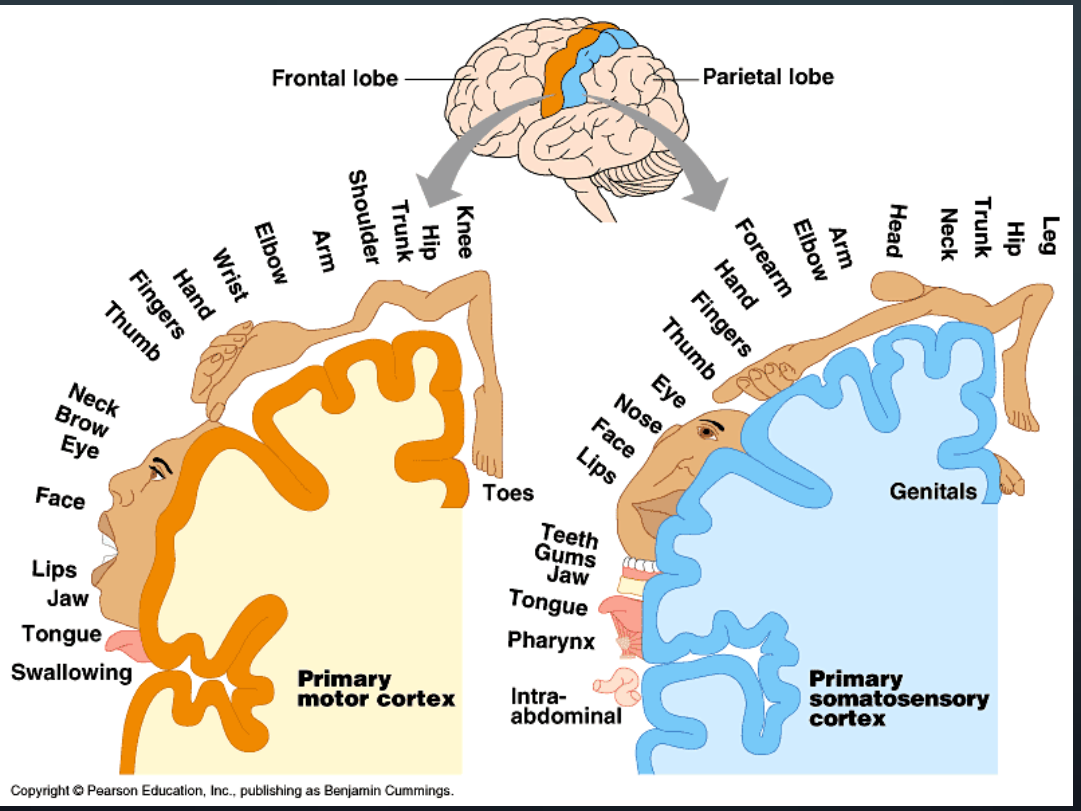
THE **PRIMARY MOTOR CORTEX**

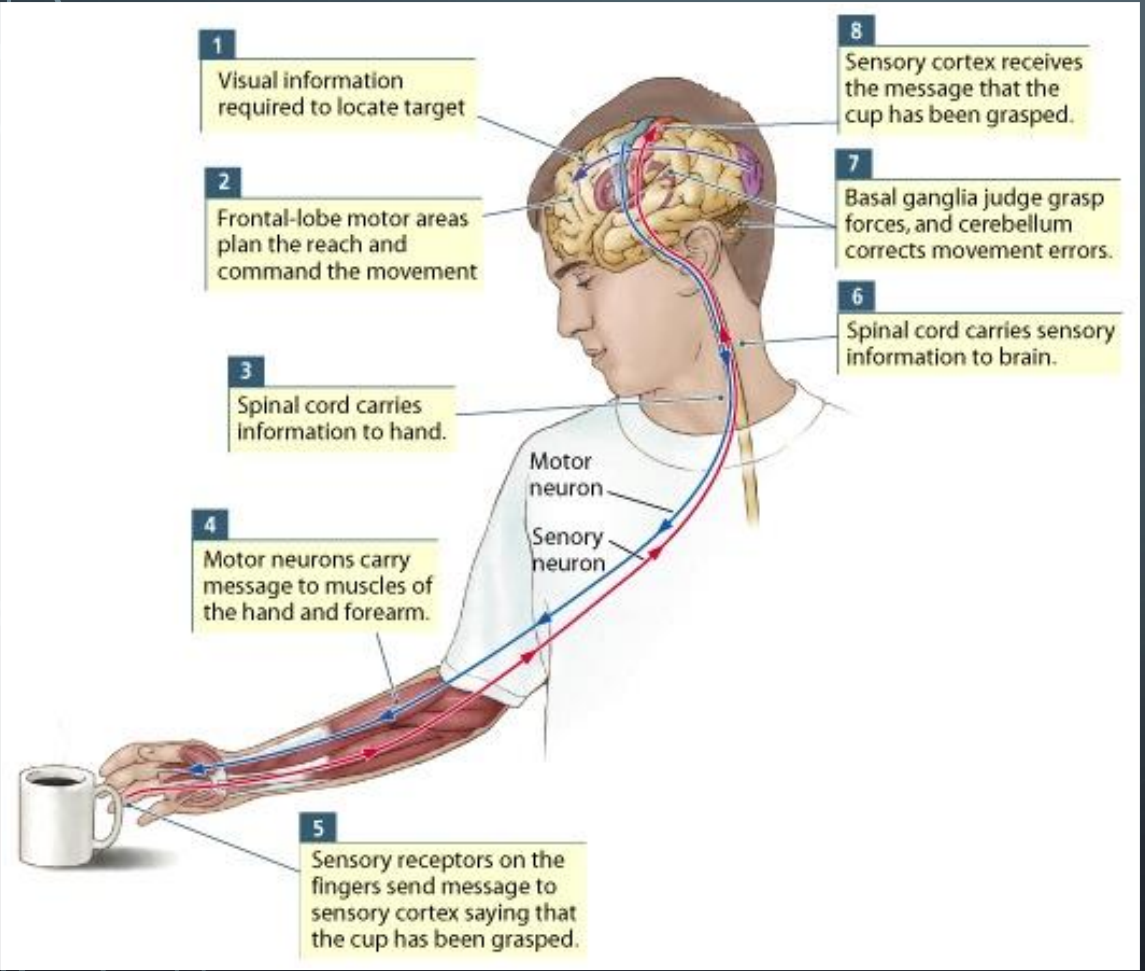
- (or **M1**) works in association with pre-motor areas to plan and execute movements.
- M1 contains large neurons known as Betz cells which send long axons down the spinal cord to synapse onto alpha motor neurons which connect to the muscles.
- Pre-motor areas are involved in planning actions (in concert with the basal ganglia) and refining movements based upon sensory input (this requires the cerebellum).
- The human primary motor cortex is located in the dorsal part of the **precentral gyrus** and the anterior bank of the central sulcus. The precentral gyrus is in front of the postcentral gyrus from which it is separated by the central sulcus. Its anterior border is the precentral sulcus, while inferiorly it borders to the lateral fissure (*Sylvian fissure*). Medially, it is contiguous with the paracentral lobule.

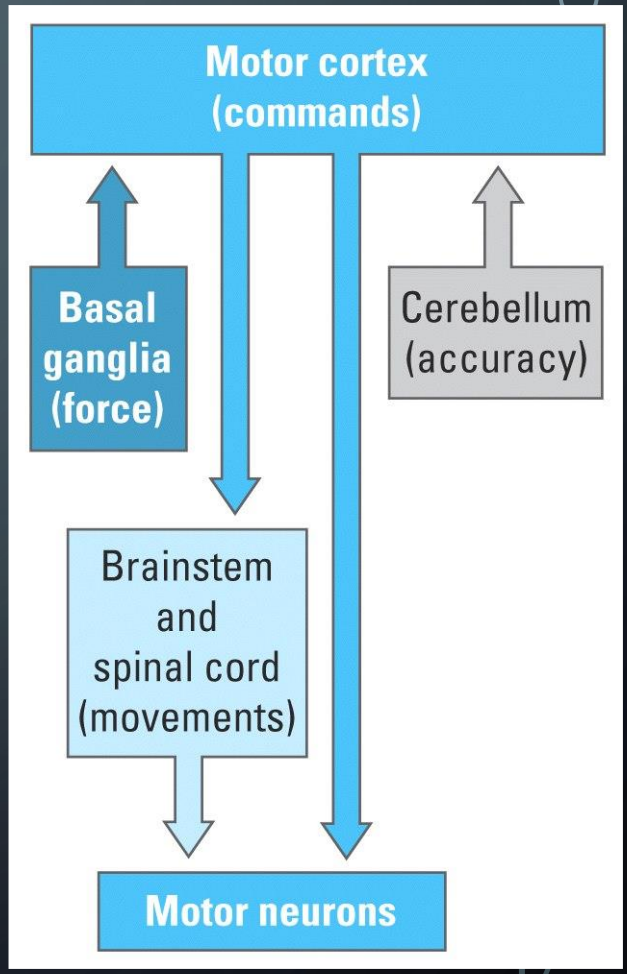
MOTORIC CONTROLLING SYSTEMS



- The upper motor neurons reside in the precentral gyrus of the frontal lobe also called the "motor strip". These upper motor neurons are arranged in a stereotypical fashion. Neurons which control movements of the face and mouth are located near the Sylvian or lateral fissue and neurons which control the muscles of the thighs and legs are located near the medial longitudinal fissure and within the central sulcus.

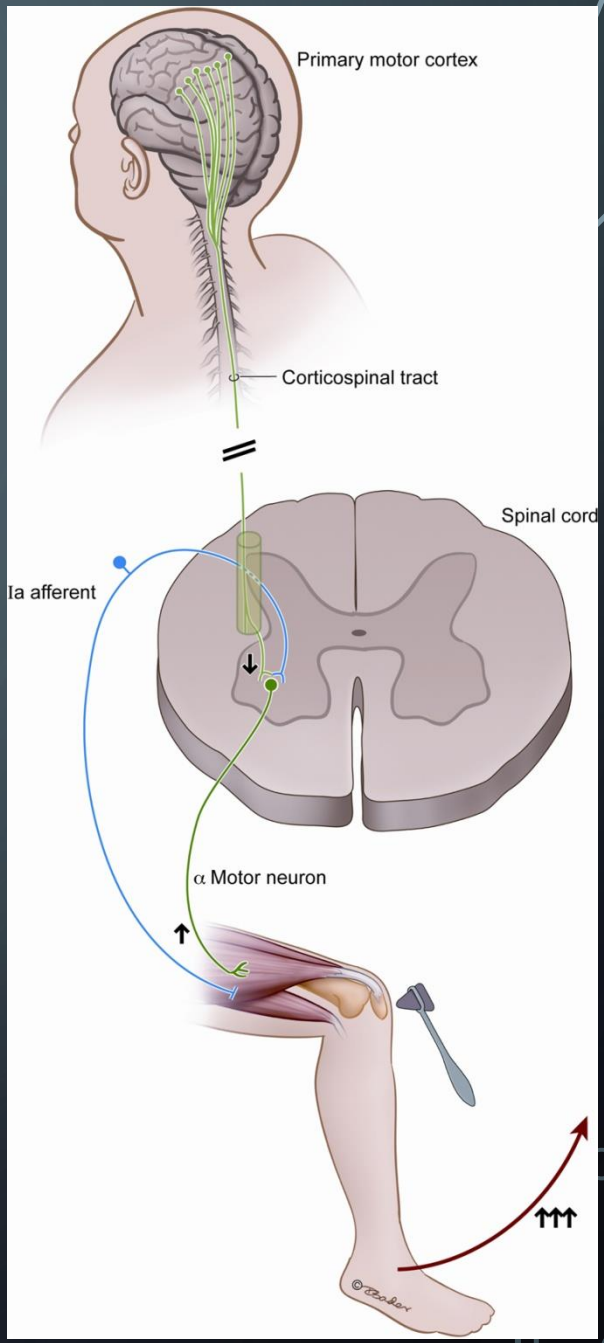
STEPS IN MOTOR ACTION





INTRODUCTION

- Skeletal muscle contraction is initiated by lower motor neuron
- Lower motor neuron is a part of local reflex circuits
- The information from several sources is integrated in the lower motor neuron
  - Higher levels of CNS
    - Upper motor neuron, tectum, n. ruber, brain stem
  - Proprioception



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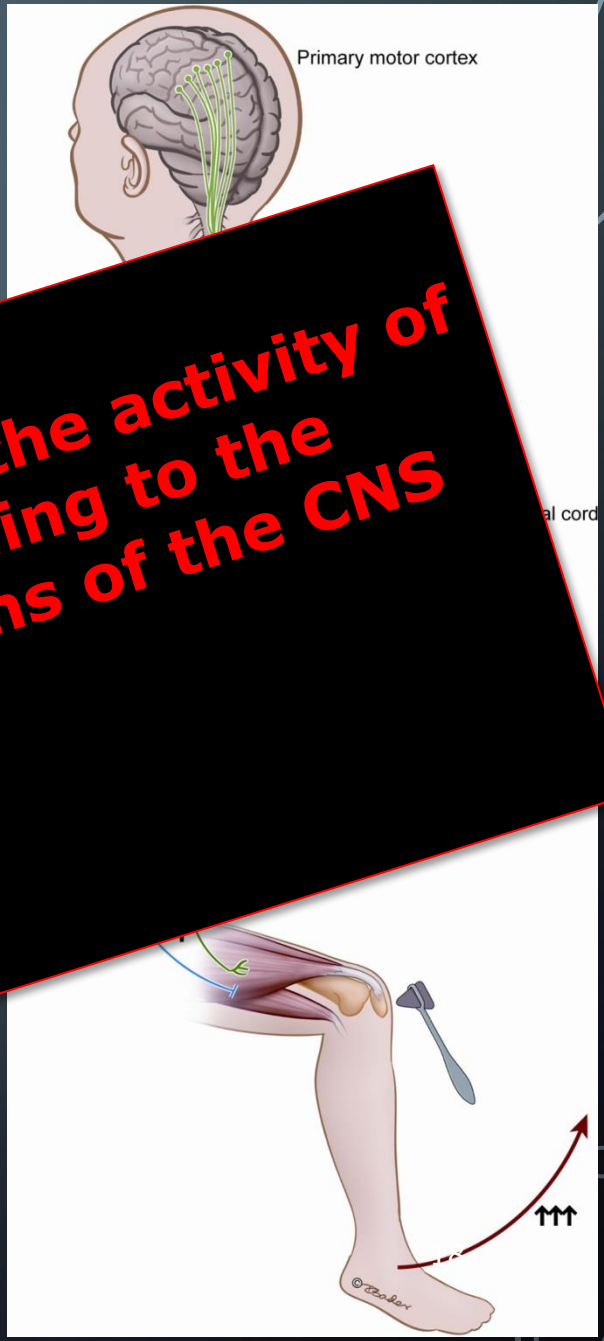
INTRODUCTION

- Skeletal muscle contraction is initiated by lower motor neuron
- Lower moto
- uber, brain
- ception

Lower motor neuron regulates the activity of local reflex circuits, according to the demands of the higher regions of the CNS



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INTRODUCTION

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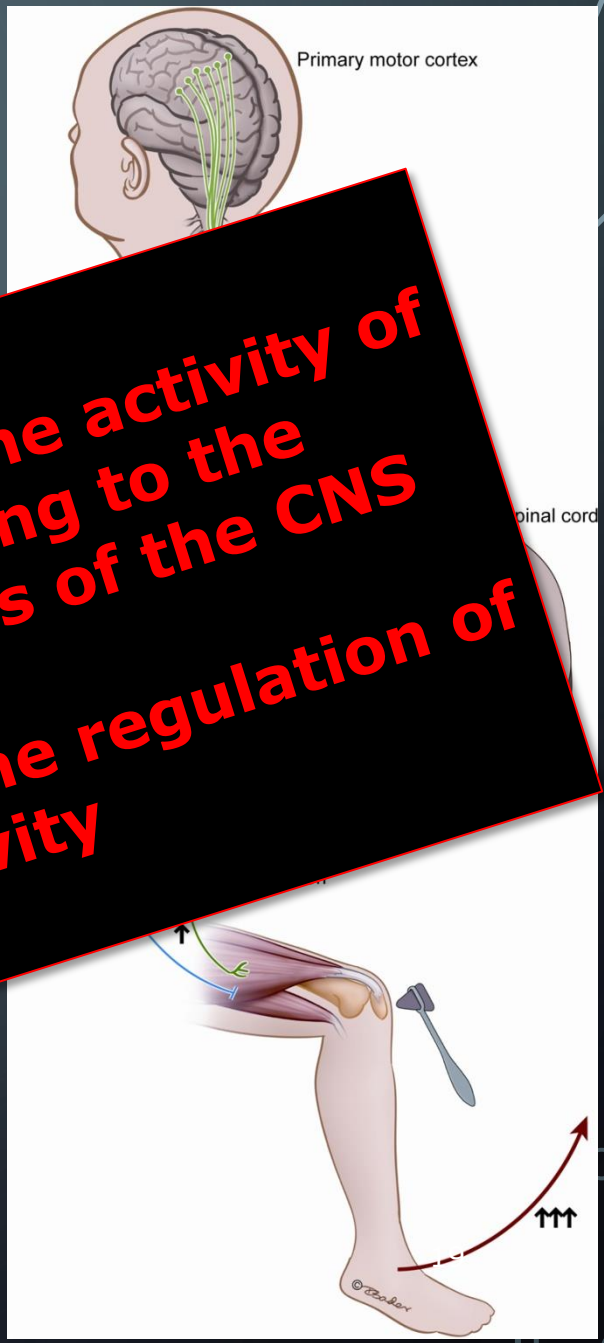
Lower motor neuron regulates the activity of local reflex circuits, according to the demands of the higher regions of the CNS

Proprioception is crucial for the regulation of local circuit activity



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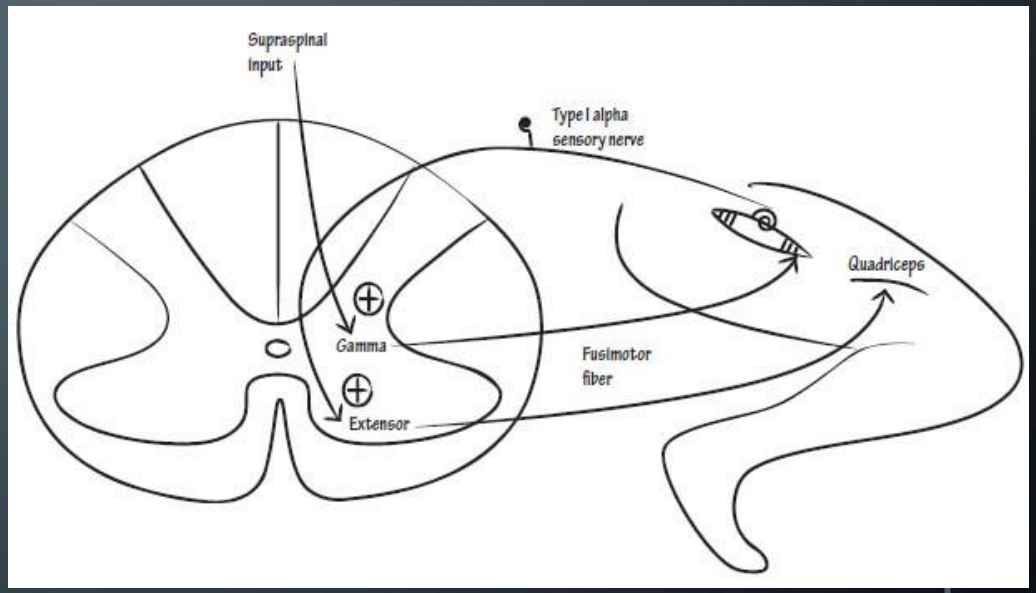
LOWER MOTOR NEURON

- **α motoneuron**
  - Innervation of contractile elements
  - Extrafusal fibers
  - Muscle contraction
- **γ motoneuron**
  - Innervation of muscle spindles
  - Intrafusal fibers
  - Alignment of muscle spindles
  - Gamma loop
- **β motoneuron**



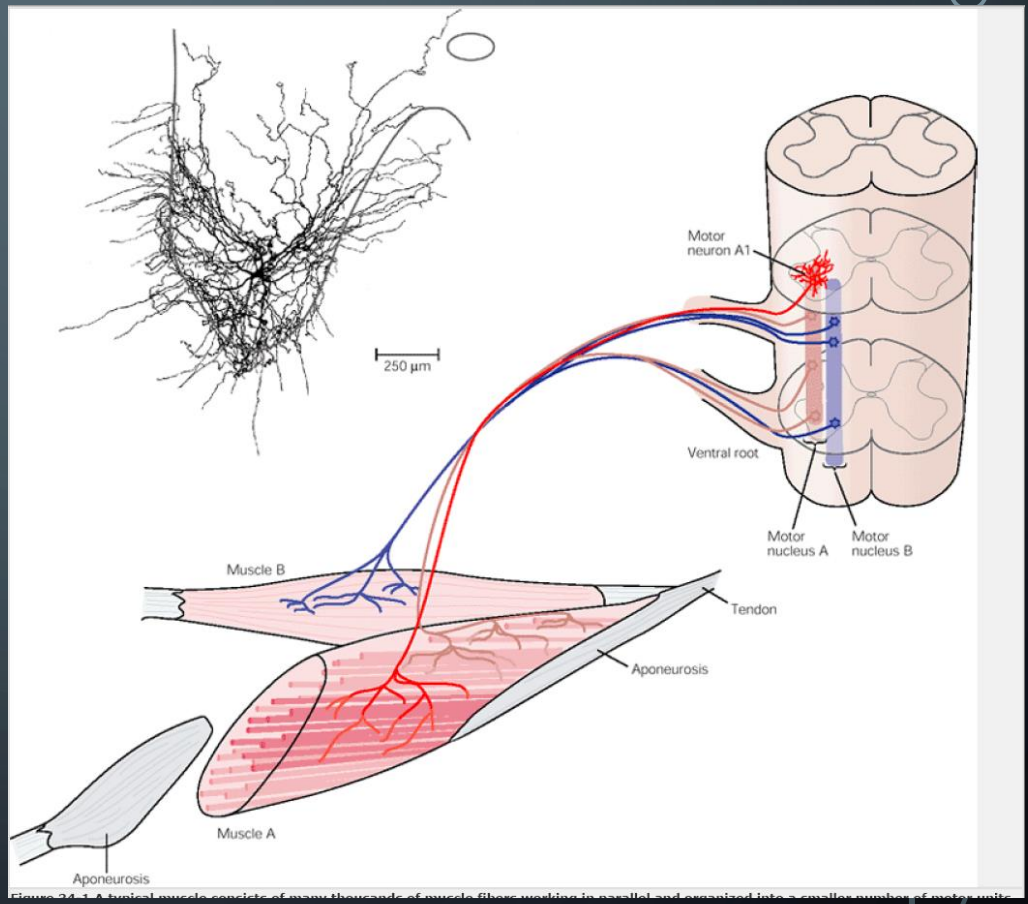
http://epomedicine.com/wp-content/uploads/2016/07/gamm

ALPHA MOTOR NEURONS (A-MNS)

- are large lower motor neurons of the brainstem and spinal cord. They innervate extrafusal muscle fibers of skeletal muscle and are directly responsible for initiating their contraction.
- Alpha motor neurons are distinct from gamma motor neurons, which innervate intrafusal muscle fibers of muscle spindles.
- While their cell bodies are found in the central nervous system (CNS), alpha motor neurons are also considered part of the somatic nervous system—a branch of the peripheral nervous system (PNS)—because their axons extend into the periphery to innervate skeletal muscles.

MOTOR UNIT

- A typical muscle is innervated by about 100 motoneurons which are localized in motor nucleus
- Each motoneuron innervate from 100 to 1000 muscle fibers and one muscle fiber is innervated by a single motoneuron
- The ensemble of muscle fibers innervated by a single neuron and corresponding motoneuron constitutes the motor unit



PROPRIOCEPTION

- Information about the position of body parts in relation to each other

  (The sum of information about lengths of particular muscles)

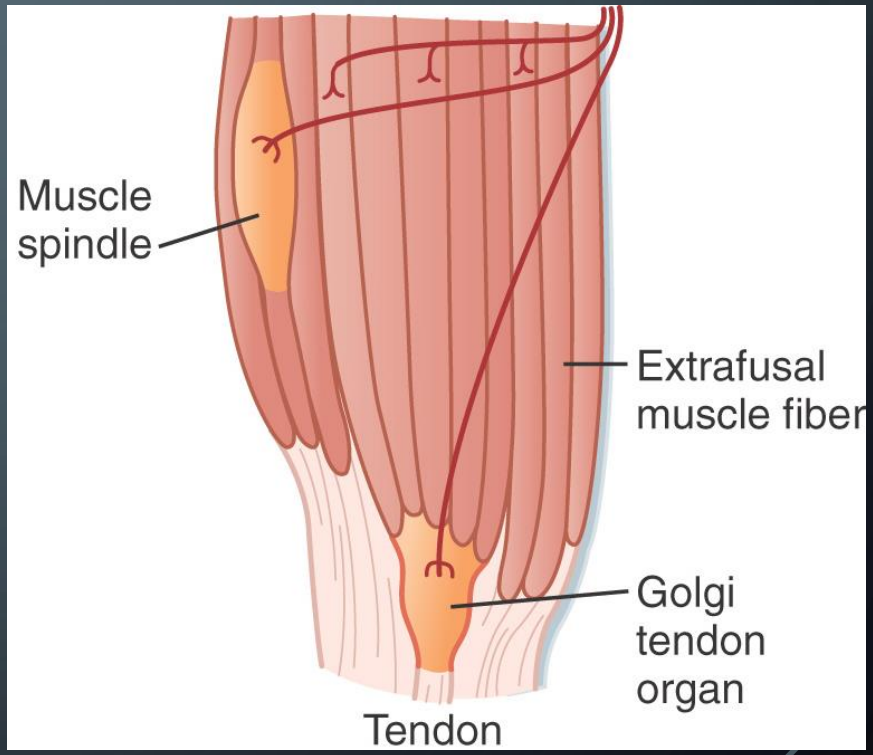
- Information about movement

  (The force and speed of muscle contraction)

- Reflex regulation of muscle activity

- Muscle spindles
  - Lie in parallel with extrafusal muscle fibers

- Golgi tendon organ
  - Arranged in series with extrafusal muscles



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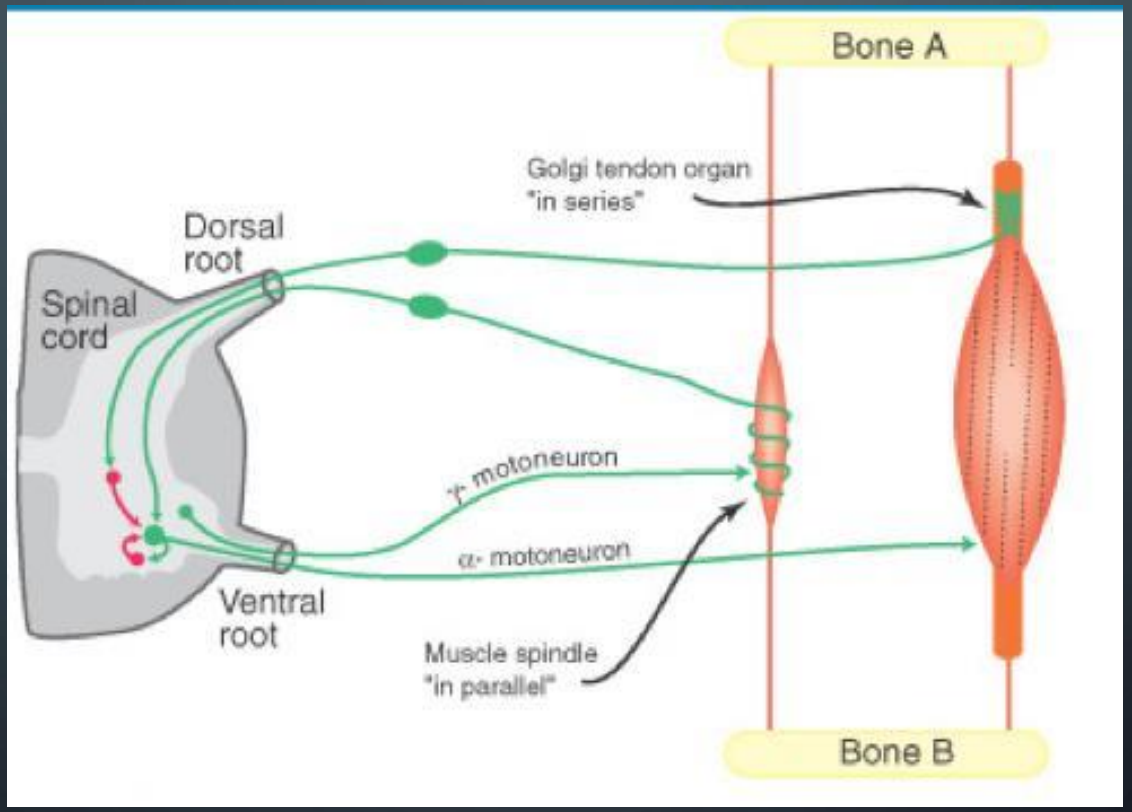
MUSCLE SPINDLE AND GOLGI TENDON ORGAN



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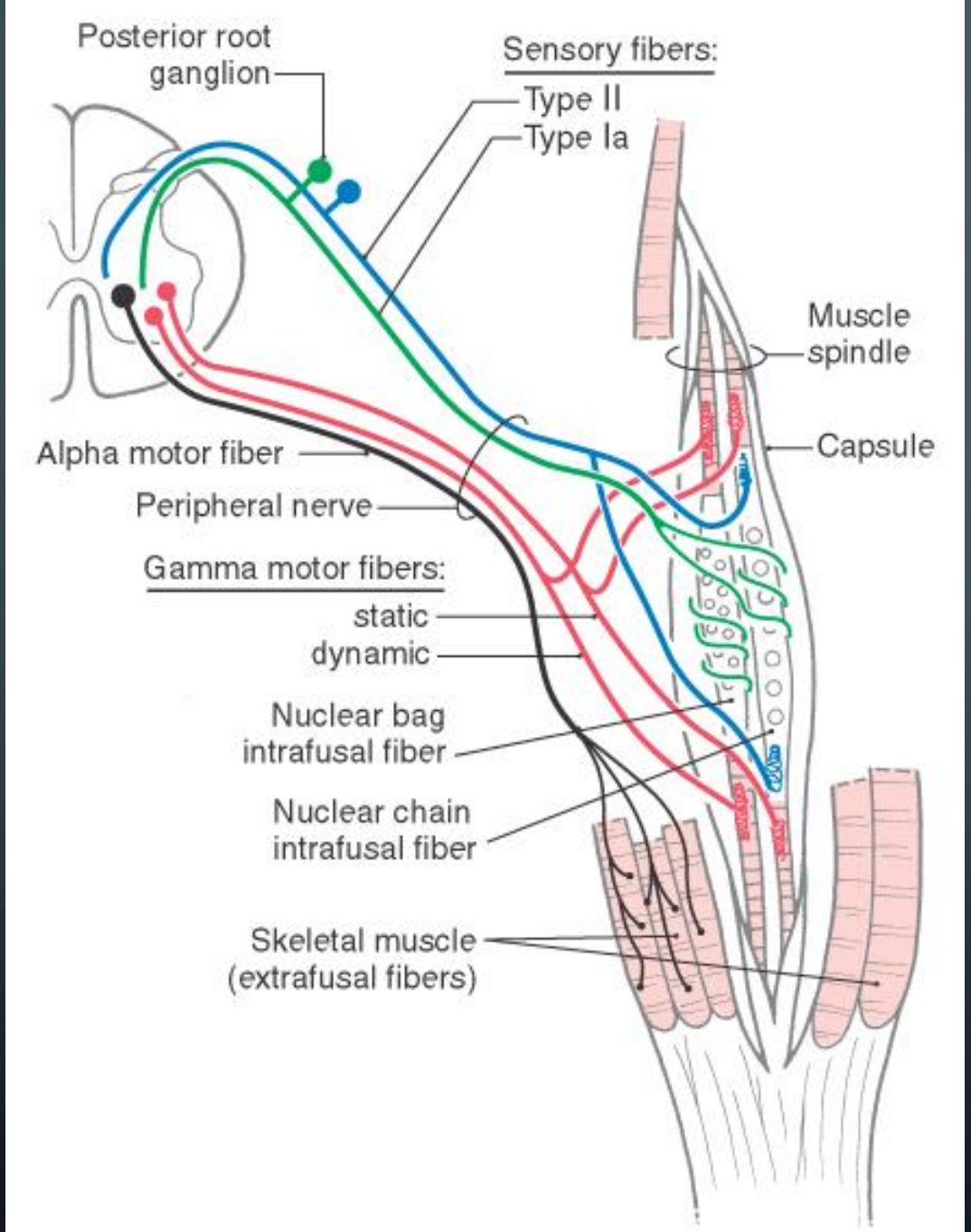
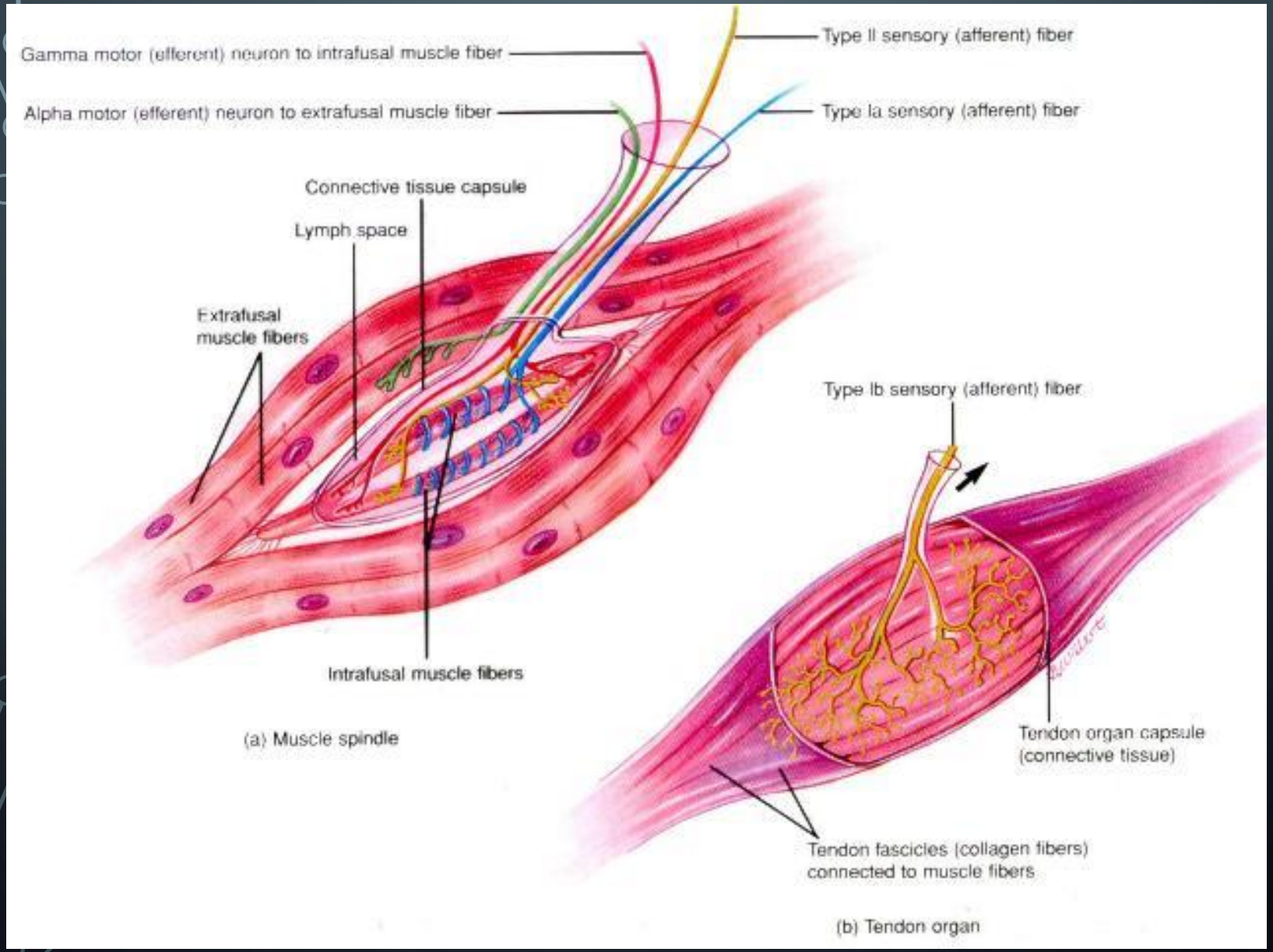
MUSCLE SPINDLES

- encapsulated structures within skeletal muscle, containing intrafusal muscle fibers, in parallel with extrafusal muscle fibers (normal skeletal muscle); multiple nuclei in central region and intrafusal fibers at each end; two morphological/functional types of spindles



Muscle spindle

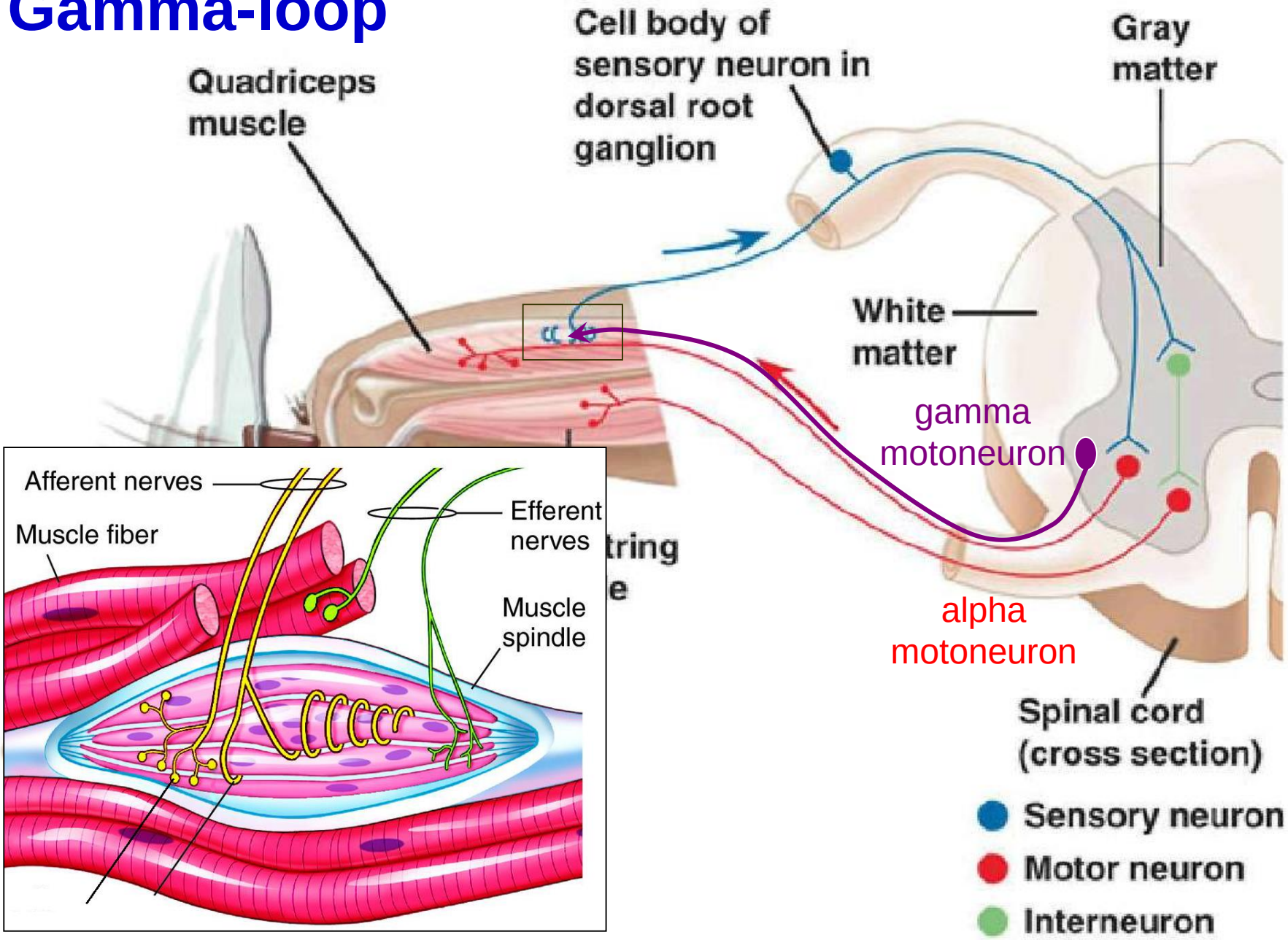

Gamma motor (efferent) neuron to intrafusal muscle fiber
Alpha motor (efferent) neuron to extrafusal muscle fiber
Type II sensory (afferent) fiber
Type Ia sensory (afferent) fiber
Connective tissue capsule
Lymph space
Extrafusal muscle fibers
Intrafusal muscle fibers
(a) Muscle spindle
Type Ib sensory (afferent) fiber
Tendon organ capsule (connective tissue)
Tendon fascicles (collagen fibers) connected to muscle fibers
(b) Tendon organ

ABOUT THE GAMMA-LOOP

- Skeletal muscles can be activated directly, by the stimulation of alpha-motoneurons or indirectly, via the gamma loop – proprioceptive reflex arc.

- Stimulation of gamma-motoneurons results in the contraction of intrafusal fibres of muscle spindles. Shorthening of the muscle spindle (similarly to the stretching of the surrounding muscles) activates the proprioceptive reflex arc. This results in the indirect contraction of extrafusal („*working*”) muscle fibres.

Gamma-loop


Quadriceps muscle
Cell body of sensory neuron in dorsal root ganglion
Gray matter
White matter
gamma motoneuron
alpha motoneuron
Spinal cord (cross section)
Sensory neuron
Motor neuron
Interneuron
Afferent nerves
Muscle fiber
Efferent nerves
Muscle spindle

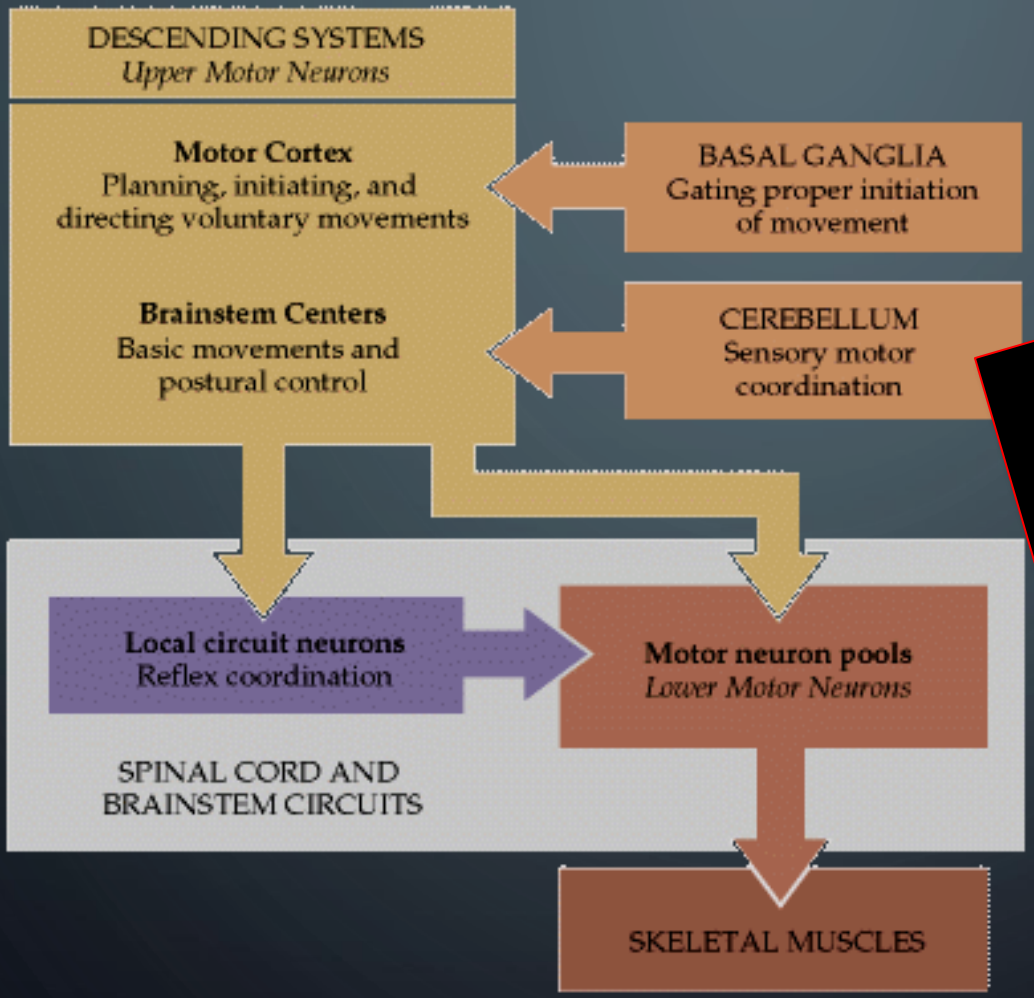
STRETCH REFLEXES

- 1. passive stretch of muscle (e.g. by tapping tendon) activates Ia afferents, which activate alpha motor neurons, causing contraction of stretched muscle: monosynaptic reflex
- 2. passive contraction of muscle (stimulation of alpha motor neurons) causes decreased activity of muscle spindles, leading to decreased activity of alpha motor neurons

STRETCH REFLEXES

- 3. gamma loop: supraspinal input (e.g. corticospinal) activates gamma motor neurons, activating intrafusal fibers that stretch the muscle spindle, activating Ia fibers, which activate alpha motor neurons
- 4. voluntary muscle contraction against a load: corticospinal fibers activate both alpha and gamma motor neurons, allowing Ia fibers to continue to sense muscle length while muscle is contracting: alpha-gamma coactivation

HIERARCHIC ORGANIZATION OF MOTOR SYSTEM



Reflex movement

Rhythmic movement

Voluntary movement

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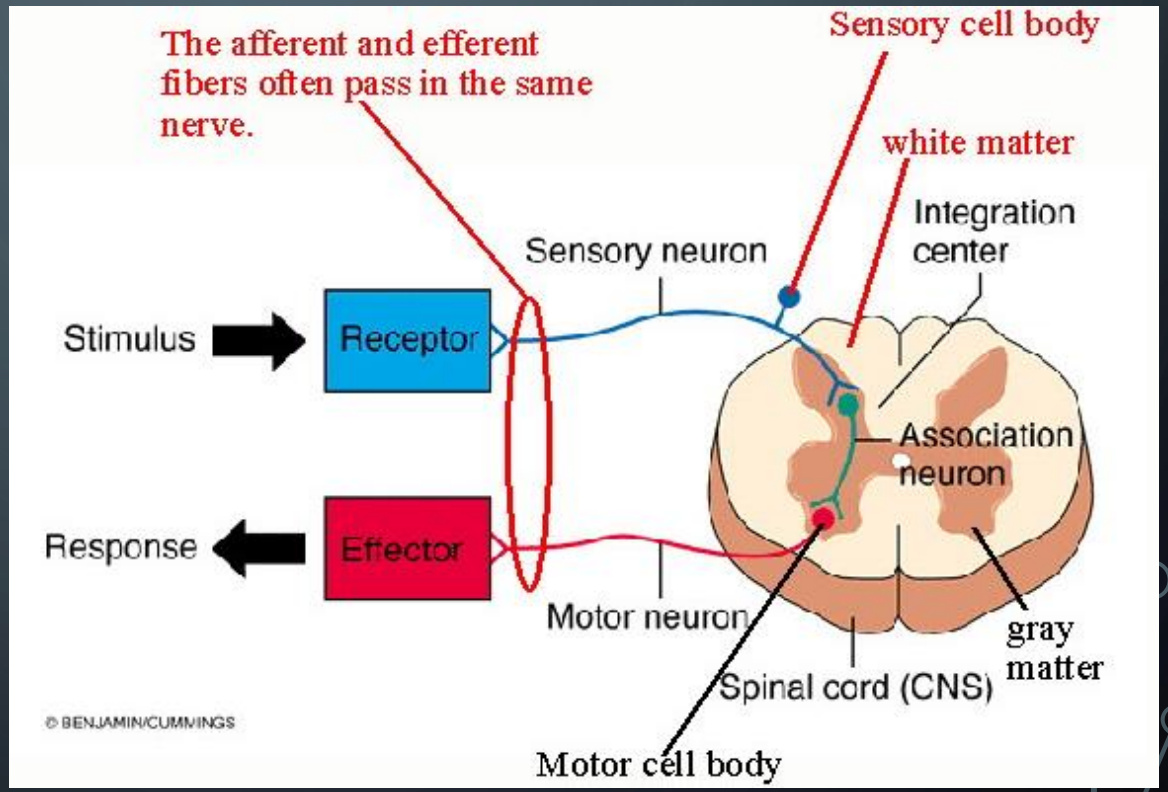
REFLEX

- Reflex movement
  - Stereotype (predictable)
  - Involuntary

- Proprioceptive
- Exteroceptive

- Monosynaptic
- Polysynaptic

- Monosegmental
- Polysegmental



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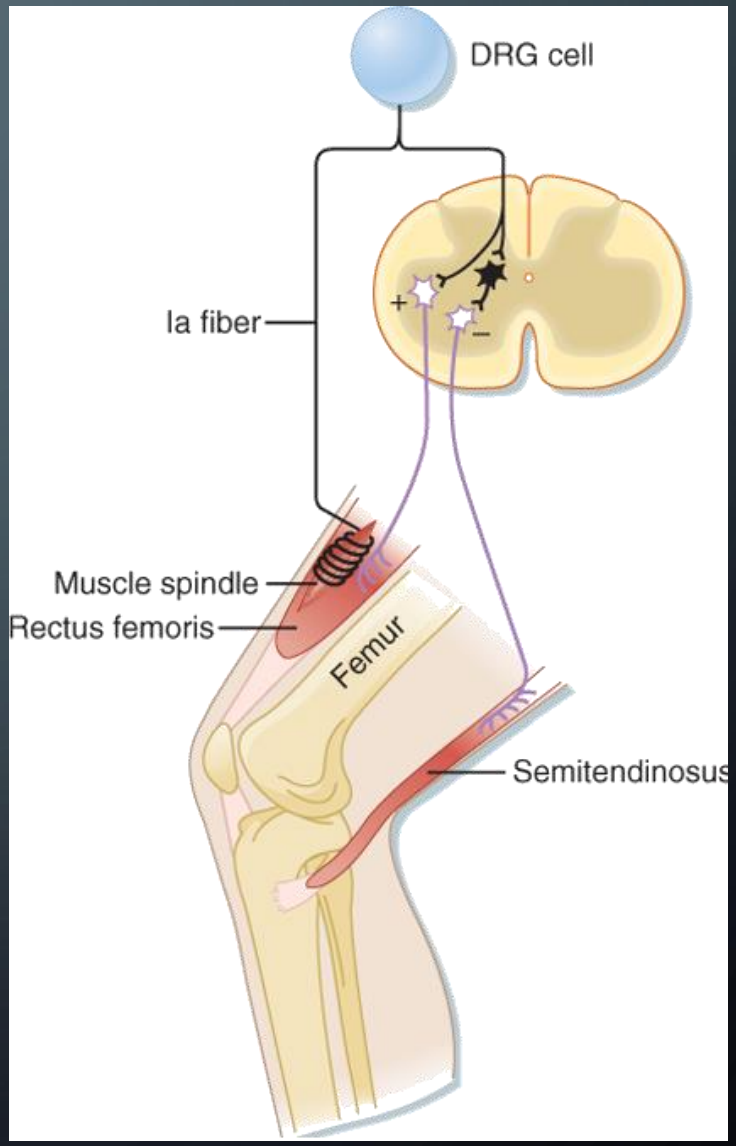
PROPRIOCEPTIVE REFLEX

- Myotatic reflex
  - Monosynaptic
  - Monosegmental
  - Muscle spindle
- Homonymous muscle - activation
- Antagonist muscle - inhibition
- Phasic response (Ia)
  - Protection against overstretch of extrafusal fibrers
- Tonic response (Ia a II)
  - Maintains muscle tone



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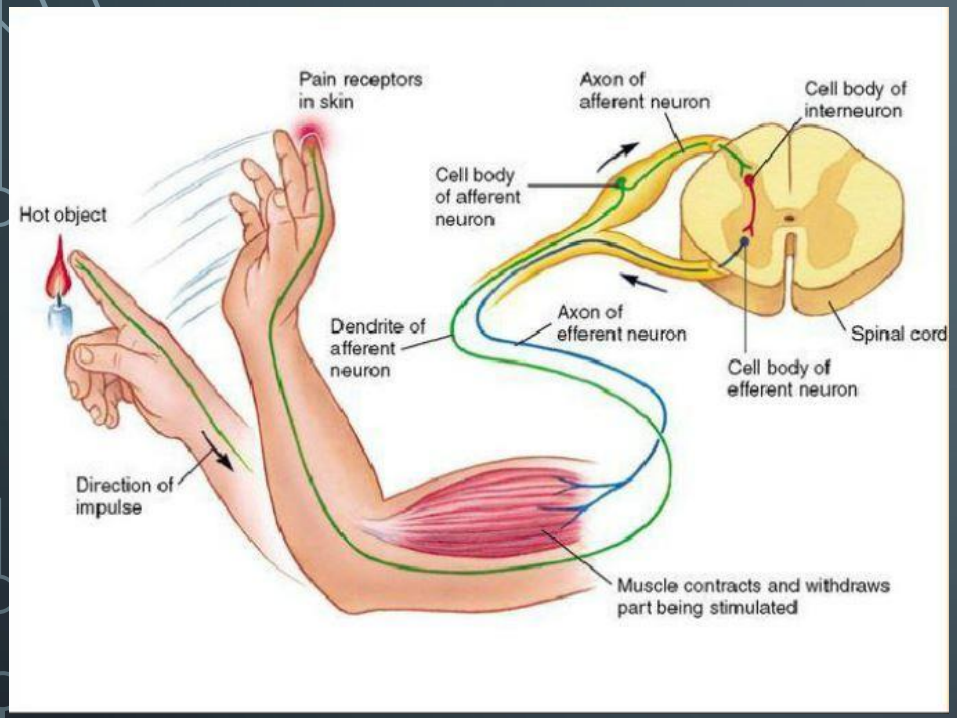
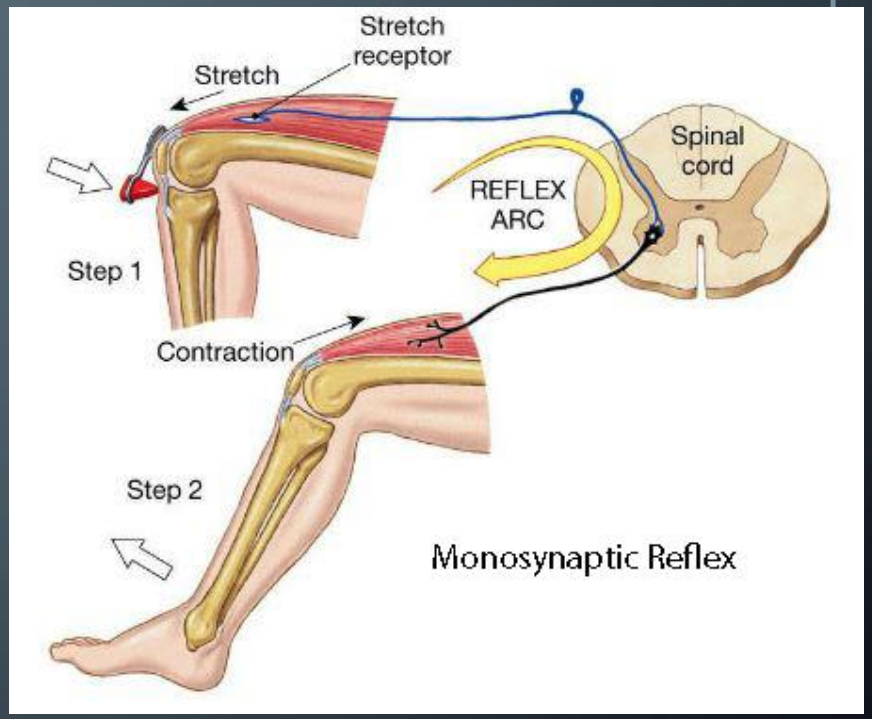
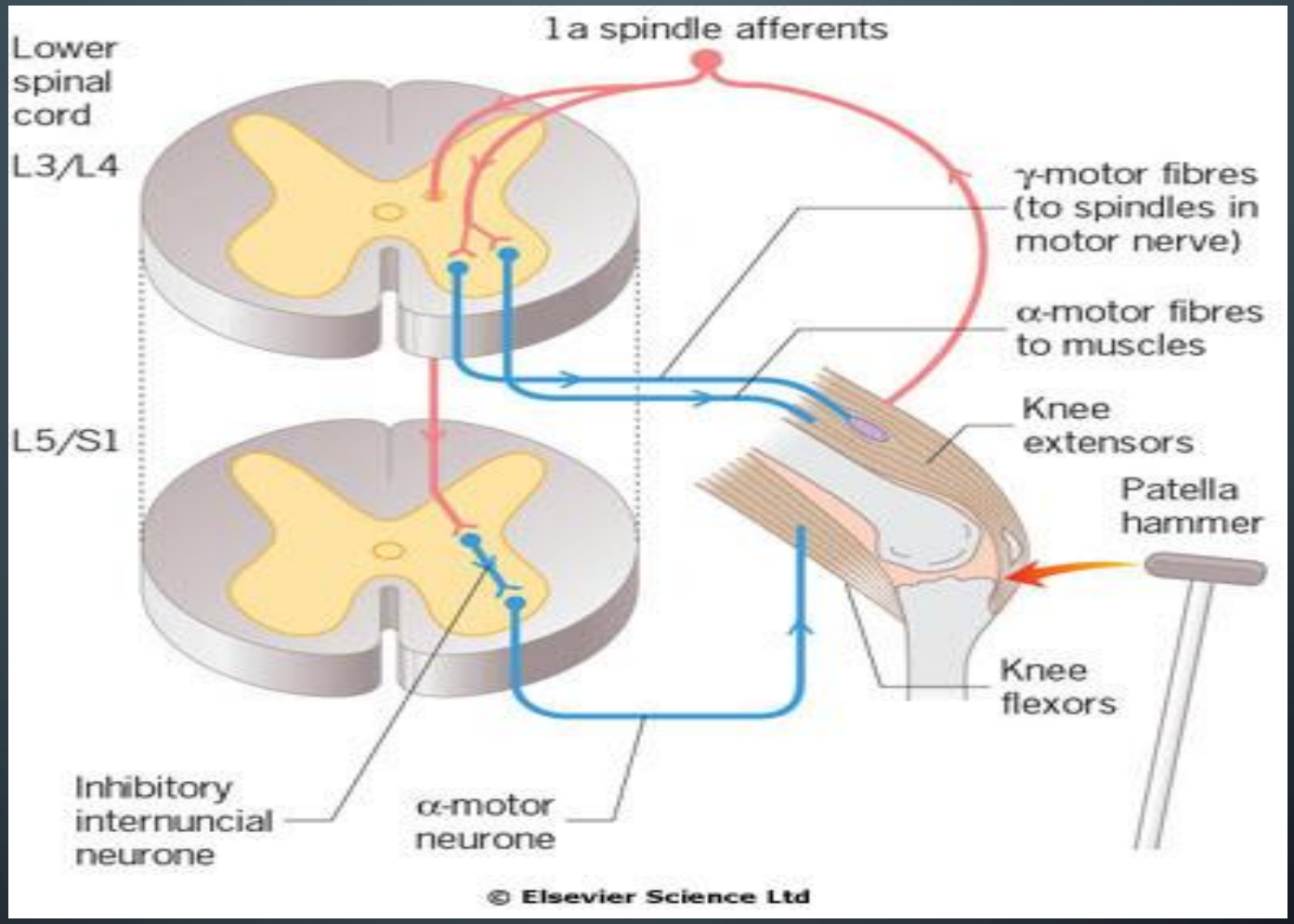
Motor systems – spinal cord



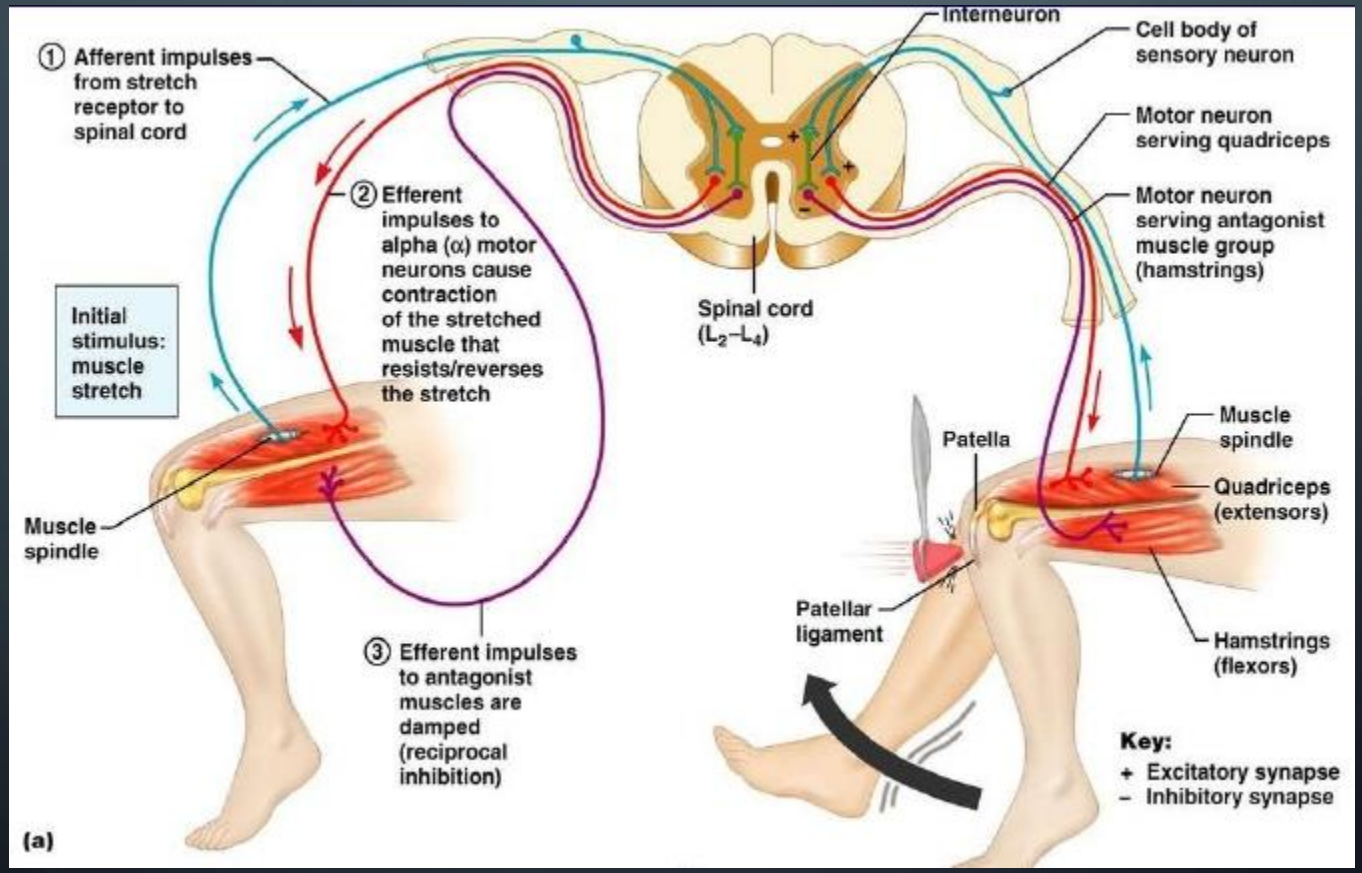


All kinds of spinal reflexes are automatic responses to a stimulus, when the dicission is made by the spinal neuronal circuits without major influence of higher centres of the nervous system!



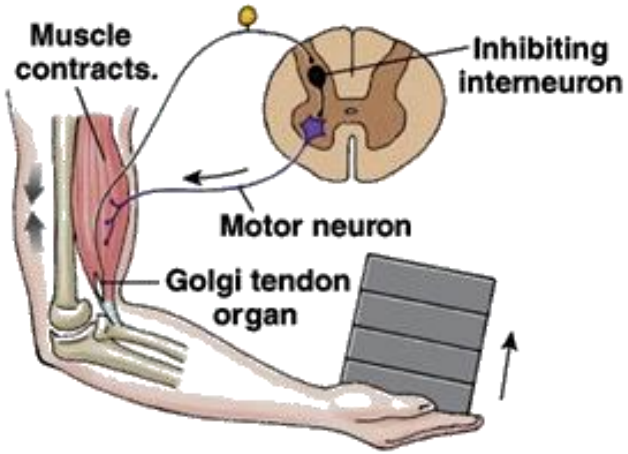
Patellar reflex

STRETCH REFLEX

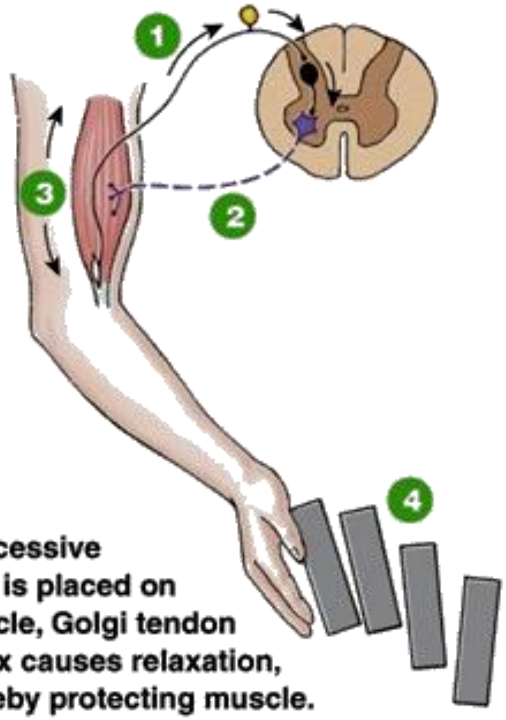


http://www.slideshare.net/ananthatiger/cns-4

Golgi tendon reflex protects the muscle from excessively heavy loads by causing the muscle to relax and drop the load.



(d) Muscle contraction stretches Golgi tendon organ.



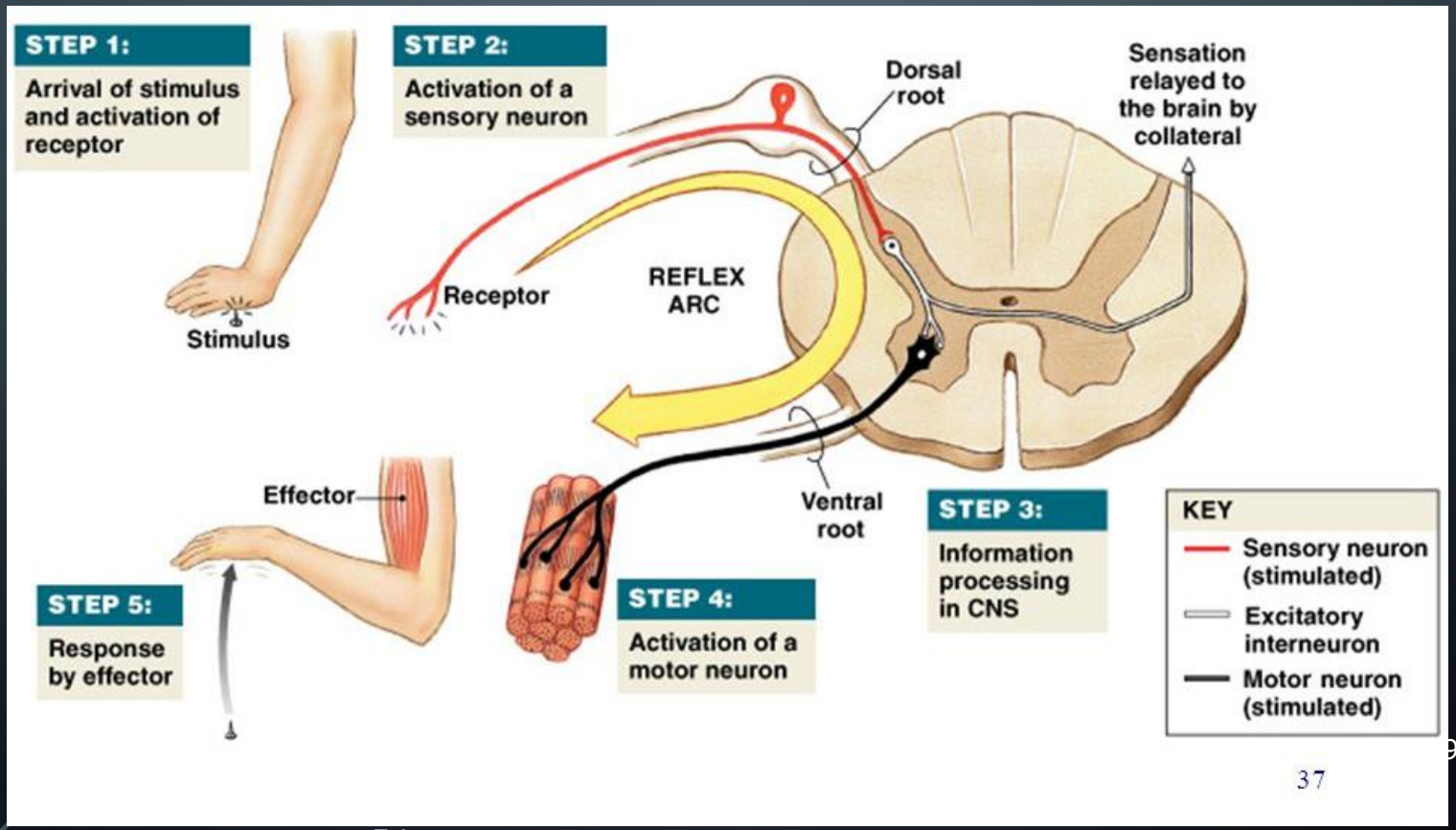
(e) If excessive load is placed on muscle, Golgi tendon reflex causes relaxation, thereby protecting muscle.

1. Neuron from Golgi tendon organ fires.
2. Motor neuron is inhibited.
3. Muscle relaxes.
4. Load is dropped.

Fig. 13-6b

EXTEROCEPTIVE REFLEX

- Polysynaptic
- Polysegmental



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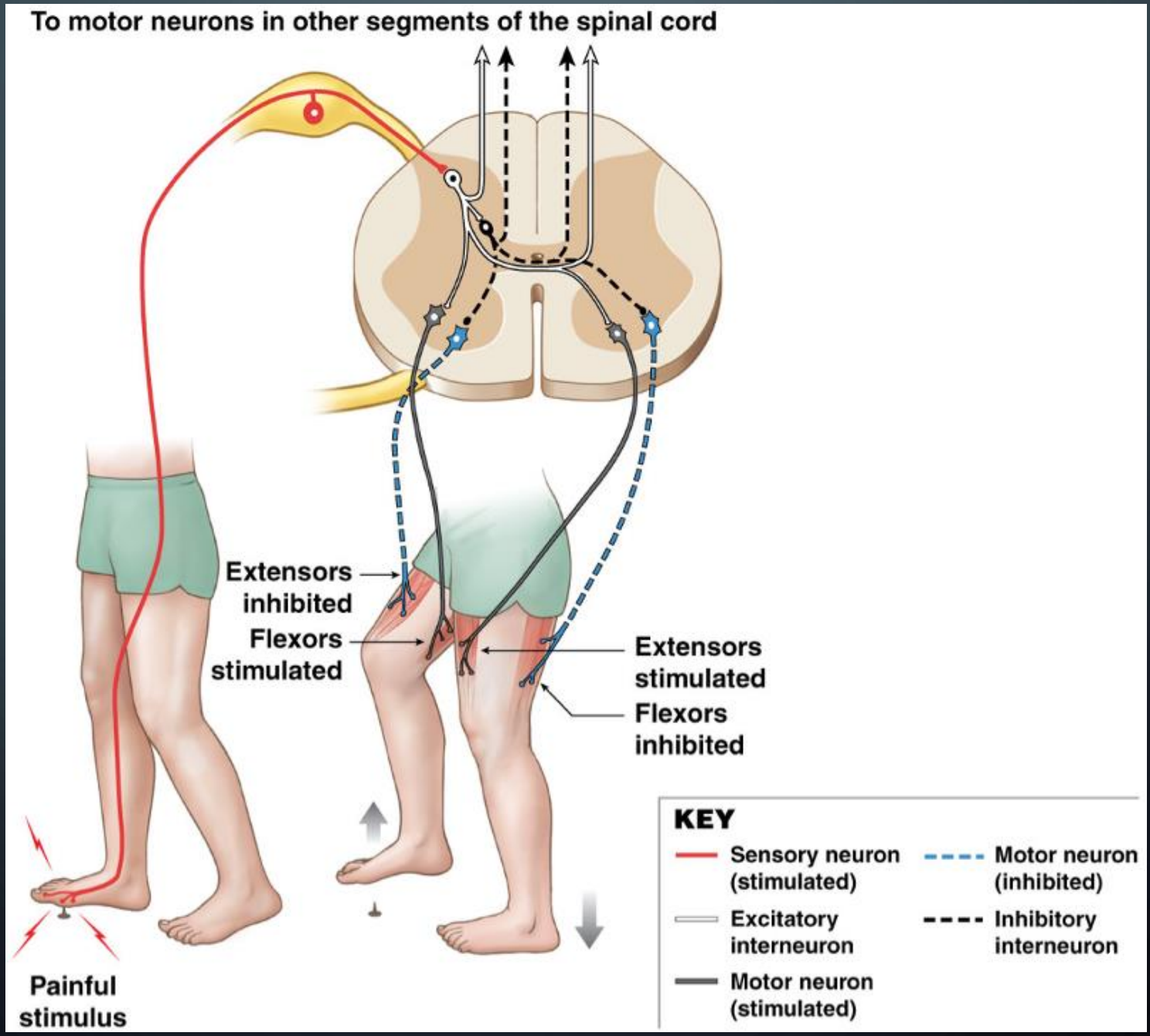

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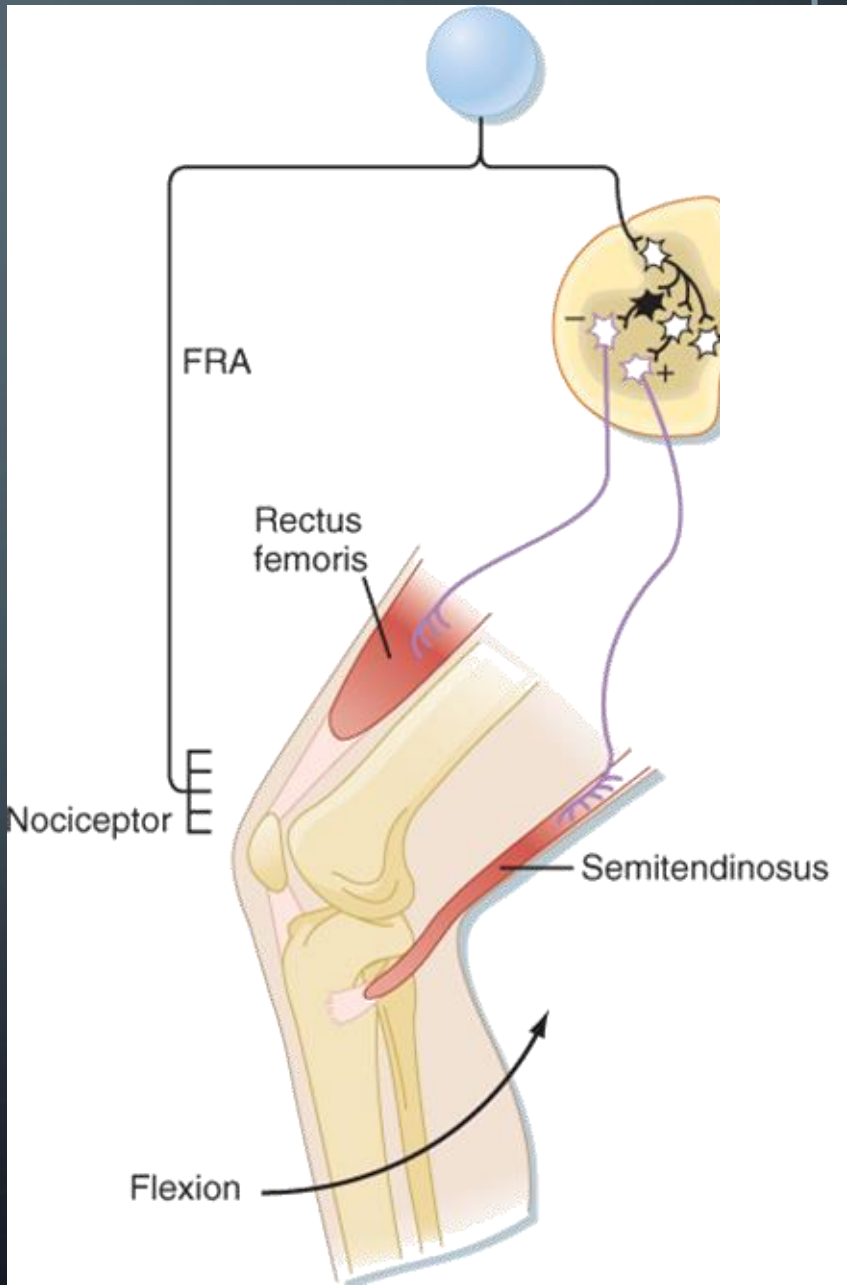
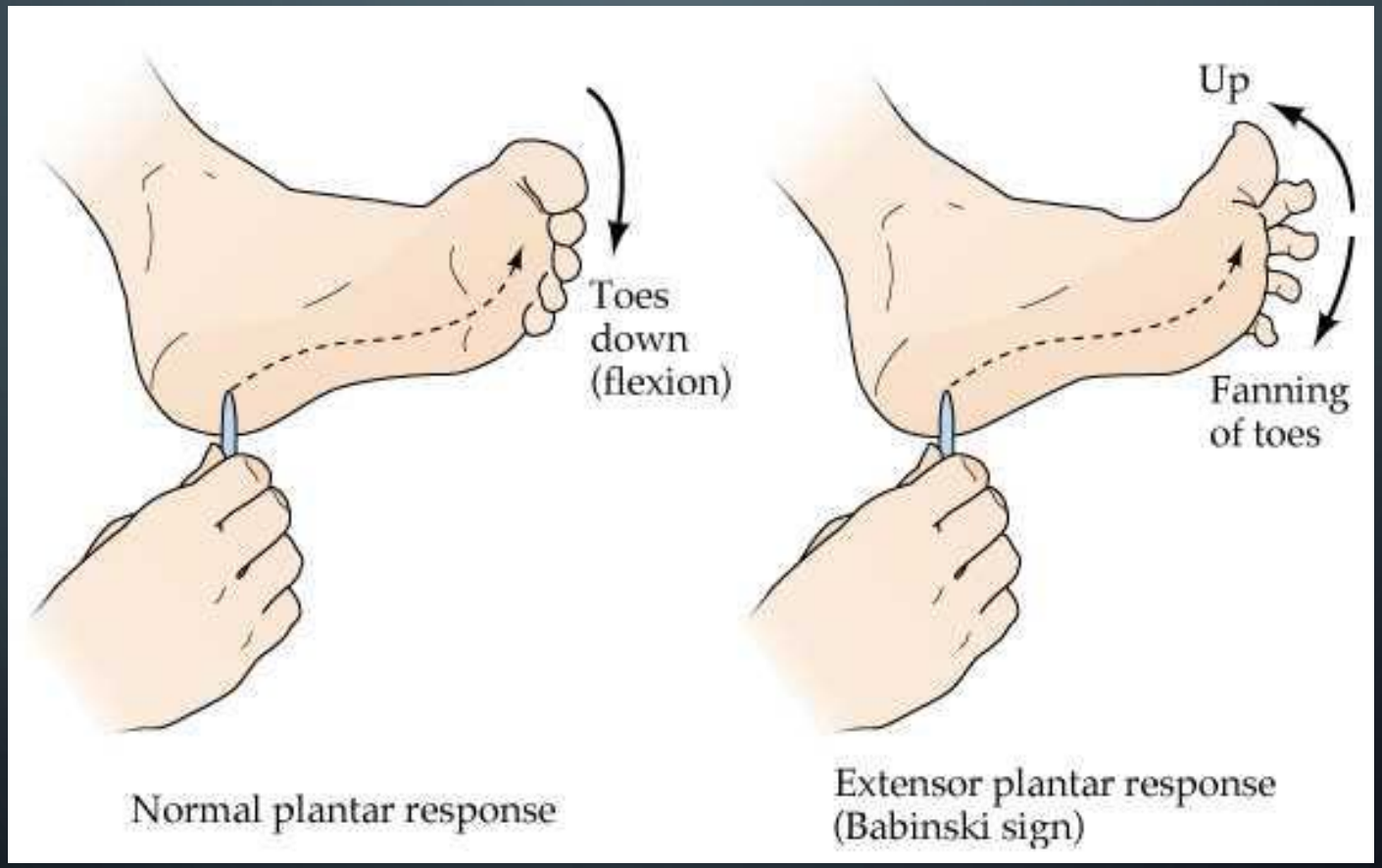
FLEXION WITHDRAWAL REFLEX

- Polysynaptic reflex mediated by FRAs (flexion reflex afferents: nociceptors, mechanoreceptors etc.)
  - flexion in response to painful stimuli
- FRAs synapse on inhibitory and excitatory interneurons which excite ipsilateral flexor motorneurons & inhibit extensor motorneurons
- Physiological importance:
  - Rapid flexion away from painful stimuli
- Clinical importance: upper motor neuron lesion impairs flexion reflex → pathalogical **Babinski sign**



UPPER MOTOR NEURON LESION: BABINSKI SIGN



(Type of flexion reflex)

(pathological reflex)

PYRAMIDAL AND EXTRAPYRAMIDAL SYSTEMS

Pyramidal and extrapyramidal systems can only be separated anatomically but not functionally! None of the two systems can work properly alone, they constitute one motor system together!!!

- Pyramidal system is the chief organizer and executor of voluntary movements.

- Extrapyramidal system includes all the motor centres and pathways that lie outside the pyramidal system and are beyond voluntary control.
- Extrapyramidal system:
  - coordinates movements of various groups of muscles both in space and time,
  - regulates job- and sport-specific automatic movements consisting of periodic elements (e.g. walking, running, riding a bike, dancing, driving a car, handwriting or typing, etc.),
  - controls emotional movements,
  - helps to control posture and balance,
  - regulates muscle tone.

SUBCORTICAL (STEM) PATHWAYS CONTROLLING LOWER MOTONEURONS

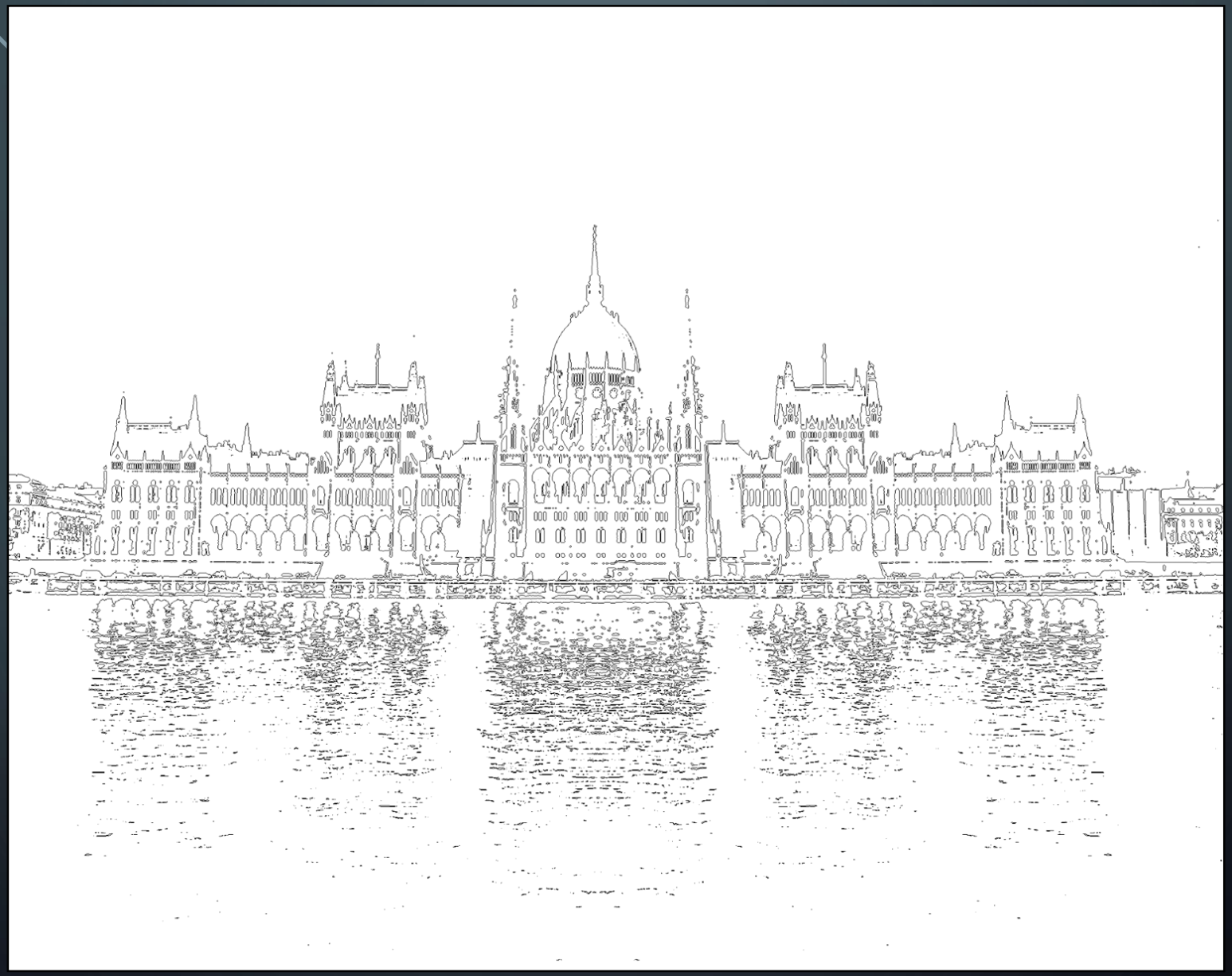
Medial system

- Axial muscle control
- Tr. Vestibulospinalis
  - Reflex control of balance and postural control
- Tr. Reticulospinalis
  - Muscle tone regulation (postural control)
- Tr. Tectospinalis
  - Coordination of head and eyes movements

Lateral system

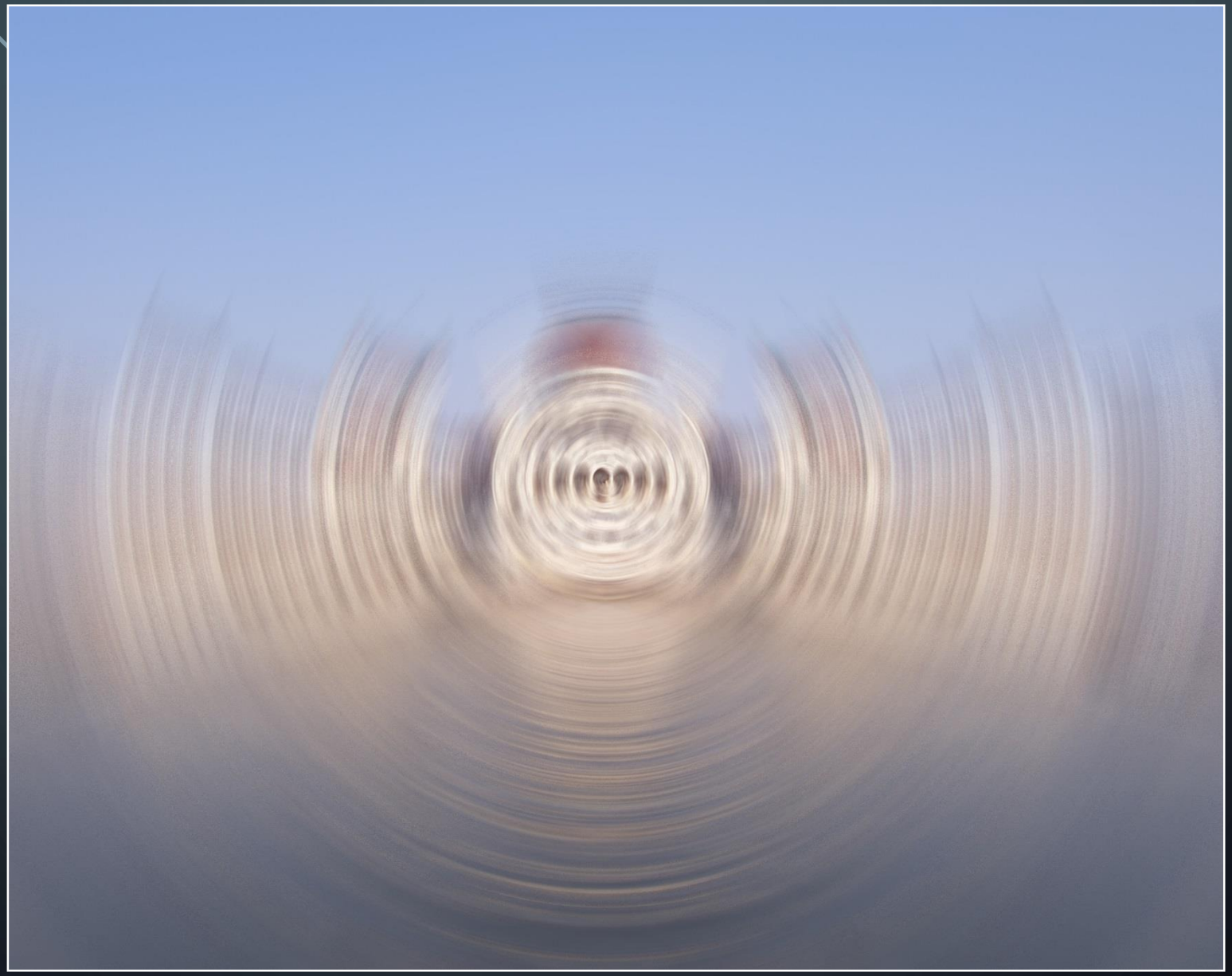
- Distal muscle control
- „Reflex" control of the limbs
- Replaced by tr. corticospinalis

- Tr. Rubrospinalis
- Tr. Rubrobulbaris



Just a sketch: only the principal components can be recognized.

PYRAMIDAL SYSTEM



Colours, beauty, harmony, regularity, but not more than an abstract art.

EXTRAPYRAMIDAL SYSTEM

Taken together: the real world.

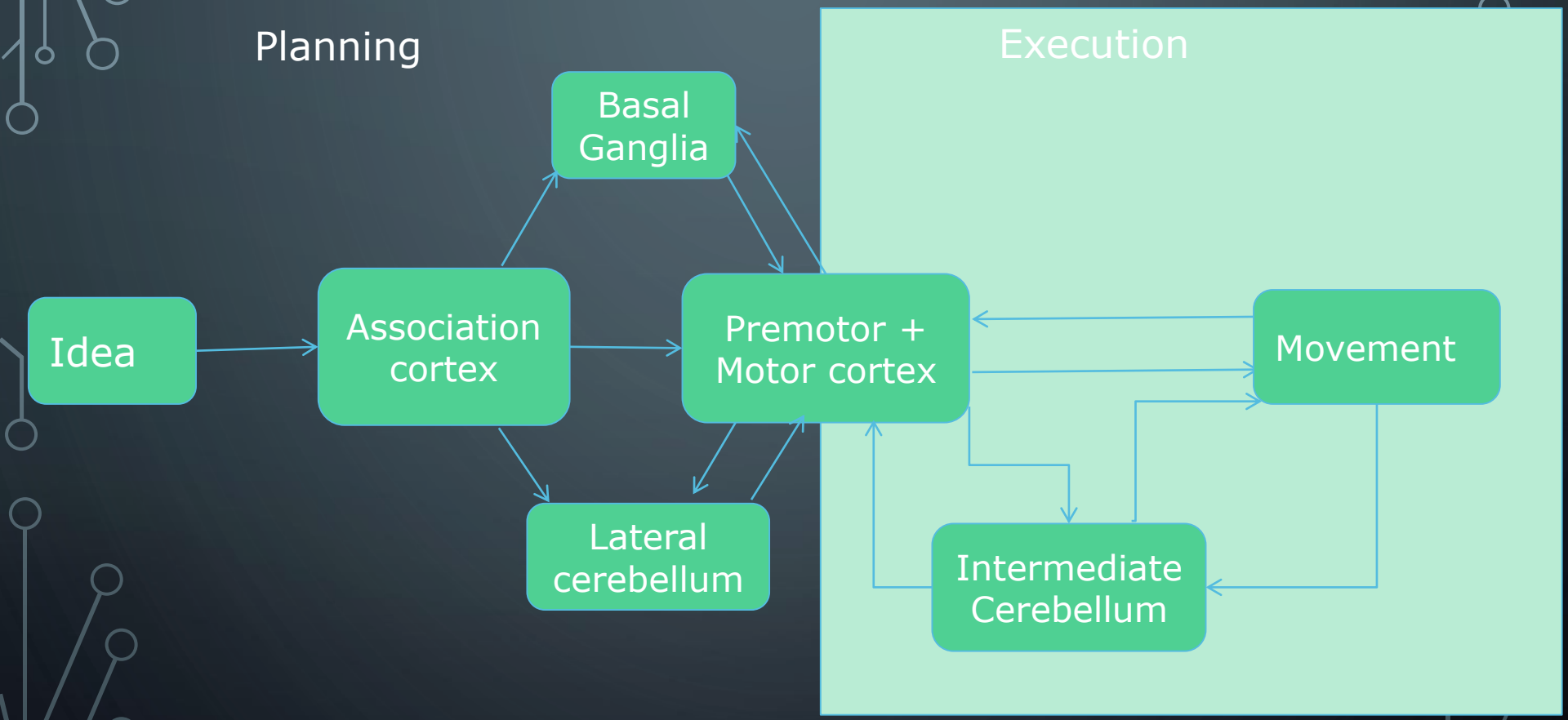
CORTICAL CONTROL OF LOWER MOTOR NEURON

Tractus corticospinalis

Tractus corticobulbaris

Voluntary motor activity

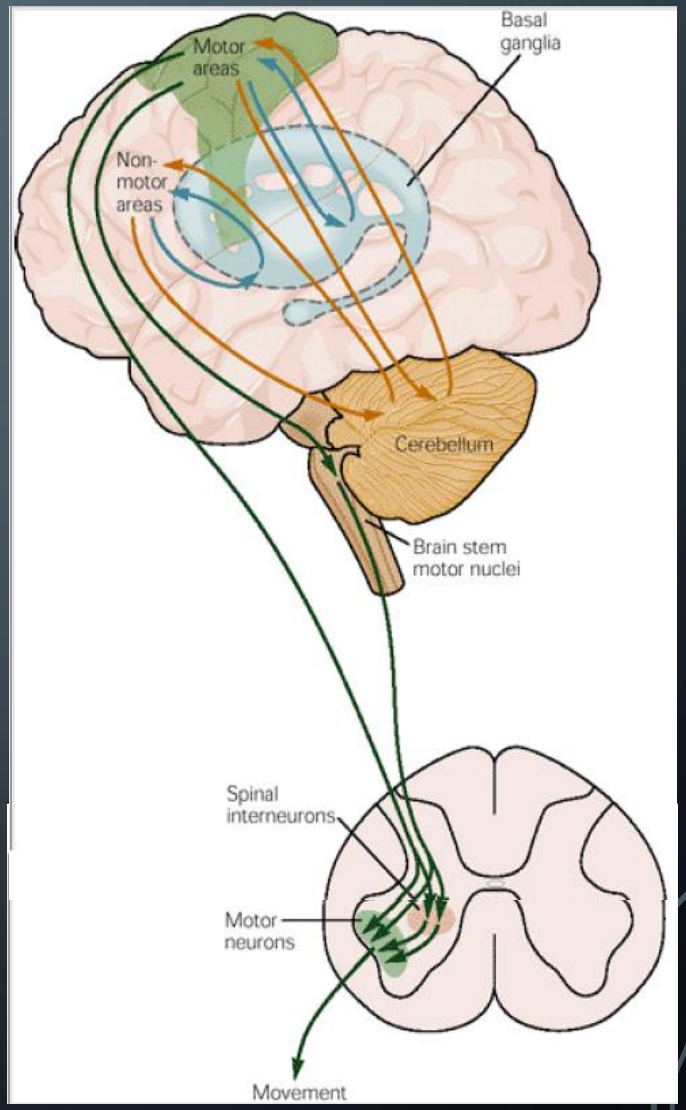
VOLUNTARY MOTOR ACTIVITY



http://www.slideshare.net/drpsdeb/presentations

VOLUNTARY MOTOR ACTIVITY

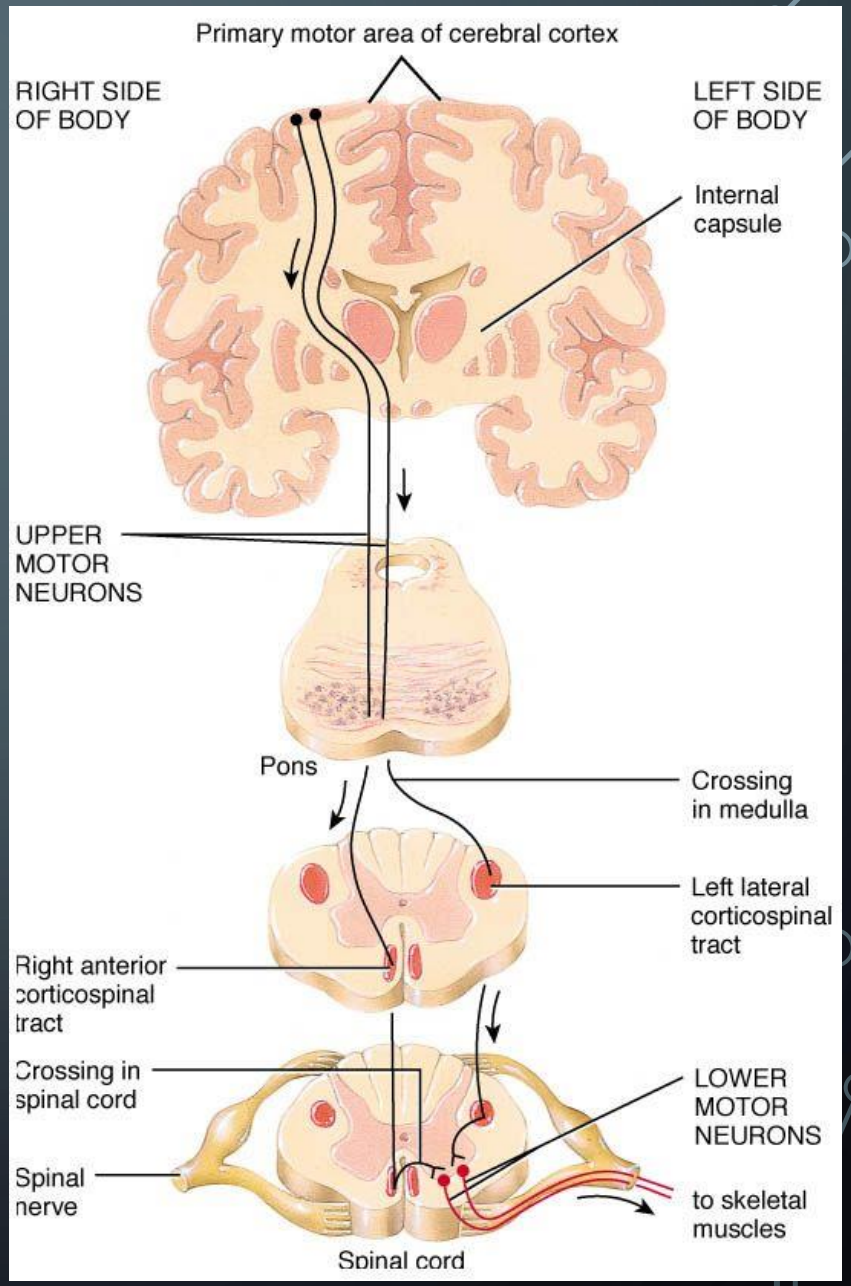
- Result of cooperation of upper and lower motor neuron
- Basal ganglia
  - Motor gating – initiation of wanted and inhibition of unwanted movements
- Cerebellum
  - Movement coordination



http://www.slideshare.net/drpsdeb/presentations

PYRAMIDAL TRACT

- Upper motor neuron
  - Primary motor cortex
- Lower motor neuron
  - Anterior horn of spinal cord
- Tractus corticospinalis lateralis
  - 90% of fibers
- Tractus corticospinalis anterior
  - 10% of fibers
  - Cervical and upper thoracic segments
- Tractus corticobulbaris



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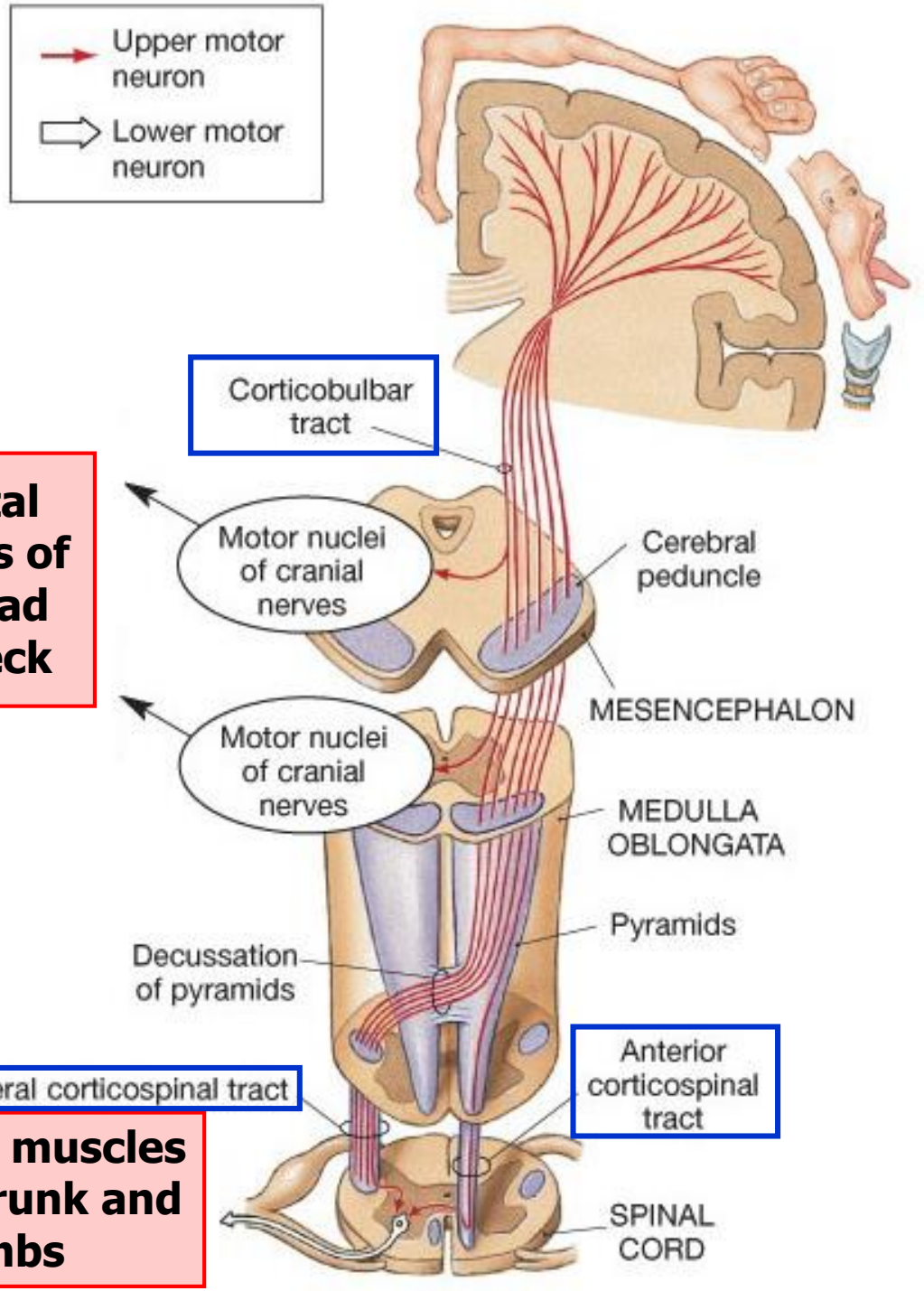
Sceletal muscles of the head and neck



Sceletal muscles of the trunk and limbs

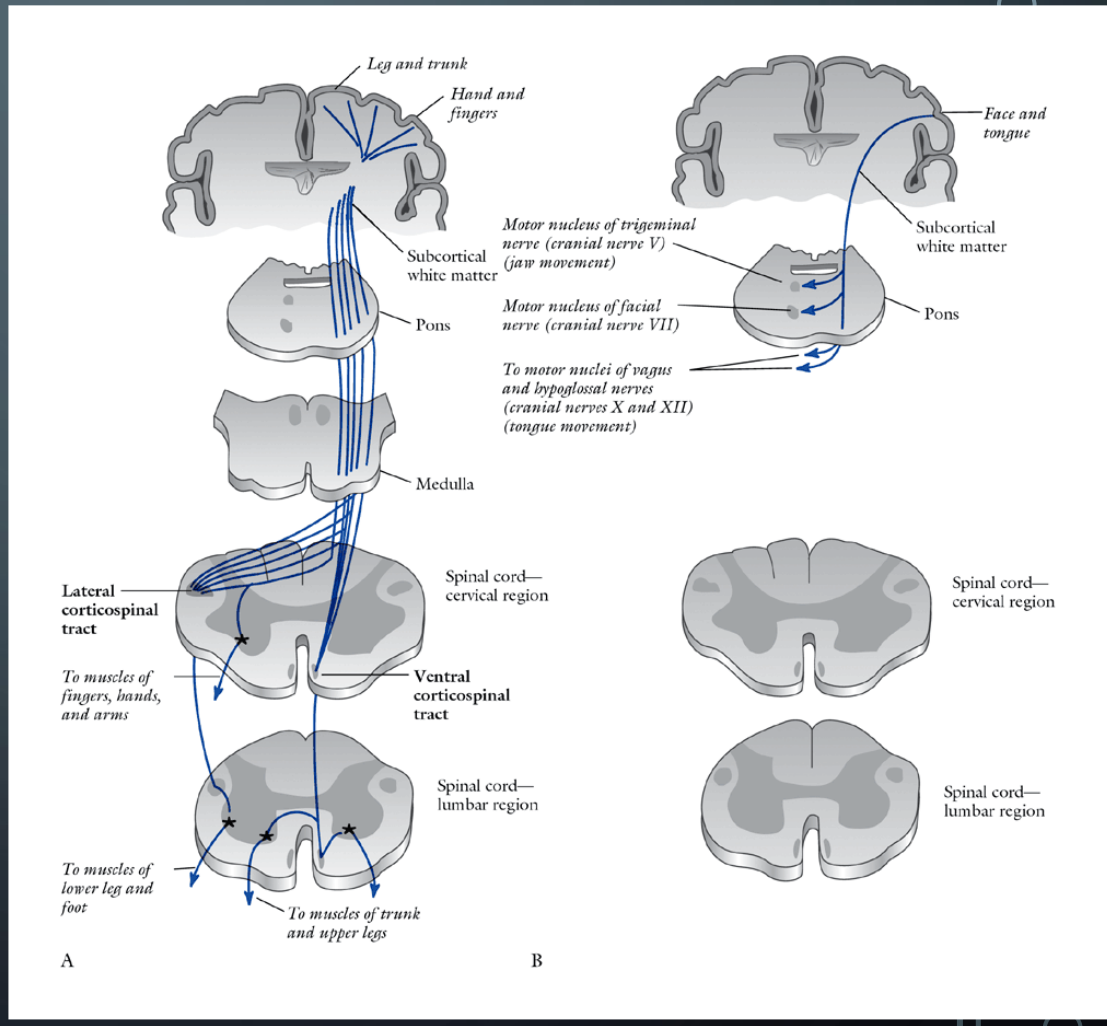
MAJOR MOTOR PATHWAYS

1. **Corticospinal** (cortex to spinal cord)

   a) ***Lateral*** – distal limb muscles (fine manipulations)

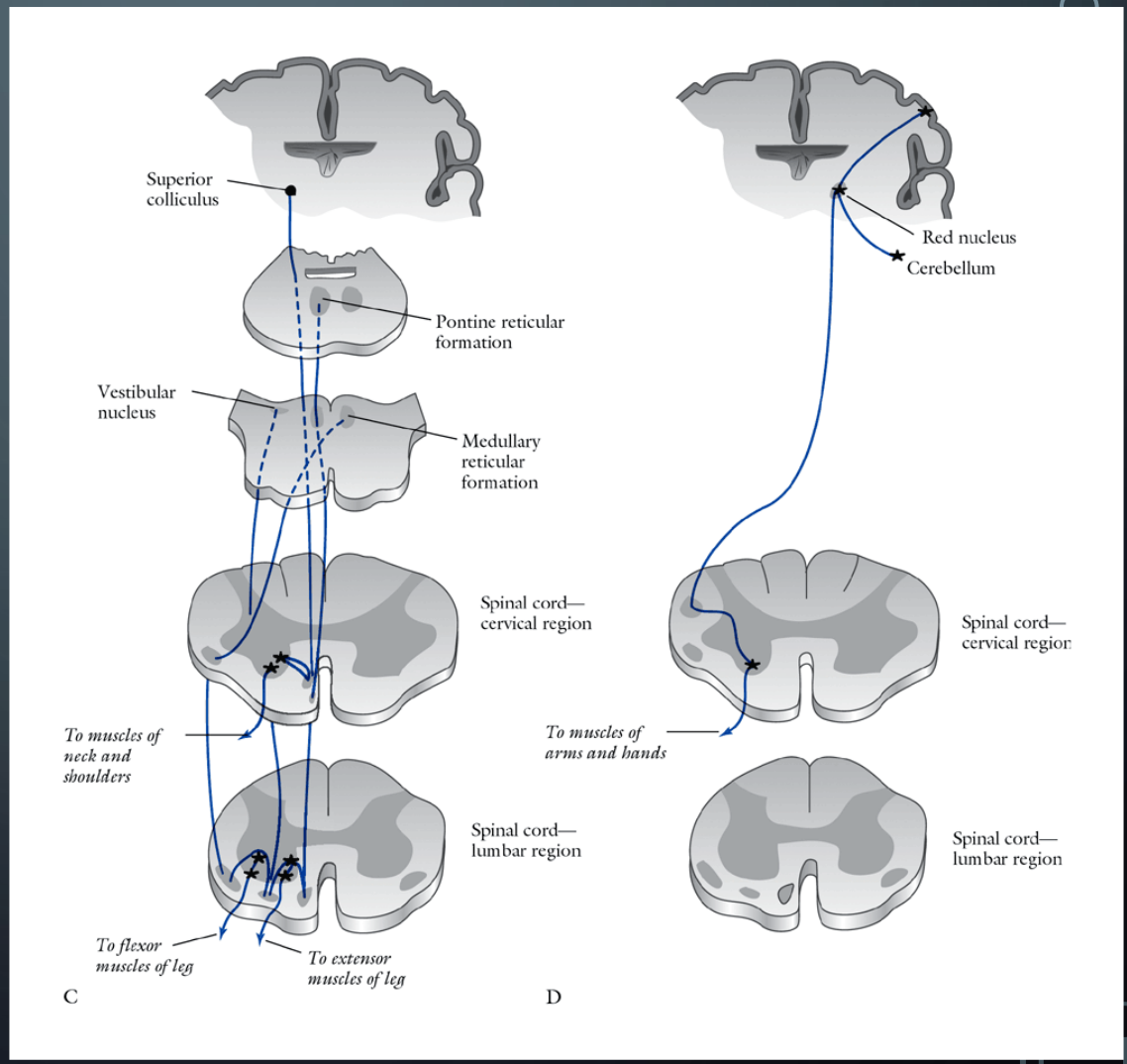
   b) ***Ventral*** – trunk and upper leg muscles (posture/locomotion)

2. **Corticobulbar** (cortex to pons, 5th, 7th, 10th and 12th cranial nerves) – control of face and tongue muscles; upper face both contralateral, lower face contralateral



MAJOR MOTOR PATHWAYS

3. **Ventromedial** (brain stem to spinal cord) – trunk and proximal limb muscles (posture, sneezing, breathing, muscle tone)
4. **Rubrospinal** (red nucleus to spinal cord) – modulation of motor movement (limb movement independent of trunk movement)

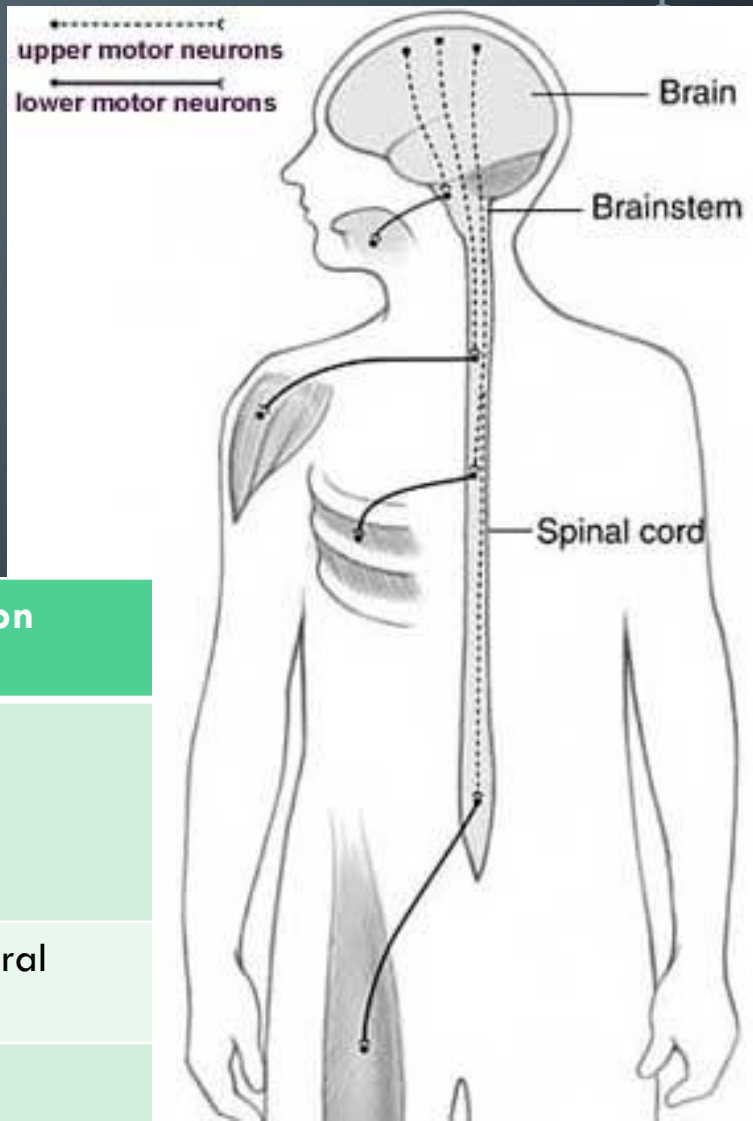


PYRAMIDAL MOTOR SYSTEM CORTICOBULBAR TRACT

- Upper motor neurons which innervate the muscles of the face and head are located near the lateral fissure of the brain.
- Their axons coalesce to form the corticobulbar tract.
- These axons then descend within the genu of the internal capsule to the medial part of the cerebral peduncle.
- The upper motor neuron axons then synapse on lower motor neurons of the cranial nerve nuclei which are located in midbrain, pons and medulla.

MOTOR NEURON LESIONS

- **Upper motor neuron lesion** of the neural pathway inside the CNS (not including the ventral horn of the spinal cord or motor nuclei of the cranial nerves)
  - stroke, traumatic brain injury or cerebral palsy
- **Lower motor neuron lesion** affects nerve fibers within the ventral horn of the spinal cord travelling to the relevant muscle(s)
  - Nerve trauma



	Upper motor neuron lesion	Lower motor neuron lesion
Reflexes	Increased, may have pathological reflex signs (Babinski sign)	Decreased,
Muscle tone	Increased, contralateral	Decreased, ipsilateral
Weakness	Yes, contralateral	Yes, ipsilateral

Table 20.13

Evidence of an upper motor neurone lesion

Drift of upper limb
Weakness with a characteristic distribution
Increase in tone of spastic type
Exaggerated tendon reflexes
An extensor plantar response
Loss of fine finger/toe movements
Loss of abdominal reflexes
No muscle wasting
Normal electrical excitability of muscle

Table 20.17
Signs of a lower motor neurone lesion

Weakness
Wasting
Hypotonia
Reflex loss
Fasciculation
Contractures of muscle
'Trophic' changes in skin and nails

} long term effects

NB: Fibrillation potentials can be detected electromyographically, see page 1156.

DIFFERENT TERMIMOLOGIES

- ***Paresis***: partial or incomplete paralysis
- ***Plegia***: complete paralysis
- ***Monoplegia*** is a paralysis of a single limb, usually an arm
- ***Hemiplegia***: total paralysis of the arm, leg, and trunk on the same side of the body.
- ***Paraplegia***: an impairment in motor or sensory function of the lower extremities.
- ***Triplegia :*** is paralysis of three limbs.
- ***Quadriplegia*** : is paralysis of all limbs, paraplegia is similar but does not affect the arms

PARAPLEGIA

- is an impairment in motor and/or sensory function of the lower extremities. It is usually the result of spinal cord injury or a congenital condition such as spina bifida which affects the neural elements of the spinal canal.
- The area of the spinal canal which is affected in paraplegia is either the thoracic, lumbar, or sacral regions. If the arms are also affected by paralysis, tetraplegia is the proper terminology.
- The causes range from trauma (acute spinal cord injury: transsection or compression of the cord, usually by bone fragments from vertebral fractures) to tumors (chronic compression of the cord), myelitis transversa and multiple sclerosis.

HEMIPLEGIA

- It can be congenital (occurring before, during, or soon after birth) or acquired (as from illness or stroke).
- It is usually the result of a stroke, although disease processes affecting the spinal cord and other diseases affecting the hemispheres are equally capable of producing this clinical state. Hemiplegia can be a more serious consequence of stroke than spasticity.

- Other causes include Type 2 diabetes mellitus, which can lead to transient hemiplegia, a type of spinal injury called Brown-Sequard syndrome, and injections of local anaesthetic given intra-arterially rapidly, instead of given in a nerve branch.
- Lesions in the posterior limb of the internal capsule can also lead to hemiplegia.

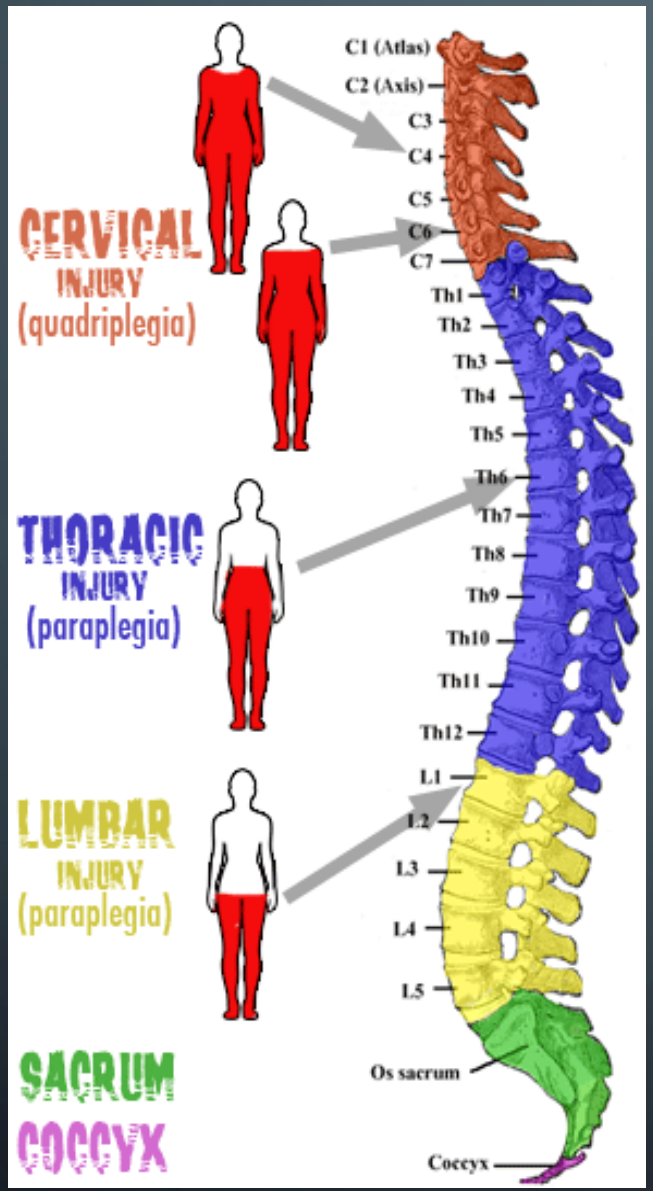
Table 20.14
Causes of a spastic paraparesis

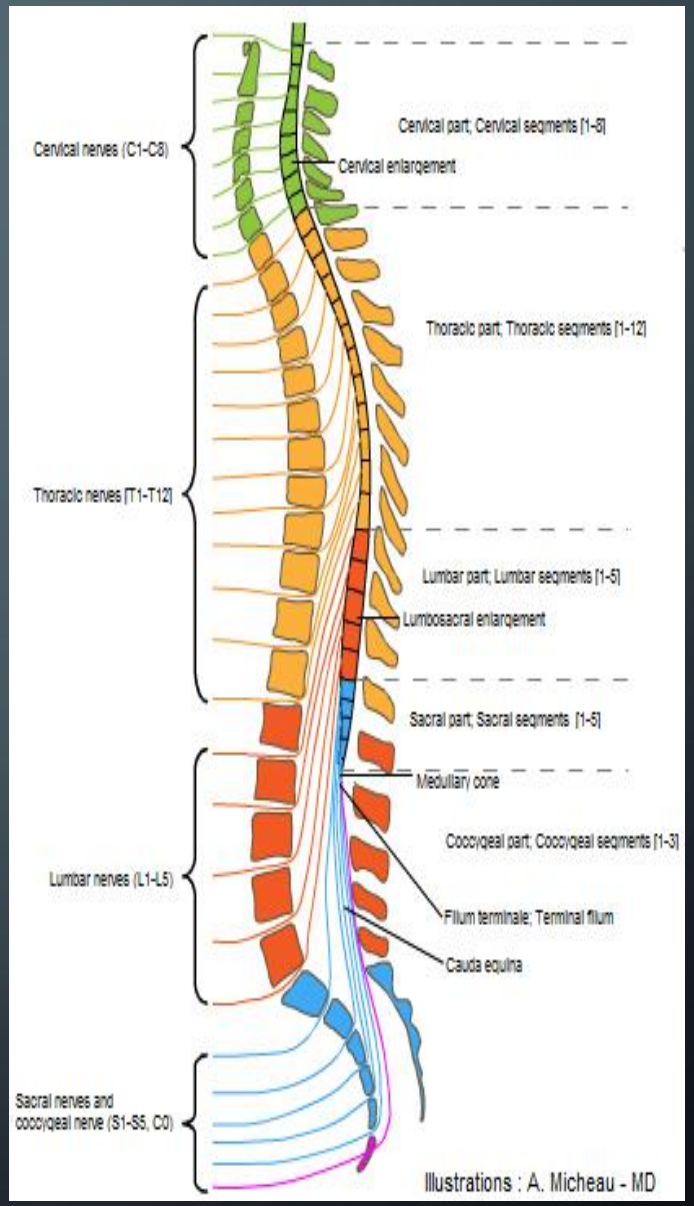
Spinal lesions
Spinal cord compression (see Table 20.49)
Multiple sclerosis
Myelitis (e.g. varicella zoster virus)
Motor neurone disease
Subacute combined degeneration of the cord
Syringomyelia
Syphilis
Familial or sporadic paraparesis
Vascular disease of the cord
Non-metastatic manifestation of malignancy
Tropical spastic paraparesis (HTLV-1)
HIV-associated myelopathy

Cerebral lesions*
Parasagittal cortical lesions:
- Meningioma
- Venous sinus thrombosis

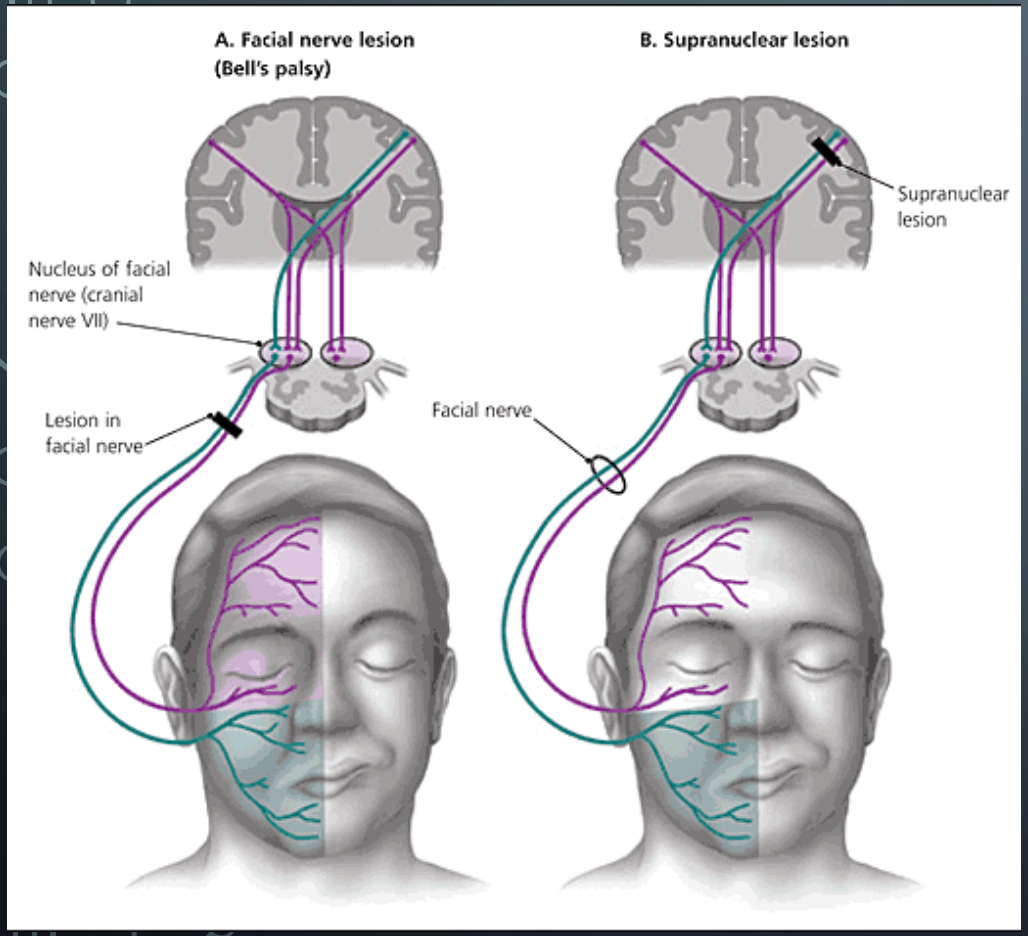
Hydrocephalus
Multiple cerebral infarction

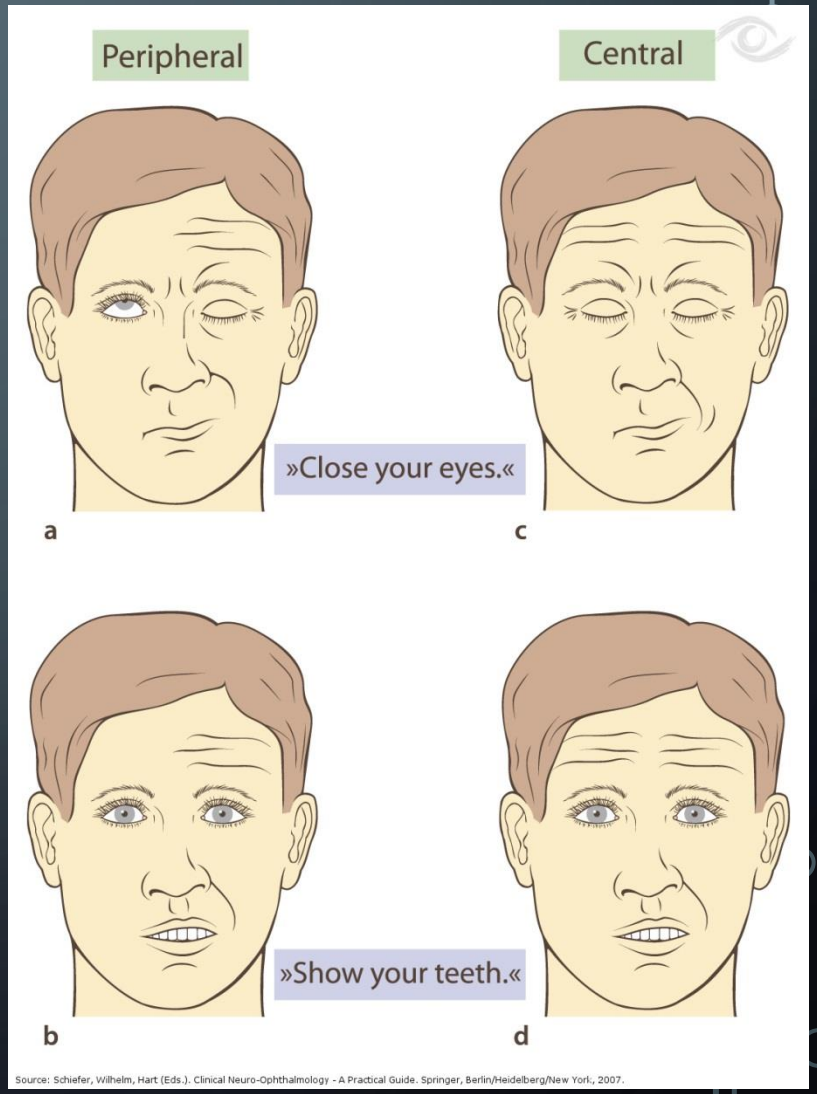
* All are rare causes of a paraparesis
HTLV-1, human T-cell leukaemia virus


CERVICAL
INJURY
(quadriplegia)
THORACIC
INJURY
(paraplegia)
LUMBAR
INJURY
(paraplegia)
SACRUM
COCCYX
C1 (Atlas)
C2 (Axis)
C3
C4
C5
C6
C7
Th1
Th2
Th3
Th4
Th5
Th6
Th7
Th8
Th9
Th10
Th11
Th12
L1
L2
L3
L4
L5
Os sacrum
Coccyx


Cervical nerves (C1-C8)
Cervical part; Cervical segments [1-8]
Cervical enlargement
Thoracic nerves (T1-T12)
Thoracic part; Thoracic segments [1-12]
Lumbar part; Lumbar segments [1-5]
Lumbosacral enlargement
Sacral part; Sacral segments [1-5]
Medullary cone
Lumbar nerves (L1-L5)
Coccygeal part; Coccygeal segments [1-3]
Filum terminale; Terminal filum
Cauda equina
Sacral nerves and coccygeal nerve (S1-S5, C0)
Illustrations : A. Micheau - MD

Peripheral and central facial palsy





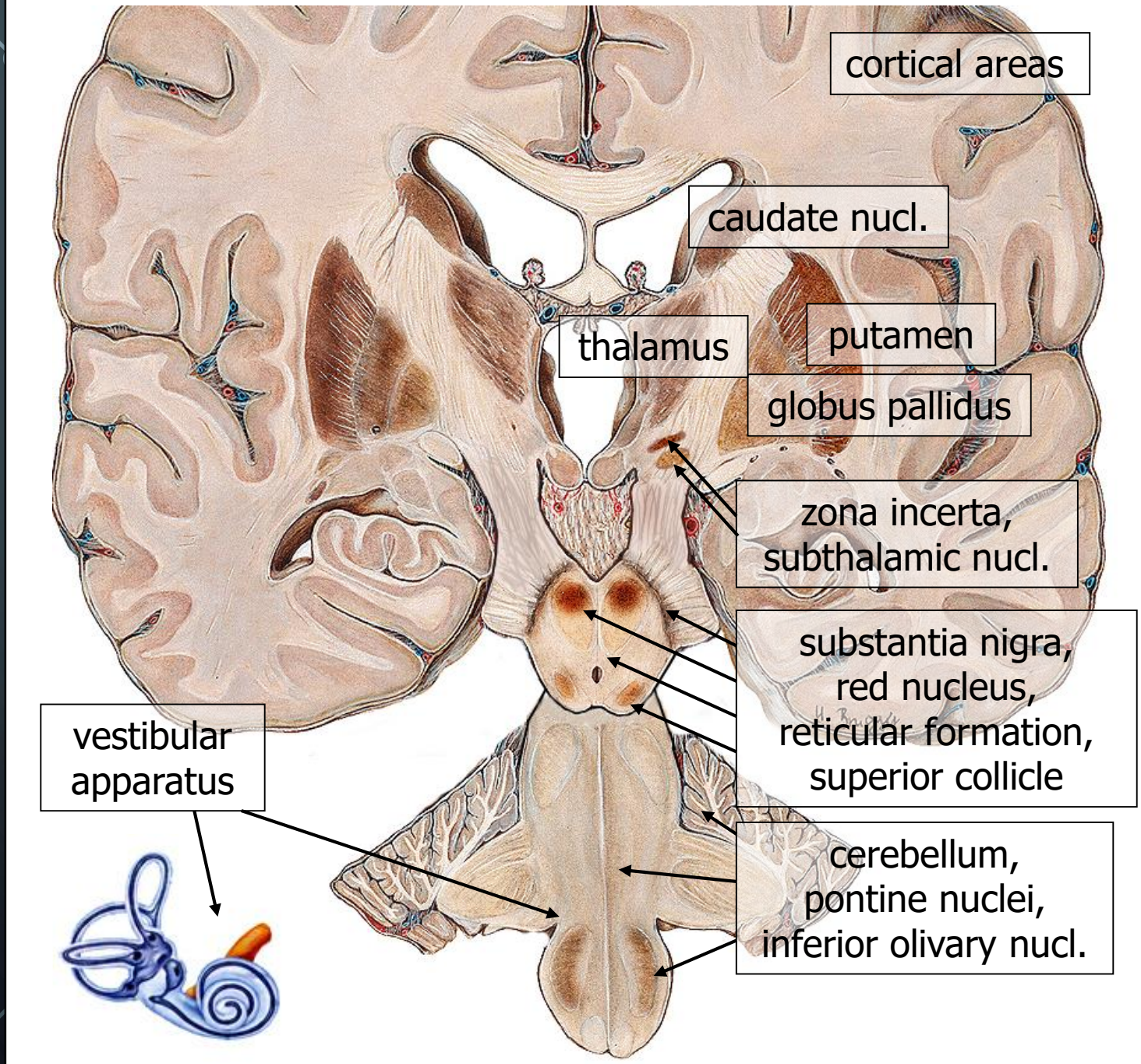
EXTRAPYRAMIDAL MOTOR SYSTEM

- The extrapyramidal system dampens erratic motions, maintains muscle tone and truncal stability. It is phylogenetically older that the pyramidal system and thus plays a relatively more important role in lower animals. Many of its synaptic connections are extremely complex and even today, poorly understood. Neurodegenerative disorders which affect the extrapyramidal system have yielded much of our knowledge about its normal function.

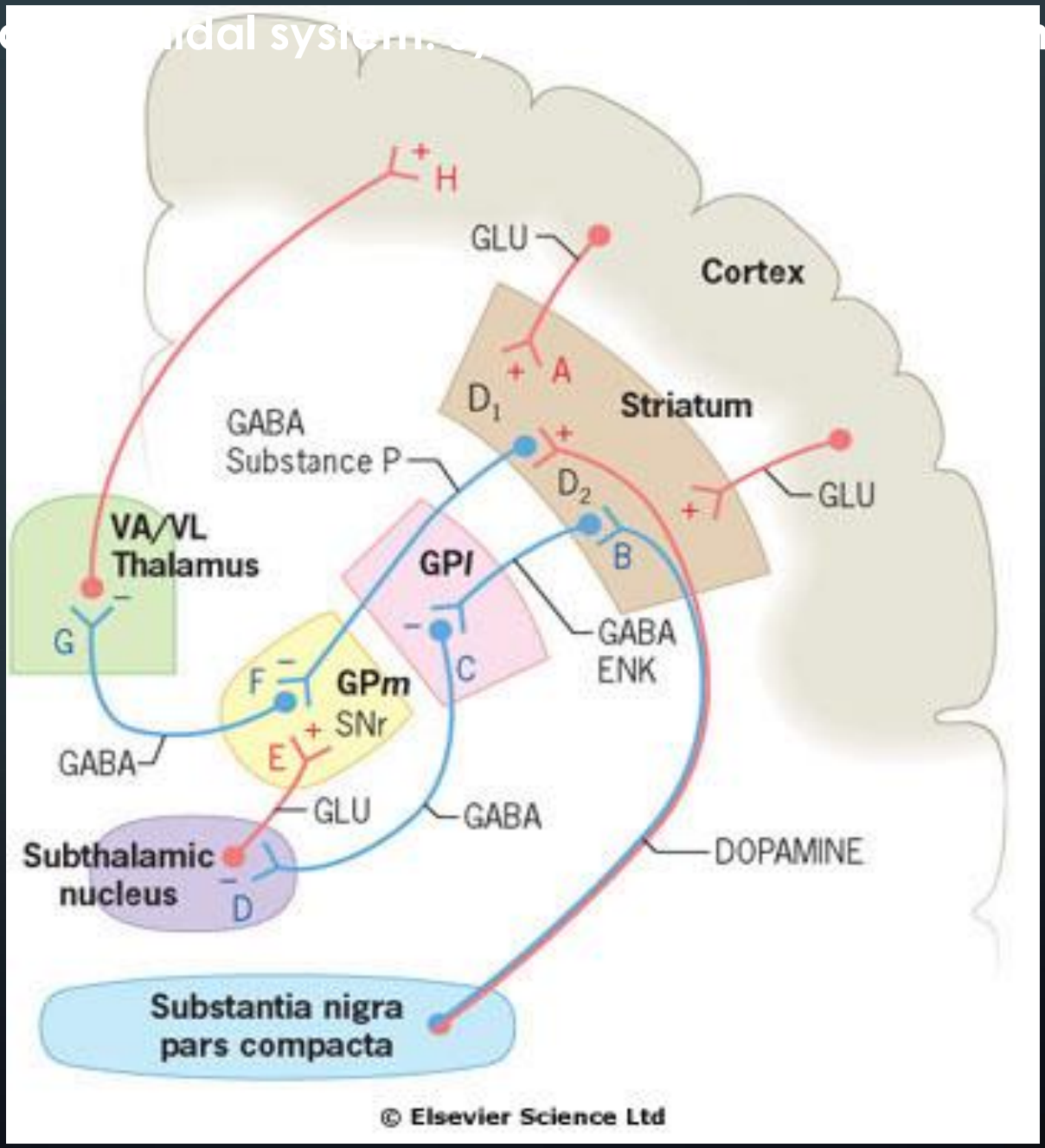
- The major parts of the extrapyramidal system are the "subcortical nuclei". This includes the **caudate**, **putamen**, and **globus pallidus** which are also known as the Basal ganglia. The caudate nucleus is especially affected in Huntington's chorea.

- The **substantia nigra**, is located in the midbrain. It is particularly affected in idiopathic Parkinson's disease.

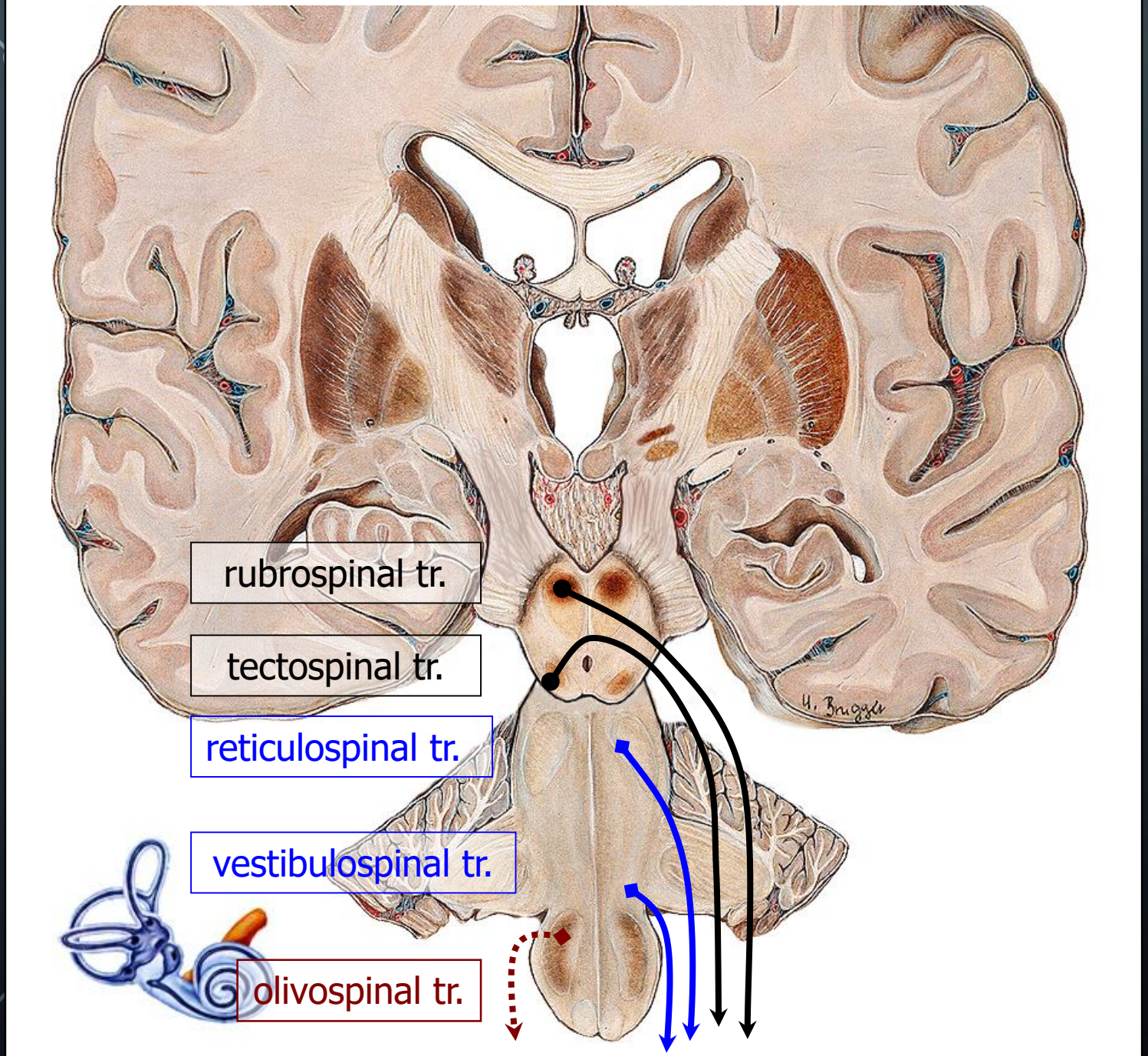
Components of the extrapyramidal system



Extr[illegible]idal system[illegible]ission



Efferent extrapyramidal pathways



EXTRAPYRAMIDAL MOTOR SYSTEM

- The **thalamus** is a very complex structure with many functions including cognition and pain perception, but parts of the thalamus are also components of the extrapyramidal system.

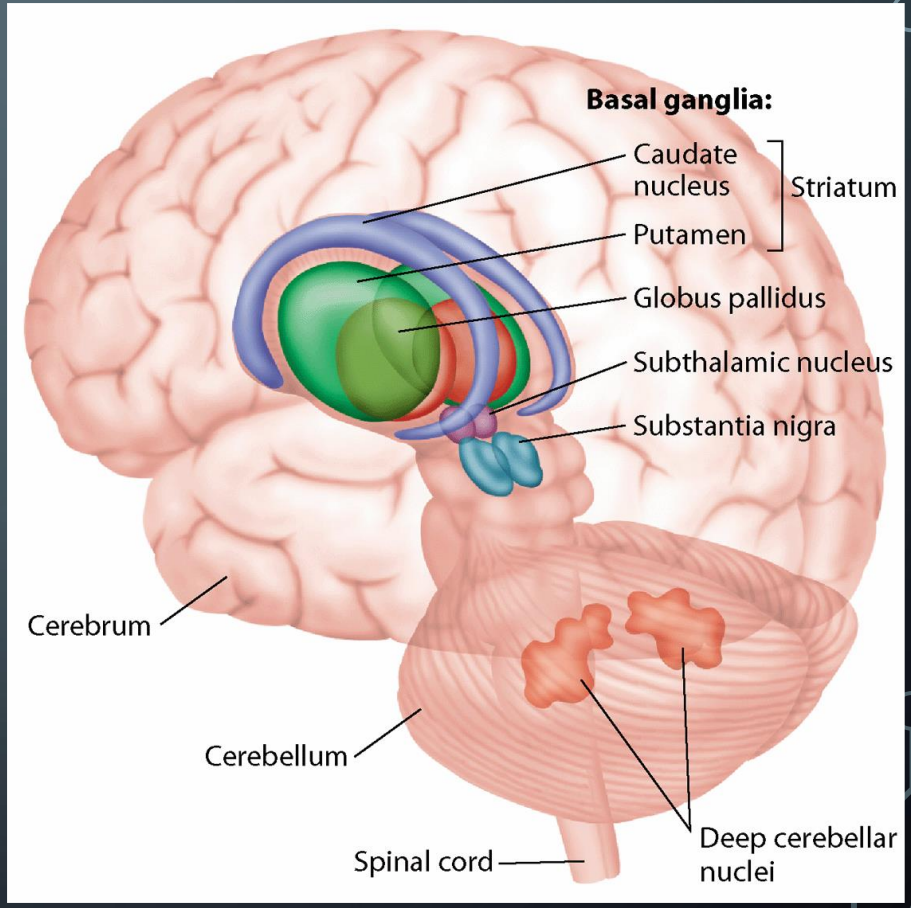
- Other nuclei include the **Subthalamic nucleus**. Unilateral damage to the subthalamic nucleus results in hemiballism.

- The final major nucleus is the **Red Nucleus** which is immediately adjacent to the substantia nigra in the midbrain.

- To summarize, the extrapymidal nuclei include the substantia nigra, caudate, putamen, globus pallidus, thalamus, red nucleus and subthalamic nucleus. All of these nuclei are synaptically connected to one another, the brainstem, cerebellum and the pyramidal system.

BASAL GANGLIA

- Unlike the cerebellum, which plays a role in rapid balistic movements, the basal ganglia are more important for the accomplishment of movements that may take some time to initiate or stop
- Important for internal guiding (rather then external) of movement
- Dopamine – nigrostriatal pathway



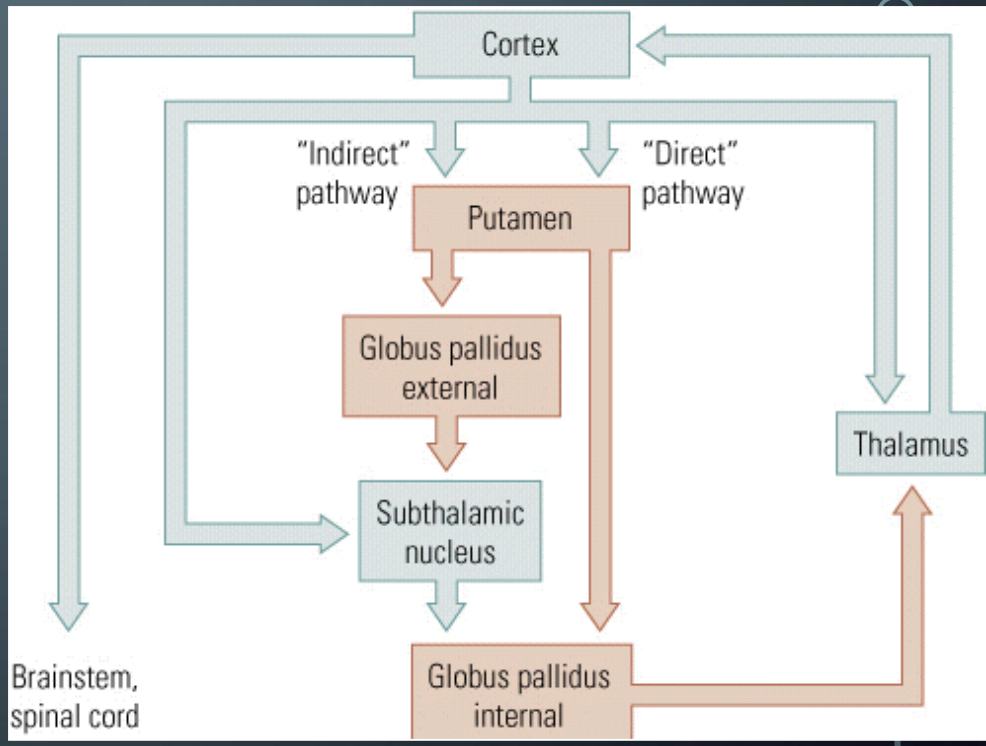
BASAL GANGLIA

Damage to the basal ganglia:

- Produces either too much activation (hyperkinetic) responses= twitches, movements bursts, jarring, etc.
- Huntington's Chorea-dominant gene based, increases glutamate in striatum which destroys GABA neurons in BG and loss of inhibition
- No cure
- Tourette's

OR

- Produces too little force (hypokinetic)=rigidity
- Parkinson's disease

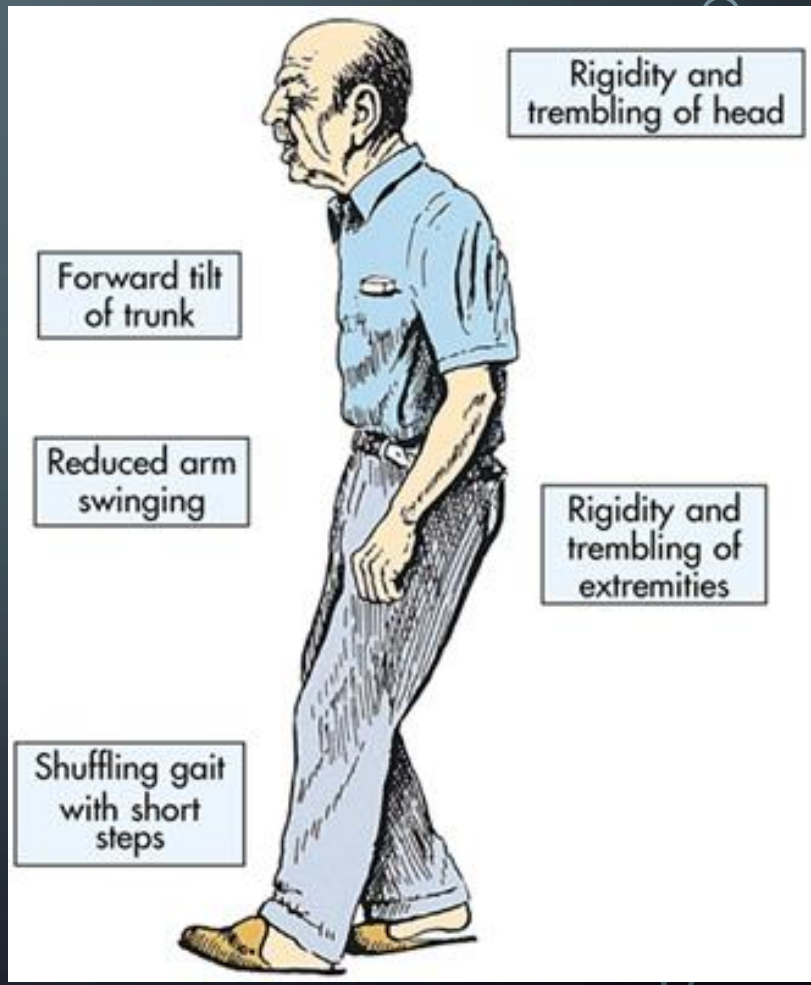


Pink=inhibition
Blue=excitation

DISORDERS OF THE BASAL GANGLIA

Parkinson's Disease

- **Parkinson's Disease** is the second most common age-related neuro- degenerative disease, affecting approximately 1% of population over 60.



- Characterized by resting tremor, slowed/absent movement (**hypokinesia**), rigidity of the extremities and neck, & reduced facial expressiveness

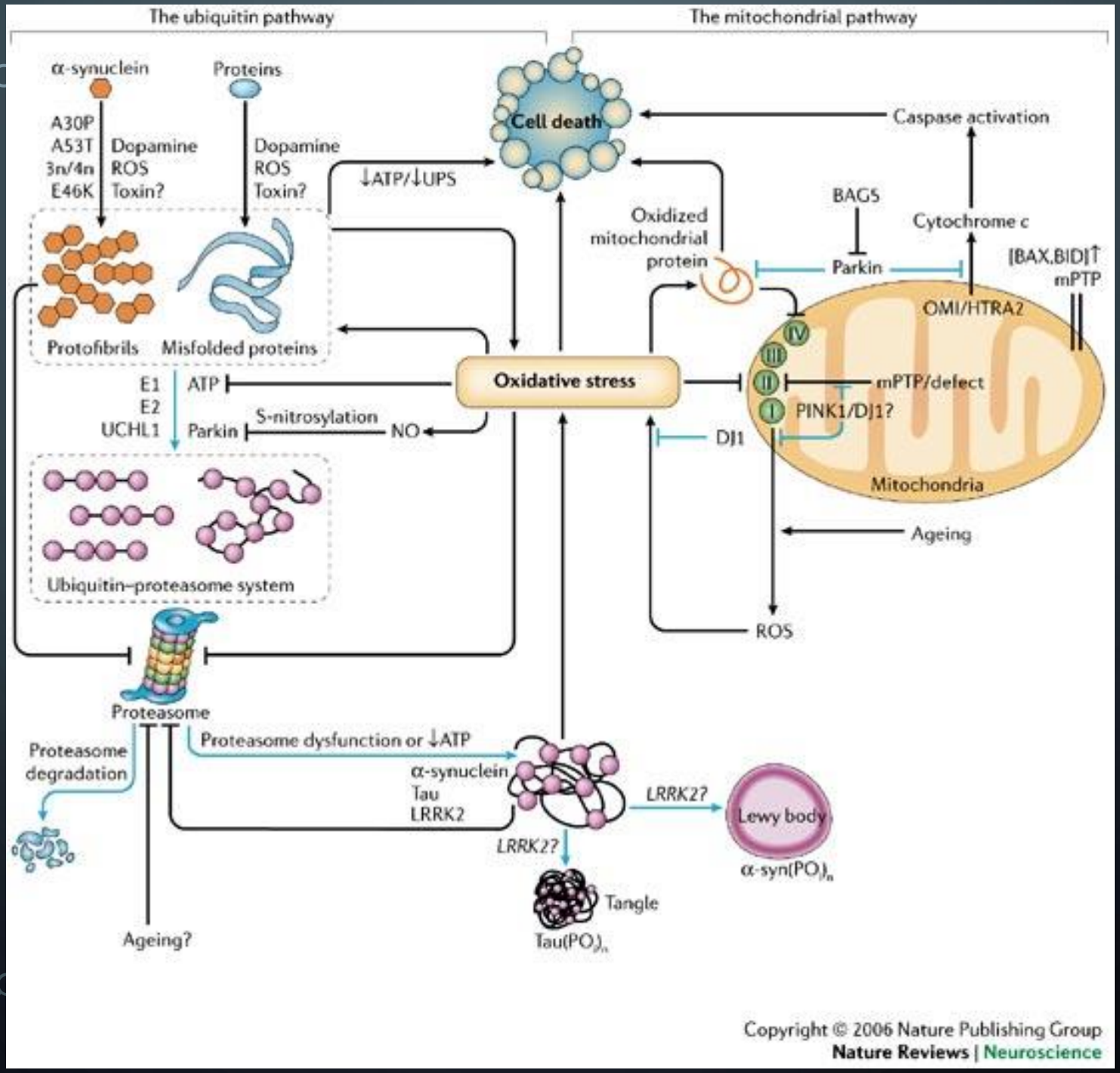
- Caused by the loss of the dopaminergic neurons in the substantia nigra pars compacta

- Typically treated with L-Dopa

PARKINSON'S DISEASE (PD)

- Emerging evidence has provided support for the hypothesis that PD is the result of complex interactions between genetic abnormalities, environmental toxins, mitochondrial dysfunction and other cellular processes.

- Recently, epigenetic modifiers have been identified as a potential mediators of environmental factors participating in the pathogenesis of PD

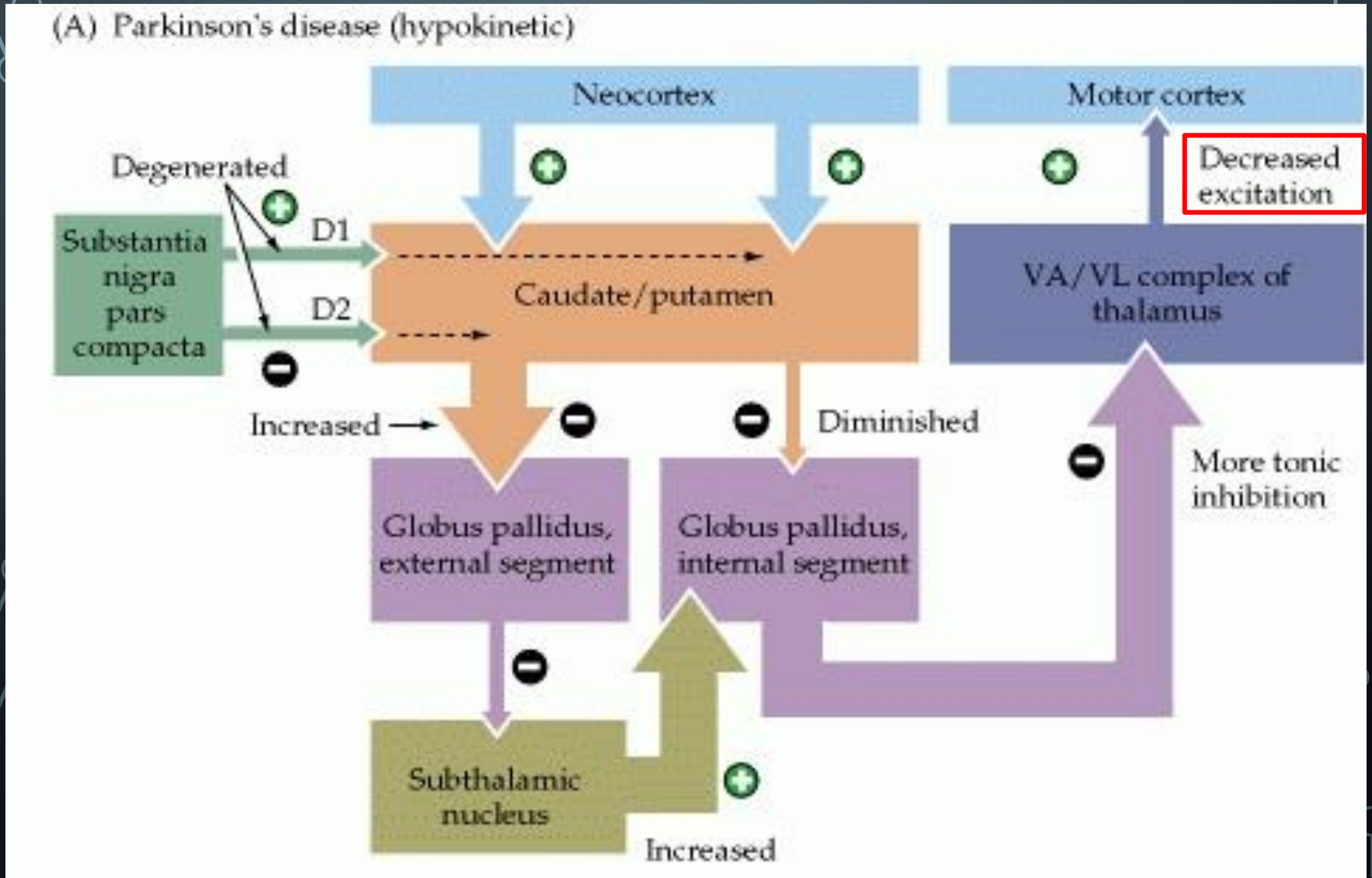


PARKINSON'S DISEASE

- Although the exact cause of Parkinson's disease is unknown, research has concentrated on genetics, environmental toxins, endogenous toxins and viral infection.

  In Parkinson's, cells are destroyed in part of the brain stem - the **substantia nigra**, which sends out fibers to the **corpus stratia**, gray and white bands of tissue in both sides of the brain. Cells there release **dopamine**, one of three major neurotransmitters (chemical messengers) which help the body respond to stress. By the time symptoms develop, patients have lost 80 to 90 percent of their dopamine-producing cells.

PARKINSON'S DISEASE



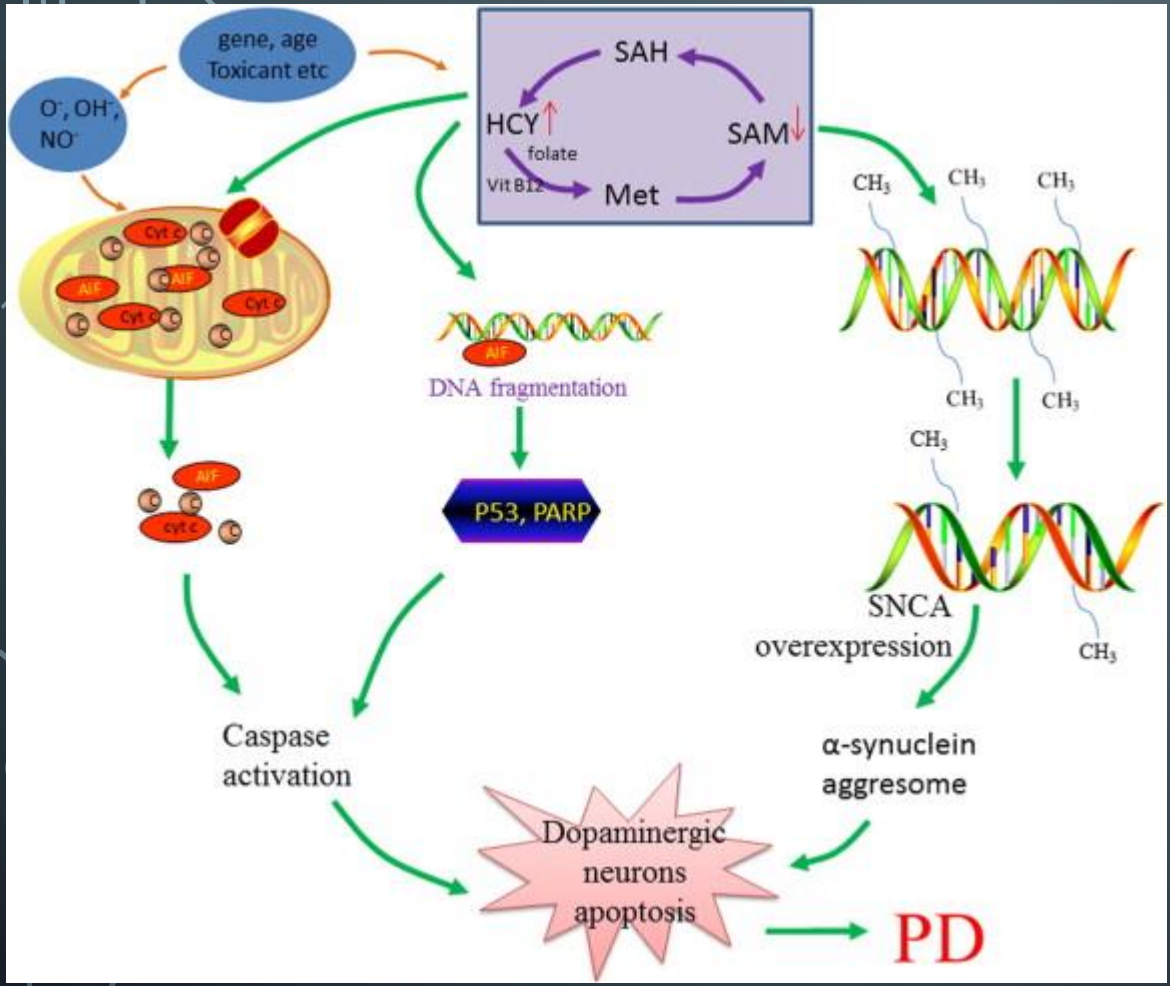
PARKINSON'S DISEASE

- Symptoms include tremors, slowed movement and postural instability.
- Other features include rigidity, flexed posture, freezing phenomenon and loss of postural reflexes.
- Patients can experience depression, sleep disturbances, dizziness and problems with speech, swallowing and sexual functioning.

PD PATHOGENESIS

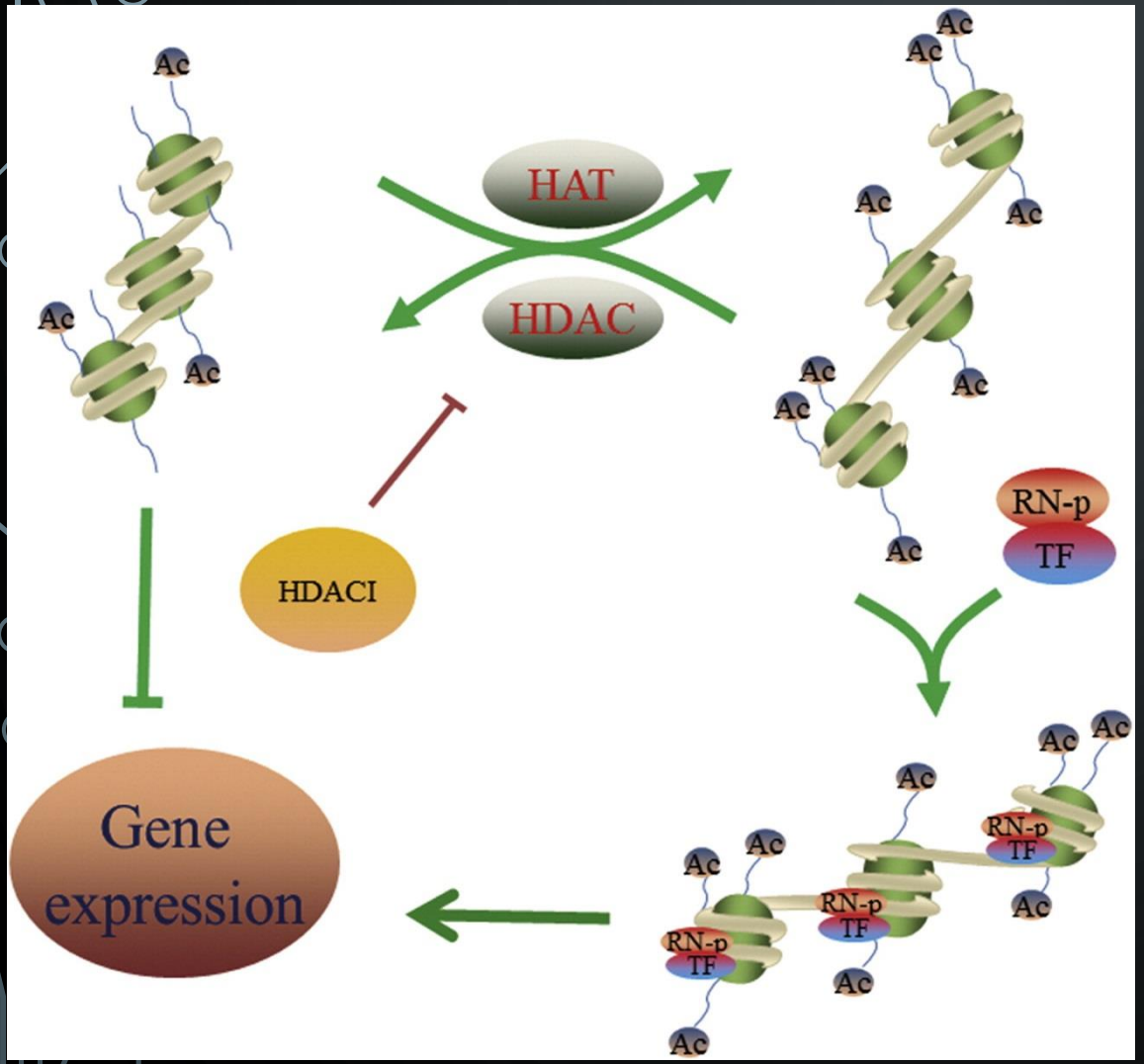
- PD is characterized by accumulation of SNCA in the presynaptic nerve terminals of dopaminergic neurons in the SN. The neurotoxicity of SNCA might be mediated through interaction with histone altering its acetylation.
- Hyperacetylation of H3 or H4 represents key epigenetic changes in dopaminergic neurons. Some environmental toxins have been found to induce a time-dependent increase or decrease of histone acetylation of DNA (Dieldrin, paraquat).
- Dysregulation of acetylation of H3 or H4 is regarded as an important mechanism underlying pesticide-induced neuron loss in PD.

Journal of the Neurological Sciences 349 (2015) 3-9



Possible role of DNA methylation and related factors in the pathogenesis of PD.
One-carbon metabolic disturbance results in decreased level of S-adenosylmethionine (SAM), which leads to hypomethylation of DNA. The decreased methylation level of specific PD-related genes changes chromosome conformation and makes much easier for transcription, such as SNCA overexpression that leads to **α-synuclein accumulation and subsequently dopaminergic neurons degeneration**. In addition, high level of homocysteine (HCY) can induce dopaminergic neuronal apoptosis via impairment of mitochondrial function and apoptosis-related gene activation, leading to caspase activation and neuronal apoptosis. AIF, apoptosis inducible factor; Met, methionine; SAH, S-adenosylhomocysteine.

Journal of the Neurological Sciences 349 (2015) 3-9



The process of histone acetylation and its effect on gene transcription.
Two main enzymes termed as acetylase (HATs) and deacetylase (HDACs) mediate the process of acetylation/deacetylation, respectively. The histone acetylation produced a more loosened chromatin structure leading to transcriptional activation, whereas histone deacetylation formed heterochromatin and then transcriptional repression.
TF, transcriptional factor; RN-p, RNA polymerase.

Journal of the Neurological Sciences 349 (2015) 3-9

Table 1. Genes Associated with Parkinson's Disease

Locus	Map Position	Gene	Inheritance	Pathology
PARK 1	4q21-q23	α-synuclein	Dominant, high penetrance	LB positive
PARK 2	6q25-q27	parkin	Recessive	LB negative
PARK 3	2p13	Unknown	Dominant, Incomplete penetrance	LB positive
PARK 4	4p15	Unknown	Dominant, high penetrance	LB positive
PARK 5	4p14	UCH-L1	Dominant	Unknown
PARK 6	1p36-p35	Unknown	Recessive	Unknown
PARK 7	1p36	DJ-1	Recessive	Unknown
PARK 8	12p11-q13	Unknown	Dominant, Incomplete penetrance	LB negative
PARK 9	1p36	Unknown	Recessive	Unknown
PARK 10	1p32	Unknown	Non-Mendelian	Unknown
PARK 11	2q36-q37	Unknown	Non-Mendelian	Unknown
? ? ? ? ? ?	2q22-q23	NR4A2	Dominant	Unknown

Adapted from Bonfante, et al., *J. Med. Chem.* (2004).

HUNTINGTON'S DISEASE

- Huntington's disease is caused by a trinucleotide repeat expansion in the Huntingtin gene, which codes for Huntingtin protein, denoted "Htt". Huntington's disease is one of several polyglutamine diseases. This expansion produces an altered form of the Htt protein, called mutant Huntingtin (mHtt), the misfunction of this protein increases neuronal cell death in select areas of the brain. This damage itself isn't fatal, but life expectancy is reduced due to complications caused by its symptoms.
- Huntington's disease's most obvious symptoms are abnormal body movements called chorea and a lack of coordination, but it also affects a number of mental abilities and some aspects of behavior. Physical symptoms occur in a large range of ages around a mean occurrence of late forthies/early fifties, but if they occur before the age of 20 then the condition is known as **Juvenile HD**. As there is currently no proven cure, symptoms are managed with various medications and supportive services.

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HUNTINGTON´S DISEASE-GENETICS

- Normal state
- DNA
- ATGCAGGTGACCTCAGTG
- TACGTCCACTGGAGTCAC

- RNA
- AUGCAGGUGACCUCAGUG

- PROTEIN
- Met-Gln-Val-Thr-Ser-Val

- **Trinucletide expansion mutation**
- DNA
- ATG$(CAGCAGCAG)_{20}$CAGGTGACCTCAGTG
- TAC$(GTCGTCGTC)_{20}$GTCCACTGGAGTCAC
- RNA
- AUG $(CAGCAGCAG)_{20}$CAGGUGACCUCAGUG
- PROTEIN
- Met-**$(Gln\text{-}Gln\text{-}Gln)_{20}$**Gln-Val-Thr-Ser-Val

PATHOPHYSIOLOGY OF HD

- Degeneration of neuronal cells, especially in the frontal lobes and caudate nucleus (the striatum) of the basal ganglia occurs. There is also astrogliosis and loss of medium spiny neurons.

- In Huntington's disease the external globus pallidus over-inhibits the flow of excitation from the subthalamic nuclei, which interferes with the initiation of motion. The subthalamic nuclei also generate reduced excitation to the internal globus pallidus, resulting in a weak inhibitory signal to the thalamus. The thalamus in turn then sends a strong excitatory signal to the putamen resulting in unmodulated motion.
- Role of epigenetics still unclear (but probable)

Table 20.15

Changes in the major neurotransmitter profile in Parkinson's and Huntington's diseases

Condition	Site	Neurotransmitter
Parkinson's disease	Putamen	Dopamine ↓ 90% Norepinephrine (noradrenaline) ↓ 60% 5-HT ↓ 60%
	Substantia nigra	Dopamine ↓ 90% GAD + GABA ↓↓
	Cerebral cortex	GAD + GABA ↓↓
Huntington's disease	Corpus striatum	Acetylcholine ↓↓ GABA ↓↓ Dopamine: normal GAD + GABA ↓↓

GABA, γ-amino butyric acid; GAD, glutamic acid decarboxylase, the enzyme responsible for synthesizing GABA; 5-HT, 5-hydroxytryptamine

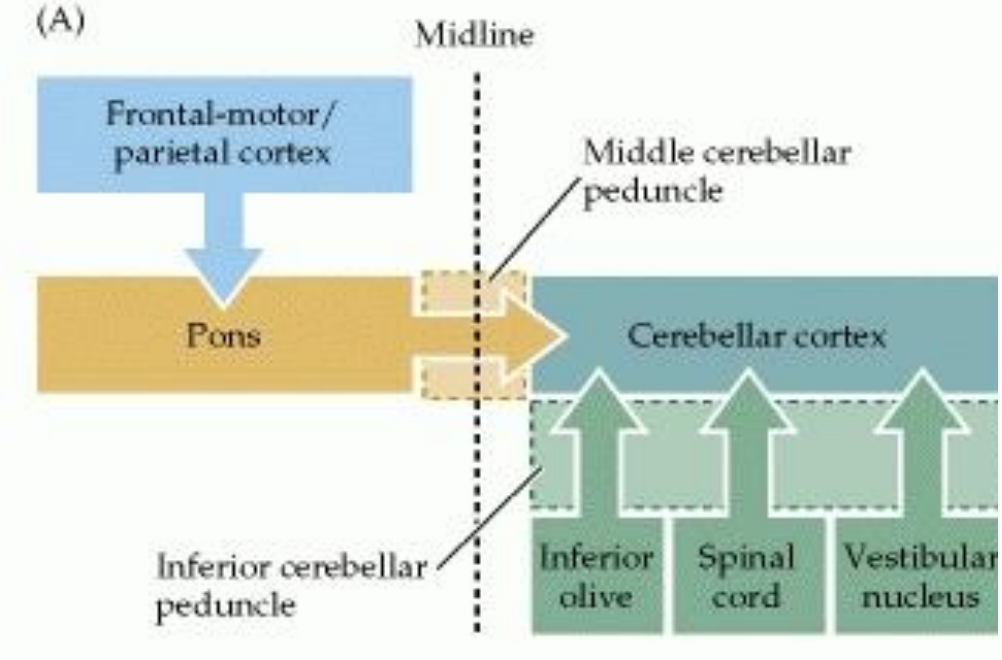
CEREBELLUM

- The cerebellum, which located inferior to the tentorium, coordinates muscle activity, equilibrium and tone.
- It is functionally and anatomically divided into three lobes. The flocculonodular lobe or archicerebellum maintains equilibrium.
- The anterior lobe or paleocerebellum maintains muscle tone.
- The posterior lateral lobes or neocerebellum controls coordination and allows us to perform intricate motor tasks like playing the piano. Recent evidence suggests that the neocerebellum also plays a role in memory, especially memory of fine motor skills.

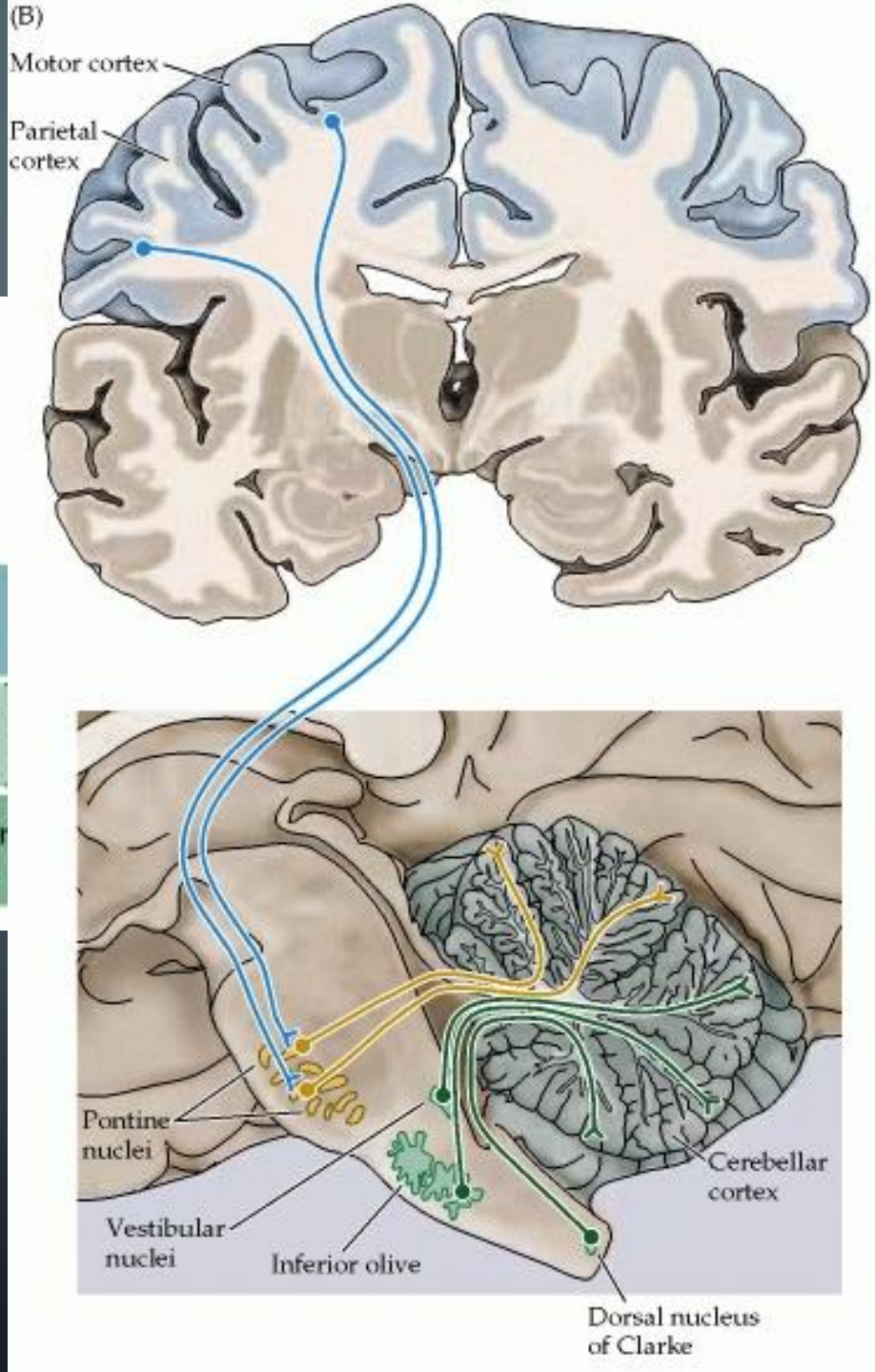
- Cebebellar motor tracts are uncrossed, so that injuries on one side will cause difficulties on the same side of the body.

- The major cerebellar tracts are the
  - Spinocerebellar, connecting the spinal cord and the cerebellum,
  - Vestibulospinal, connecting the vestibular system and the cerebellum,
  - Corticopontocerebellar, connecting the cortex, pons and cerebellum and the
  - Dentatorubrothalamic connecting the dentate nucleus of the cerebellum, the red nucleus and the thalamus.

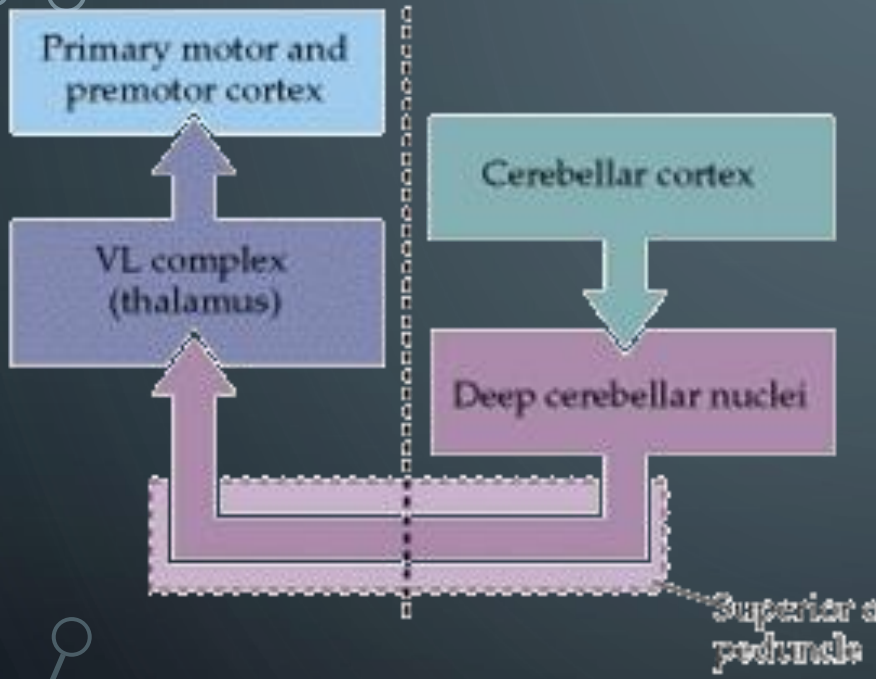
CEREBELLUM: INPUTS



Receive many inputs from periphery, spinal cord and brain regions



CEREBELLUM: OUTPUTS



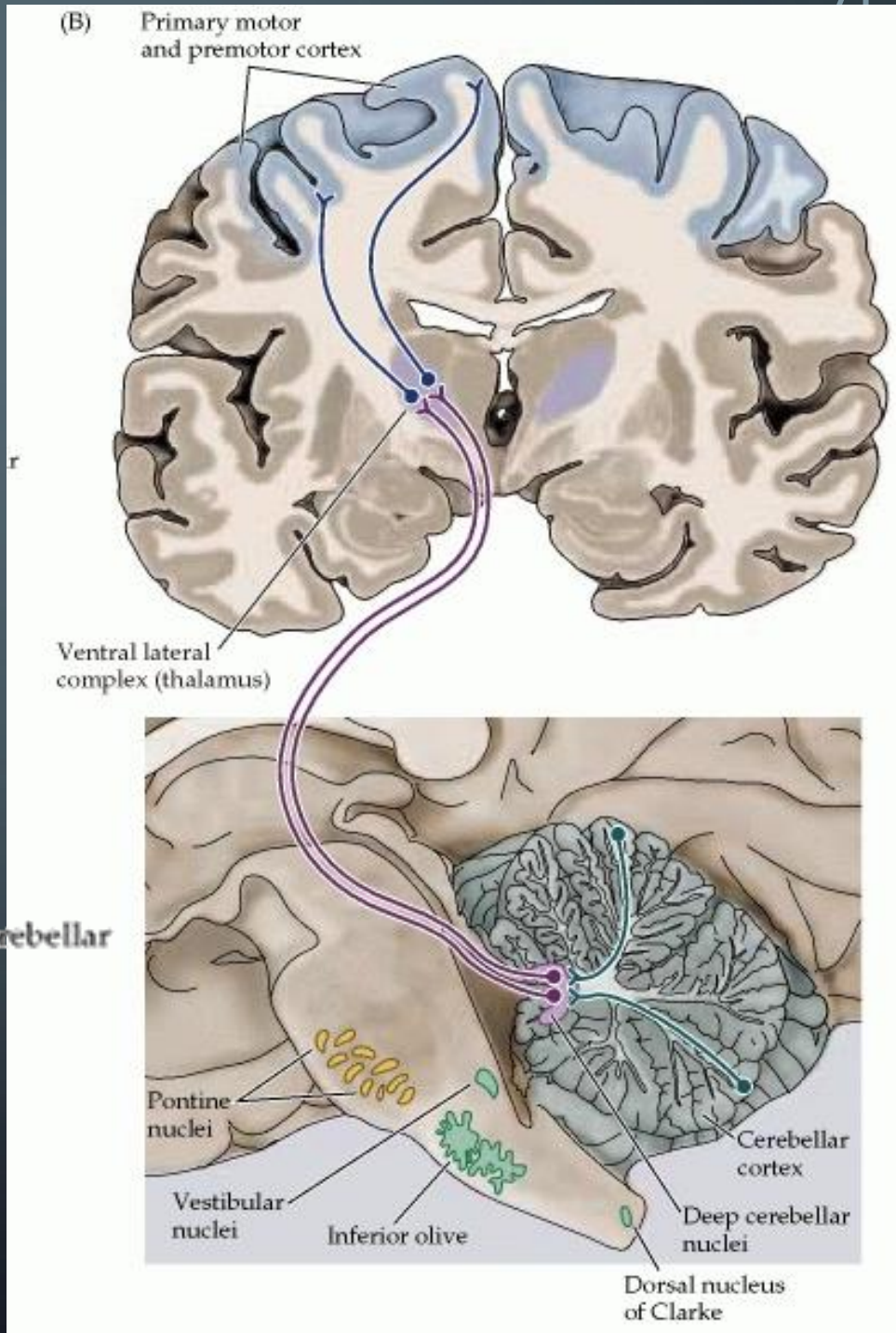


Table 20.16
Principal causes of cerebellar syndromes

Tumours	Haemangioblastoma Medulloblastoma Secondary neoplasm Compression by acoustic neuroma
Vascular lesions	Haemorrhage Infaction Arteriovenous malformation
Infection	Abscess HIV Kuru
Developmental	Arnold-Chiari malformation Basilar invagination Cerebral palsy
Toxic and metabolic	Anticonvulsant drugs Chronic alcohol abuse Following carbon monoxide poisoning Lead poisoning Solvent abuse
Inherited	Friedreich's ataxia Ataxia telangiectasia Essential tremor
Miscellaneous	Multiple sclerosis Hydrocephalus Postinfective cerebellar syndrome of childhood Hypothyroidism Non-metastatic manifestation of malignancy Cerebral oedema of chronic hypoxia

VESTIBULAR SYSTEM

- The vestibular system controls balance. It is synaptically linked to the extrapyramidal system. So that persons with extrapyramidal neurodenerative disorders frequently also have problems with balance and may experience frequent falls.

- The semicircular canals are lined by hair cells and filled with endolymph. The endolymph moves when the head moves and thus stimulates the hair cells. The hair cells then project synaptically to the Vestibular ganglion which is located within the bone of the skull. The ganglion then sends projections to the Superior and lateral vestibular nuclei which are located in the medulla adjacent to the base of the fourth ventricle. These nuclei in turn send axons via the Inferior cerebellar peduncle to the Flocculonodular lobe of the cerebellum to maintain equilibrium.

VESTIBULAR SYSTEM

- The major tracts of the vestibular system include the lateral vestibulospinal which maintains equilibrium, the vestibuloocular which controls saccadic eye movements and the vestibulocortical which causes dizziness when stimulated.

- The practical implications are that diseases of the inner ear cause loss of equilibrium, dizziness and saccadic eye movements when the head is turned.

TREMOR

TREMOR

- is an unintentional, somewhat rhythmic, muscle movement involving to-and-fro movements (oscillations) of one or more parts of the body.
- It is the most common of all involuntary movements and can affect the hands, arms, head, face, vocal cords, trunk, and legs. Most tremors occur in the hands. In some people, tremor is a symptom of another neurological disorder.

TREMOR

- is generally caused by problems in parts of the brain or spinal cord that control muscles throughout the body or in particular areas, such as the hands.
- Neurological disorders or conditions that can produce tremor include multiple sclerosis, stroke, traumatic brain injury and neurodegenerative diseases that damage or destroy parts of the brainstem or the cerebellum.
- Other causes include the use of some drugs (such as amphetamines, caffeine, corticosteroids, and drugs used for certain psychiatric disorders, alcohol abuse or withdrawal, mercury poisoning, overactive thyroid or liver failure.

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TREMOR

- Tremors can be an indication of hypoglycemia, along with palpitations, sweating and anxiety. A magnesium and Vitamin B1 deficency has also been known to cause a tremor or shaking, soon resolved when the nutrients are taken.

- Tremor may occur at any age but is most common in middle-aged and older persons. It may be occasional, temporary, or occur intermittently. Tremor affects men and women equally.

TREMOR CLASSIFICATION

- Tremor is most commonly classified by clinical features and cause or origin. Some of the better known forms of tremor, with their symptoms, include the following:
- **Essential tremor** (sometimes called benign essential tremor) is the most common of the more than 20 types of tremor. The hands are most often affected but the head, voice, tongue, legs, and trunk may also be involved. Head tremor may be seen as a "yes-yes" or "no-no" motion.

  Essential tremor may be accompanied by mild gait disturbance. Tremor frequency may decrease as the person ages, but the severity may increase, affecting the person's ability to perform certain tasks or activities of daily living.

  Heightened emotion, stress, fever, physical exhaustion, or low blood sugar may trigger tremors and/or increase their severity. Onset is most common after age 40, although symptoms can appear at any age. It may occur in more than one family member. Children of a parent who has essential tremor have a 50 percent chance of inheriting the condition. Essential tremor is not associated with any known pathology.

TREMOR CLASSIFICATION

- **Parkinsonian tremor** is caused by damage to structures within the brain that control movement. This resting tremor, which can occur as an isolated symptom or be seen in other disorders, is often a precursor to Parkinson's disease (more than 25 percent of patients with Parkinson's disease have an associated action tremor).

  The tremor, which is classically seen as a "pill-rolling" action of the hands that may also affect the chin, lips, legs, and trunk, can be markedly increased by stress or emotions. Onset of parkinsonian tremor is generally after age 60. Movement starts in one limb or on one side of the body and usually progresses to include the other side.

TREMOR CLASSIFICATION

- **Dystonic tremor** occurs in individuals of all ages who are affected by dystonia, a movement disorder in which sustained involuntary muscle contractions cause twisting and repetitive motions and/or painful and abnormal postures or positions.

  Dystonic tremor may affect any muscle in the body and is seen most often when the patient is in a certain position or moves a certain way. The pattern of dystonic tremor may differ from essential tremor. Dystonic tremors occur irregularly and often can be relieved by complete rest. Touching the affected body part or muscle may reduce tremor severity (a geste antagoniste). The tremor may be the initial sign of dystonia localized to a particular part of the body.

TREMOR CLASSIFICATION

- **Psychogenic tremor** (also called hysterical tremor) can occur at rest or during postural or kinetic movement. The characteristics of this kind of tremor may vary but generally include sudden onset and remission, increased incidence with stress, change in tremor direction and/or body part affected, and greatly decreased or disappearing tremor activity when the patient is distracted. Many patients with psychogenic tremor have a conversion disorder or another psychiatric disease.

TREMOR CLASSIFICATION

- **Orthostatic tremor** is characterized by fast (>12Hz) rhythmic muscle contractions that occur in the legs and trunk immediately after standing. Cramps are felt in the thighs and legs and the patient may shake uncontrollably when asked to stand in one spot. No other clinical signs or symptoms are present and the shaking ceases when the patient sits or is lifted off the ground. The high frequency of the tremor often makes the tremor look like rippling of leg muscles while standing. Orthostatic tremor may also occur in patients who have essential tremor.

TREMOR CLASSIFICATION

- **Physiologic tremor** occurs in every normal individual and has no clinical significance. It is rarely visible to the eye and may be heightened by strong emotion (such as anxiety or fear), physical exhaustion, hypoglycemia, hyperthyroidism, heavy metal poisoning, stimulants, alcohol withdrawal or fever.
- It can be seen in all voluntary muscle groups and can be detected by extending the arms and placing a piece of paper on top of the hands. Enhanced physiologic tremor is a strengthening of physiologic tremor to more visible levels. It is generally not caused by a neurological disease but by reaction to certain drugs, alcohol withdrawal, or medical conditions including an overactive thyroid and hypoglycemia. It is usually reversible once the cause is corrected.

THE DEGREE OF TREMOR SHOULD BE ASSESSED IN FOUR POSITIONS. THE TREMOR CAN THEN BE CLASSIFIED BY WHICH POSITION MOST ACCENTUATES THE TREMOR:

Position	Name	Description
At rest	Resting tremors	Tremors that are worse at rest include Parkinsonian syndromes and essential tremor if severe. This includes drug-induced tremors from blockers of dopamine receptors such as haloperidol and other antipsychotic drugs.
During contraction (eg. a tight fist while the arm is resting and supported)	Contraction tremors	Tremors that are worse during supported contraction include essential tremor and also cerebellar and exaggerated physiologic tremors such as a hyperadrenergic state or hyperthyroidism[1]. Drugs such as adrenergics, anti-cholinergics, and xanthines can exaggerate physiologic tremor.
During posture (eg with the arms elevated against gravity such as in a 'bird-wing' position)	Posture tremors	Tremors that are worse with posture against gravity include essential tremor and exaggerated physiologic tremors[1].
During intention (eg finger to nose test)	Intention tremors	Intention tremors are tremors that are worse during intention, e.g. as the patient's finger approaches a target, including cerebellar disorders

THANK YOU FOR YOUR ATTENTION