Pathophysiology of nervous system I:
Control of motor function and its disorders

Organization of nervous system

Neurons, synapses, neurotransmitters

Proprioception and spinal reflexes

Hierarchy of the motoric control systems

Palsy/paralysis – distinction between upper and lower motoneuron disease

Disorders of extrapyramidal system (incl. Parkinson's disease)

Neuromuscular junction and its disorders (myasthenia syndromes)

Muscles diseases (muscular dystrophy)

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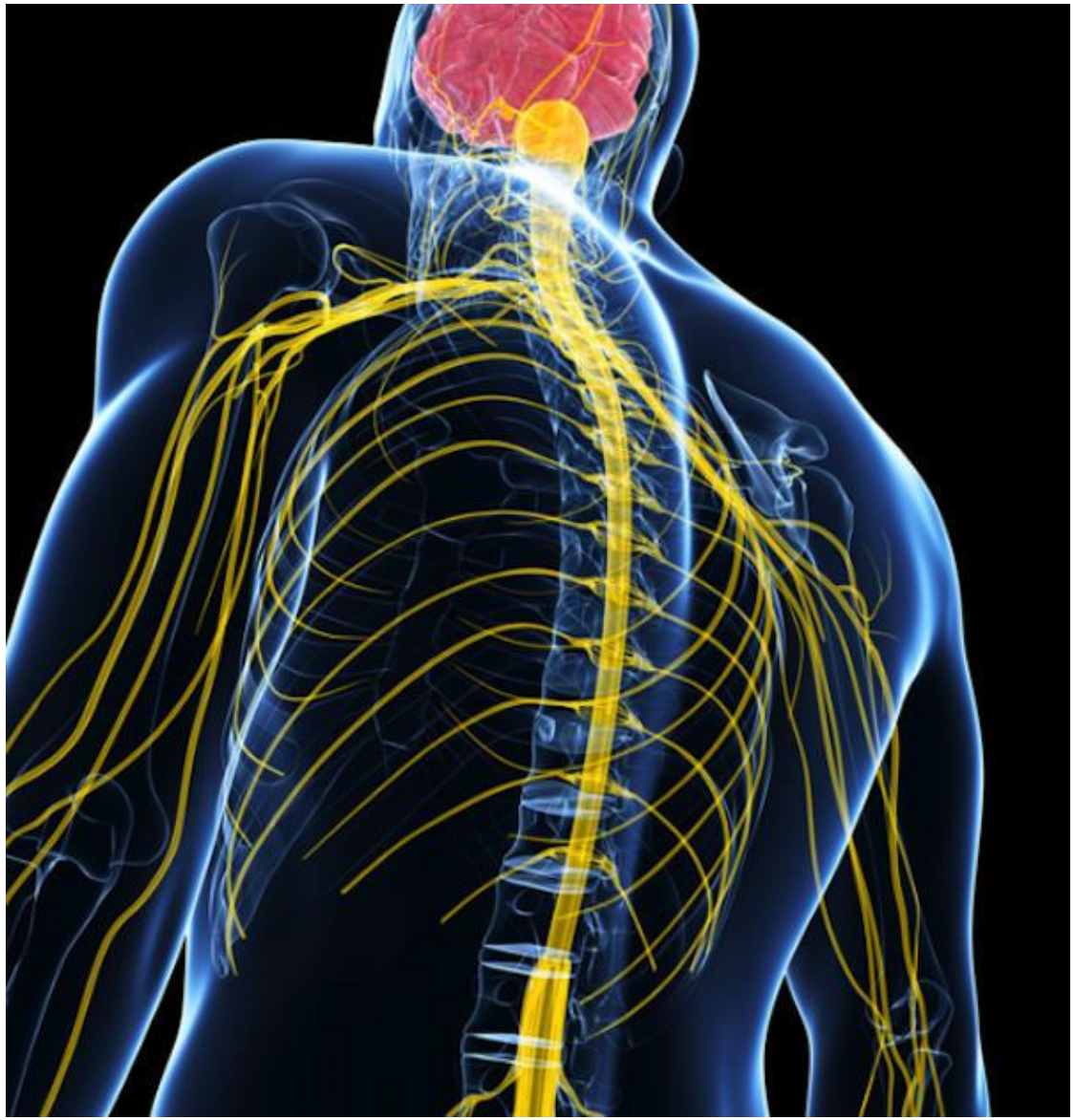
Anatomy and physiology of NS



- **central nervous system**
  - **spinal cord**
    - receives and processes sensory information from skin, joints, and muscles (dorsal horns)
    - passes motor commands on to the muscles (ventral horns)
  - **brain**
    - brainstem (hindbrain)
      - medulla oblongata
        - digestion, breathing, heart-beat
      - pons
        - passes information about movements from the cerebrum and the cerebellum
      - midbrain
        - controls many sensory and motor functions, e.g. eye movements, and the coordination of visual and acoustic reflexes
      - reticular formation
        - runs along the whole brainstem, and contains the summary of all incoming information
    - cerebellum
      - controls force and movements, and is involved in motor learning
    - forebrain
      - diencephalon
        - thalamus - processing most incoming (sensory) information, on its way to the cerebrum
        - hypothalamus - regulates the autonomous system, controls the glands
      - cerebral hemispheres (telencephalon)
- **peripheral nervous system**

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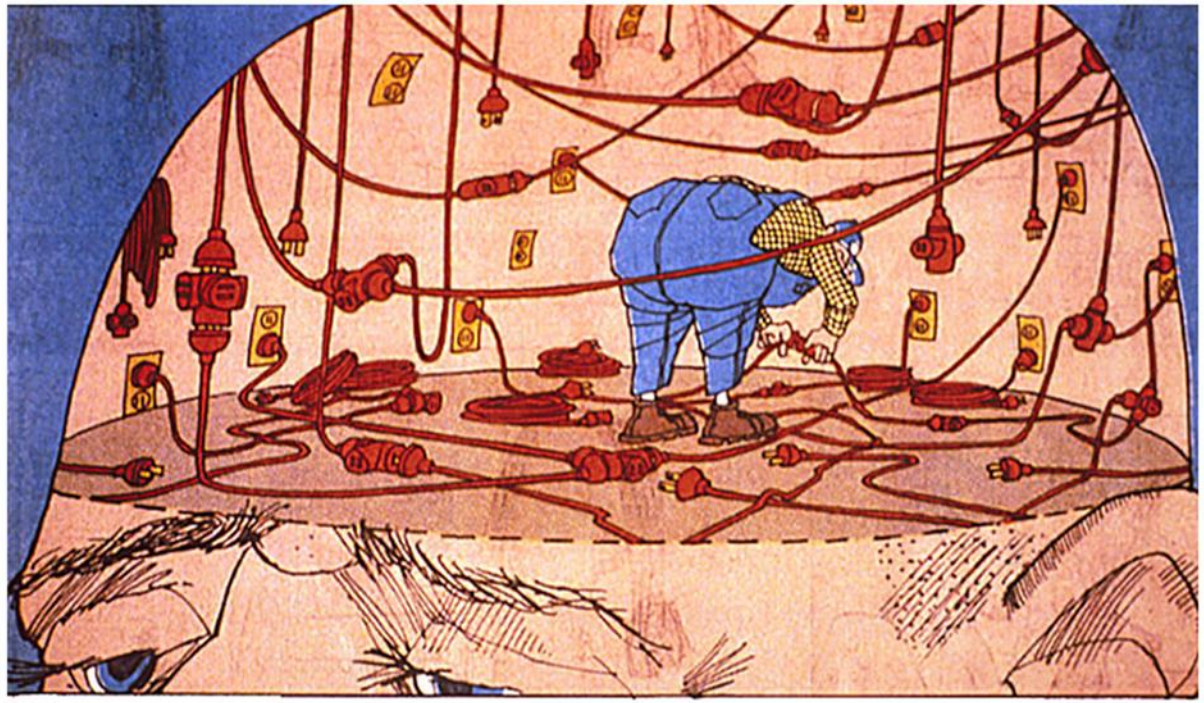
Functions of nervous system (NS)



HOW THE BRAIN WORKS

- regulation of body homeostasis and functions
  - together with endocrine and immune system
  - communication with environment
  - mental activity
- direct regulation of the
  - skeletal muscles (somatic NS)
  - myocardium (autonomous NS)
  - smooth muscles of vascular and visceral systems (autonomous NS)
  - glands (autonomous NS)
- cells of nervous system
  - neurons – excitability, conductivity, synthesis and release of neurotransmitters
    - axons and dendrites
    - excitability (action potential)
      - myelin sheath
    - synthesis and release of neurotransmitters
    - synapses
      - receiving and transmitting of information
  - supporting cells – metabolic support, protection (blood-brain barrier), conduction (myelin)
    - glia (astrocytes, oligodendroglia, microglia, ependymal cells)
    - Schwann cells

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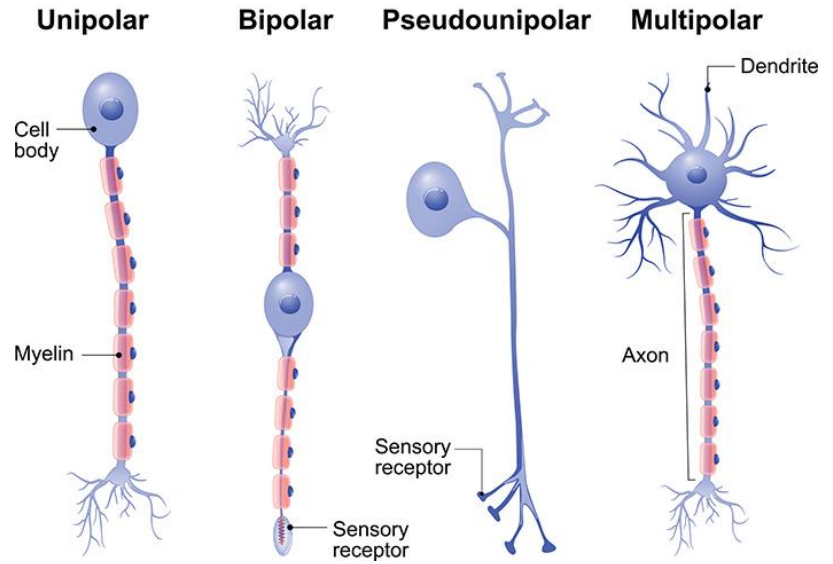
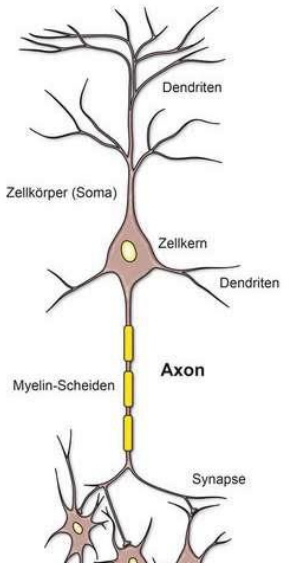
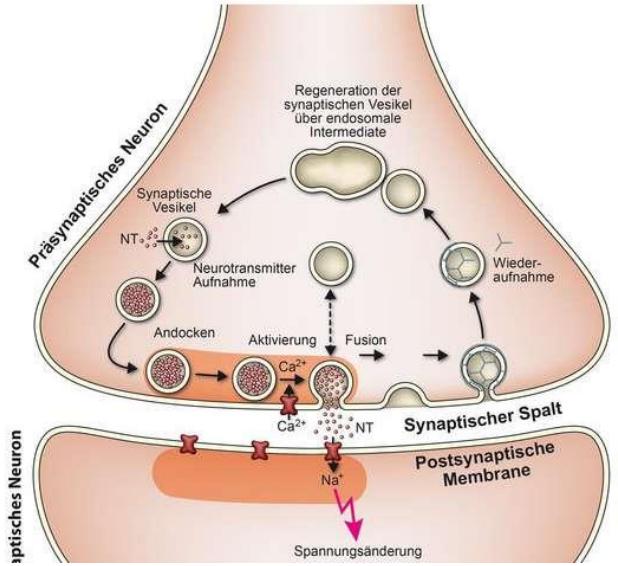
Cell of NS - neuron as a functional unit

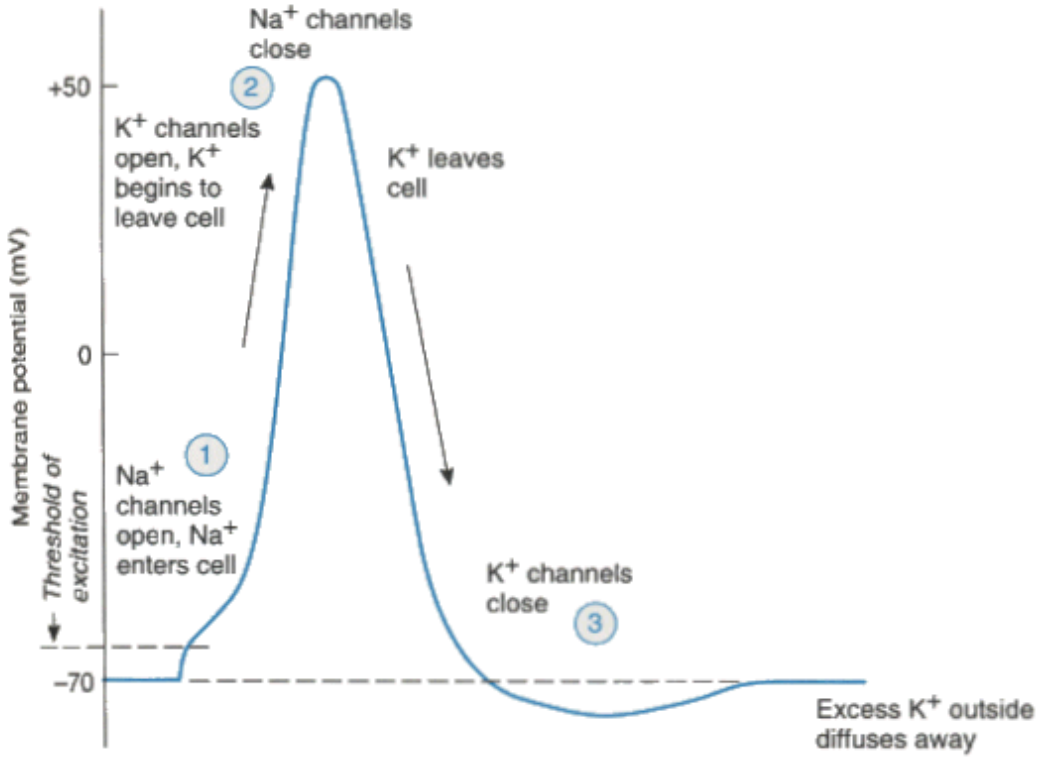
- large variability of neurons reflecting their specificity, seize and type
  - single α-motoneuron in anterior horns of spinal cord in thoracic region can have a length of axon more than a 1 m and it innervates several hundred to thousands of muscle fibrils (forming a so called motor unit)
  - other neurons can have a length of less than a 100 µm and they terminate on bodies of neighbouring neurons

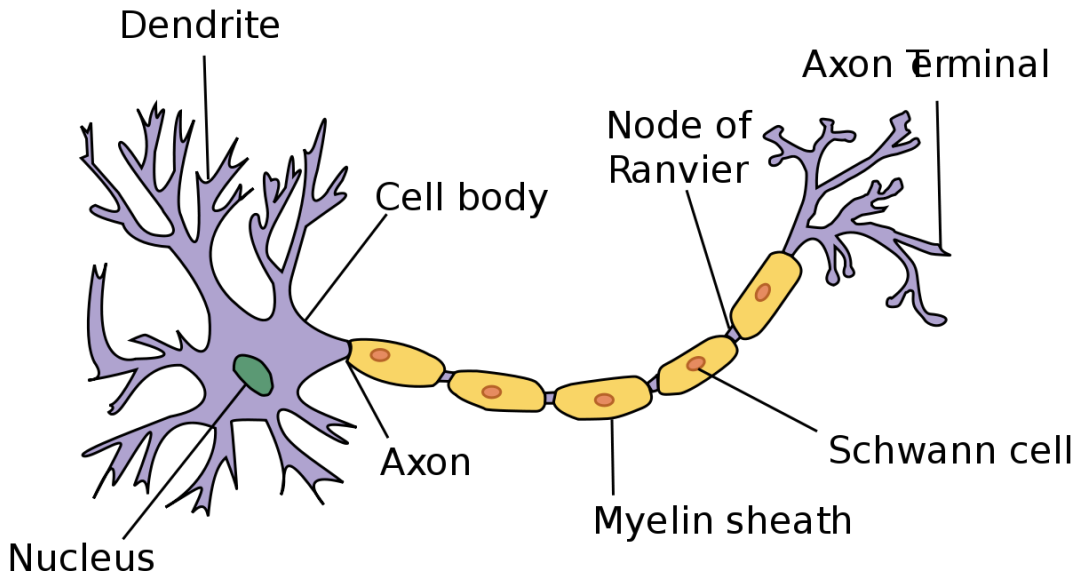


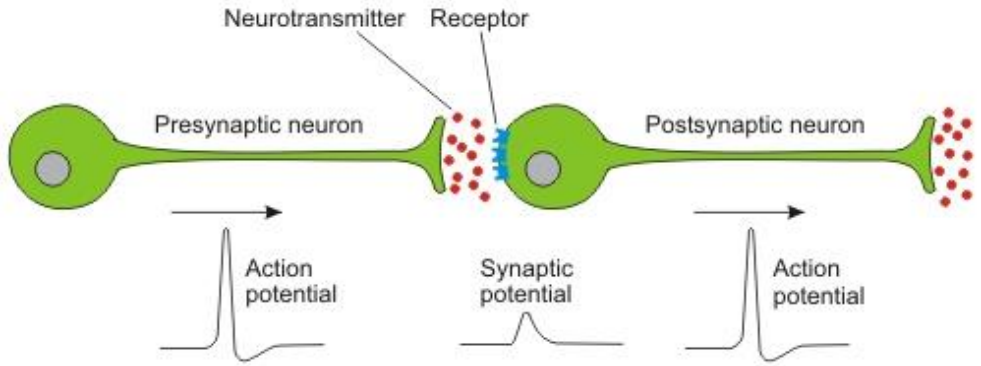




Neurons/action potential/nerve transmission







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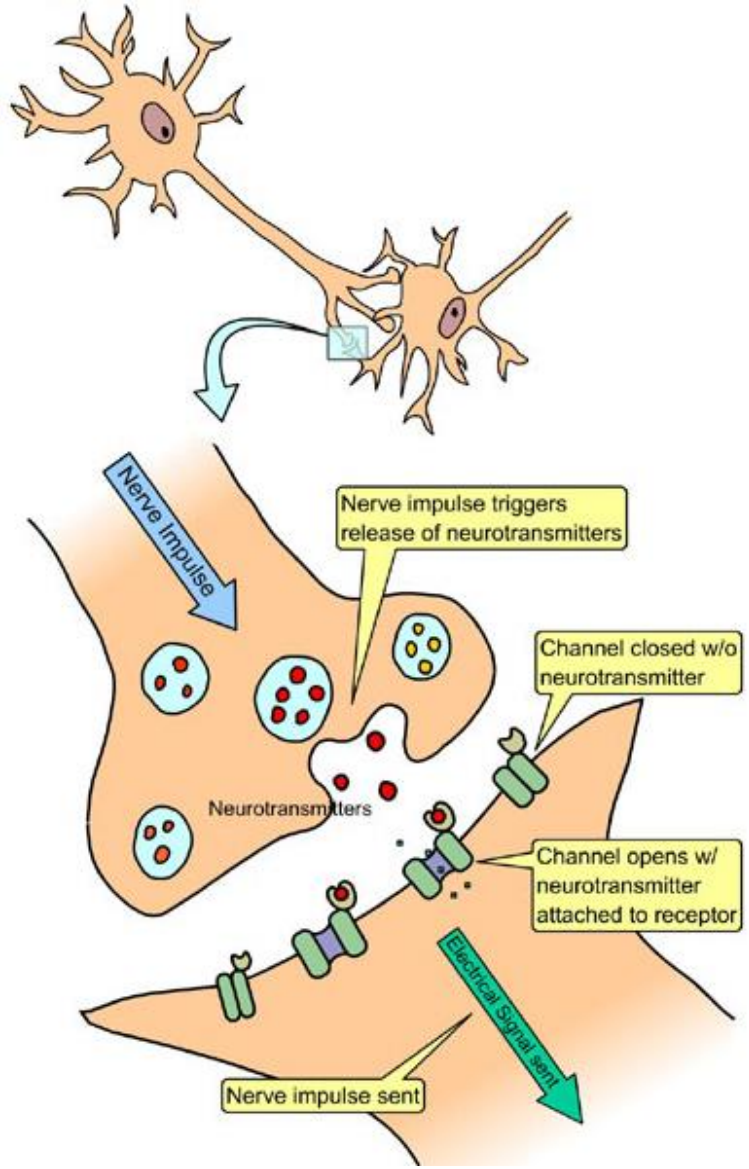
Synapses/neurotransmitters

- electrical synapses
- chemical synapses
  - excitatory – induce depolarisation
  - inhibitory – induce hyperpolarisation (↑ K^+ or Cl^- permeability)
- messenger molecules
  - neurotransmitters – synthesis, storage and release
    - AA – Ach, glutamate, glycine, GABA
    - peptides – substance P, endorphins
    - monoamines (1× NH_2) – serotonine, dopamine, norepinephrine, epinephrine
  - neuromodulators
    - endocanabinoids, substance P, endorphins
  - nerve growth factors
- removal of neurotransmitters
  - enzymatic degradation (e.g. Ach)
  - re-uptake by pre-synaptic neurons (e.g. catecholamines)
  - diffusion away



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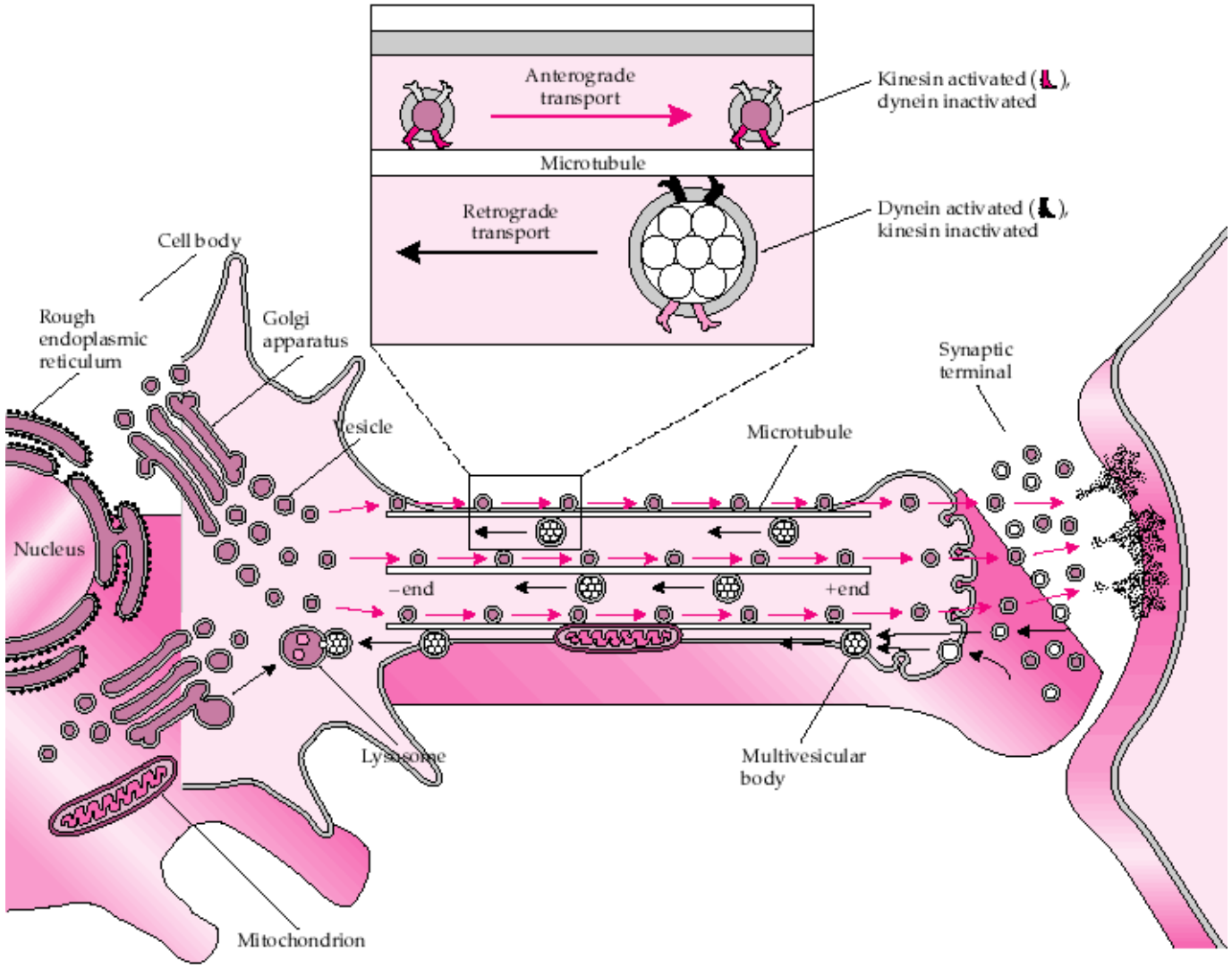
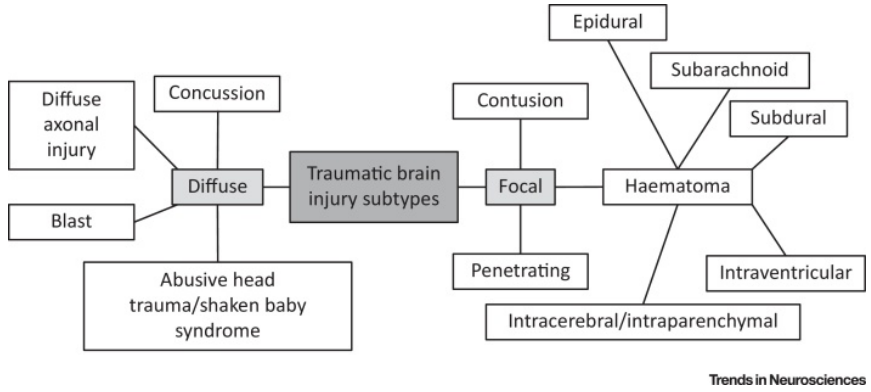
Axonal transport



- disorders
  - acute
    - toxic disruption
    - traumatic axonal injury as apart of traumatic brain injury



  - chronic (inherited)
    - mutations in motoric proteins, microtubules etc.

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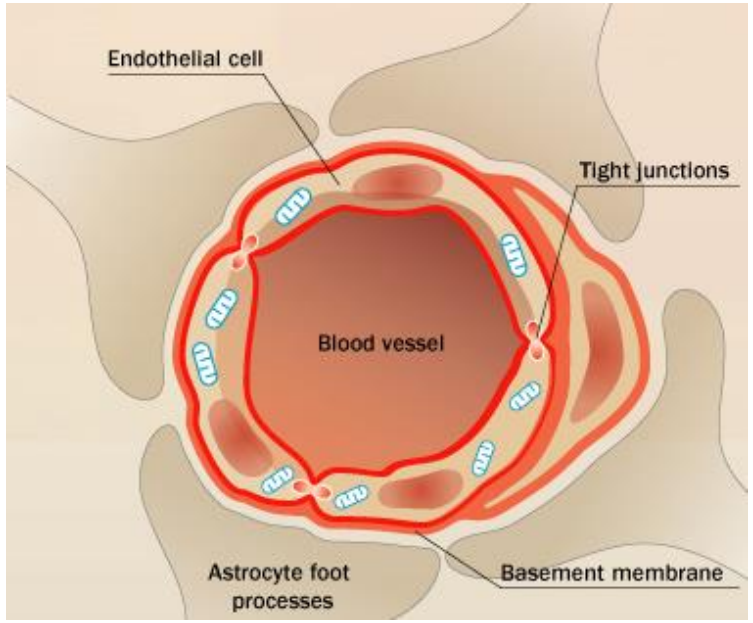
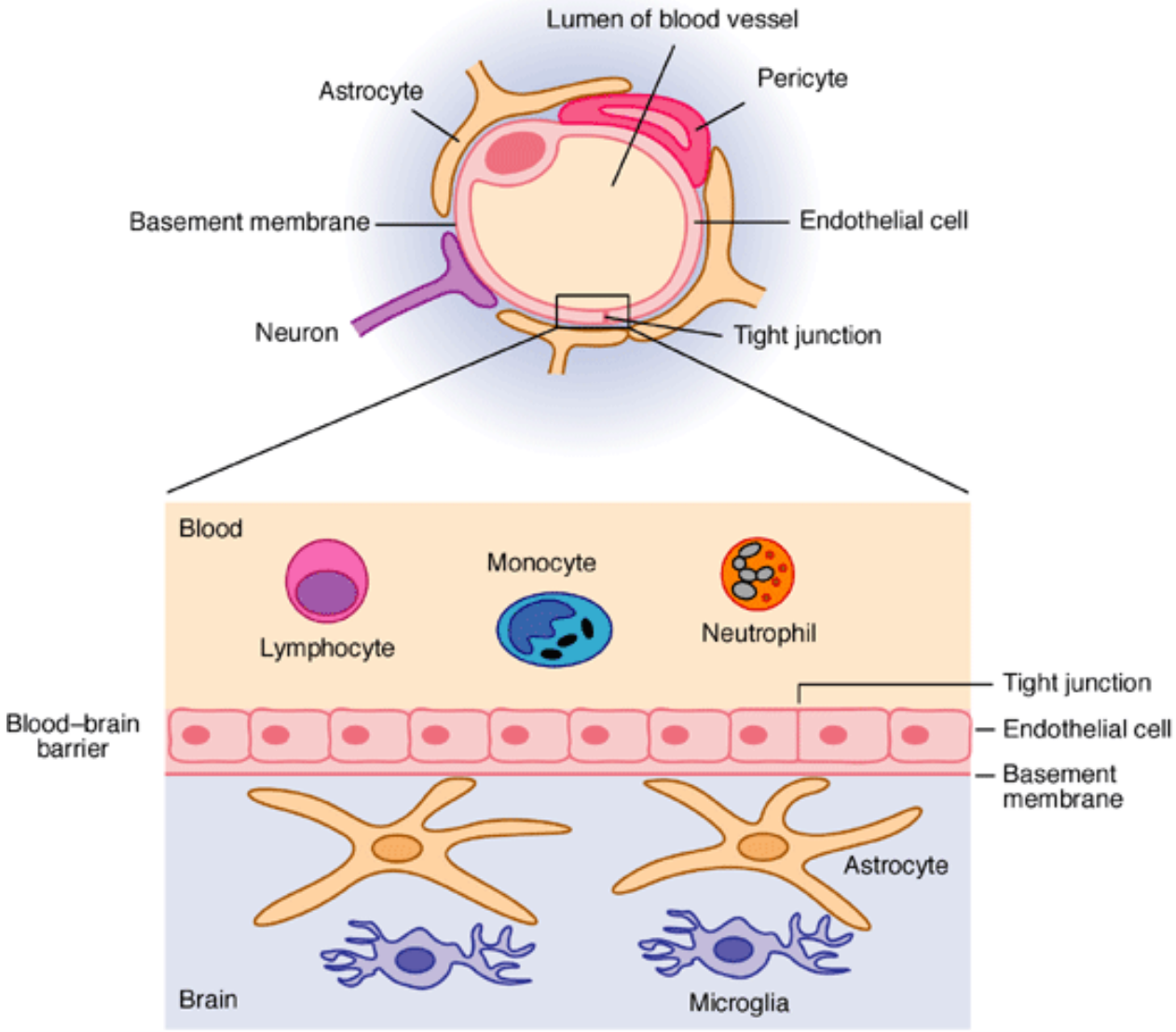
Blood-brain barrier (BBB)





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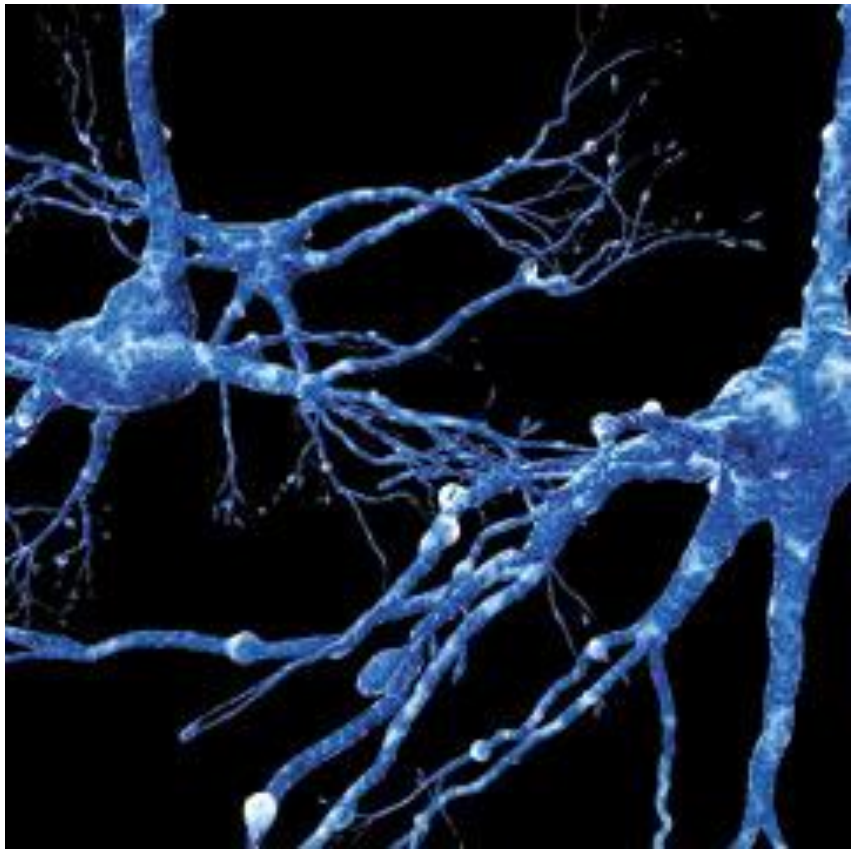
Neural plasticity



- brain's natural **ability to change or adapt**
- changes occur in the complex network of neurons that make up brain
- experiences, thoughts, or memories create **new or stronger connections among neurons**
- even in the adult brain, some new neurons are formed and migrate out into the cortex, taking up the new roles
- at the same time, neural connections and neurons that aren't used or are ineffective atrophy and die

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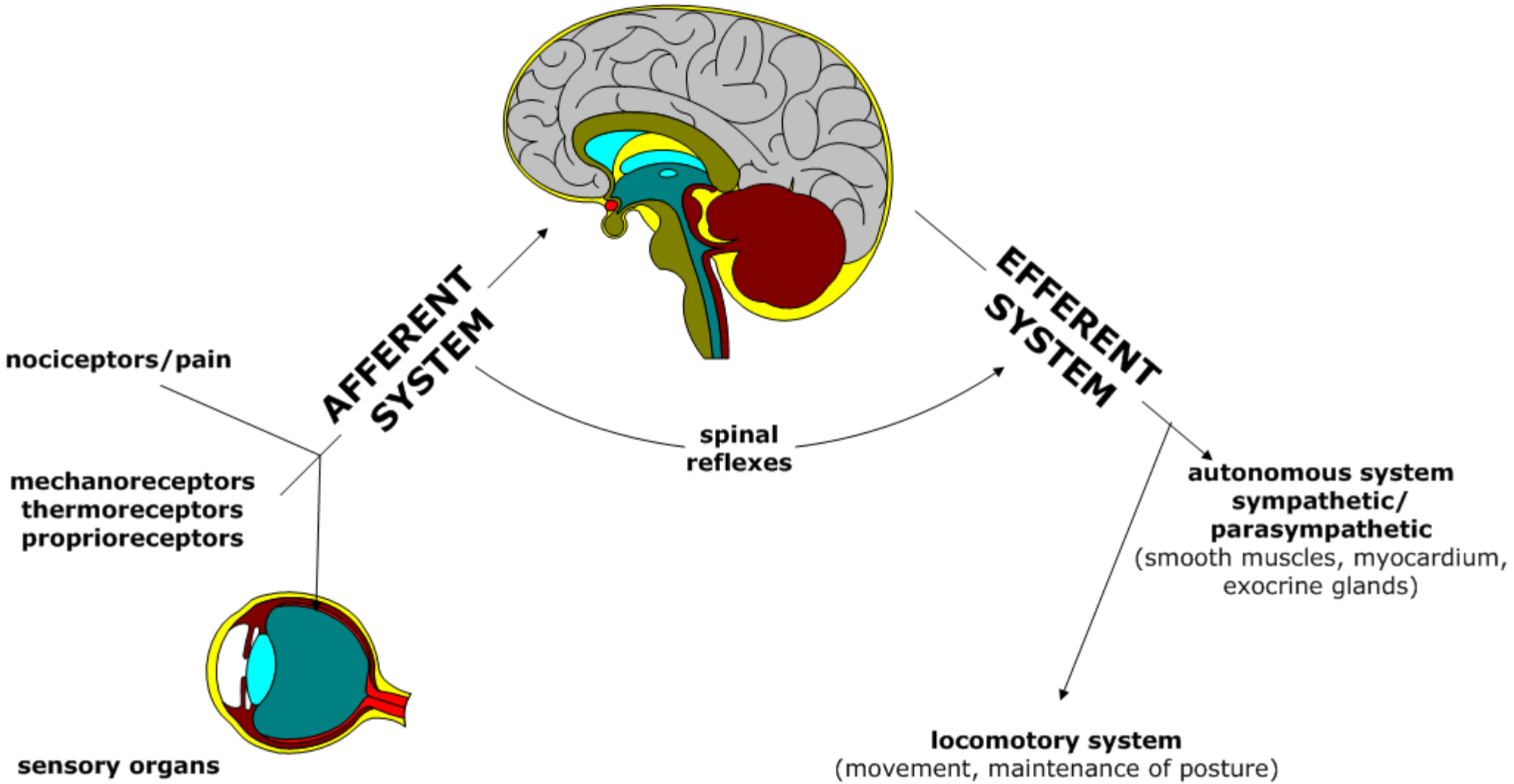
Organization of NS



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Disorders of nervous system

Categories

- afferent system
  - disorders of individual senses (sensor organs)
  - sensory neuropathies
  - pain
- perception of afferent signals and adequate reactions
  - quantitative and qualitative disorders of conscience
- efferent system
  - disorders of somatic motoric (pyramidal) system
  - disorders of extrapyramidal system
  - disorders of cerebellum
  - disorders of hypothalamus and vegetative nervous system
- abnormal electric activity of the brain
  - epilepsy
- mental abilities
  - cognitive disorders
  - dementia
- sleep disorders

Aetiology of nervous disorders

- unspecific = disturbances of the body's internal environment
  - hypoxia
  - temperature
  - ion concentrations
  - substrate/energy availability
- specific for nervous system
  - inherited
    - genetic
  - acquired
    - (auto)immune
    - ischemia
    - haemorrhage
    - mechanical injury

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Motor system a its disorders

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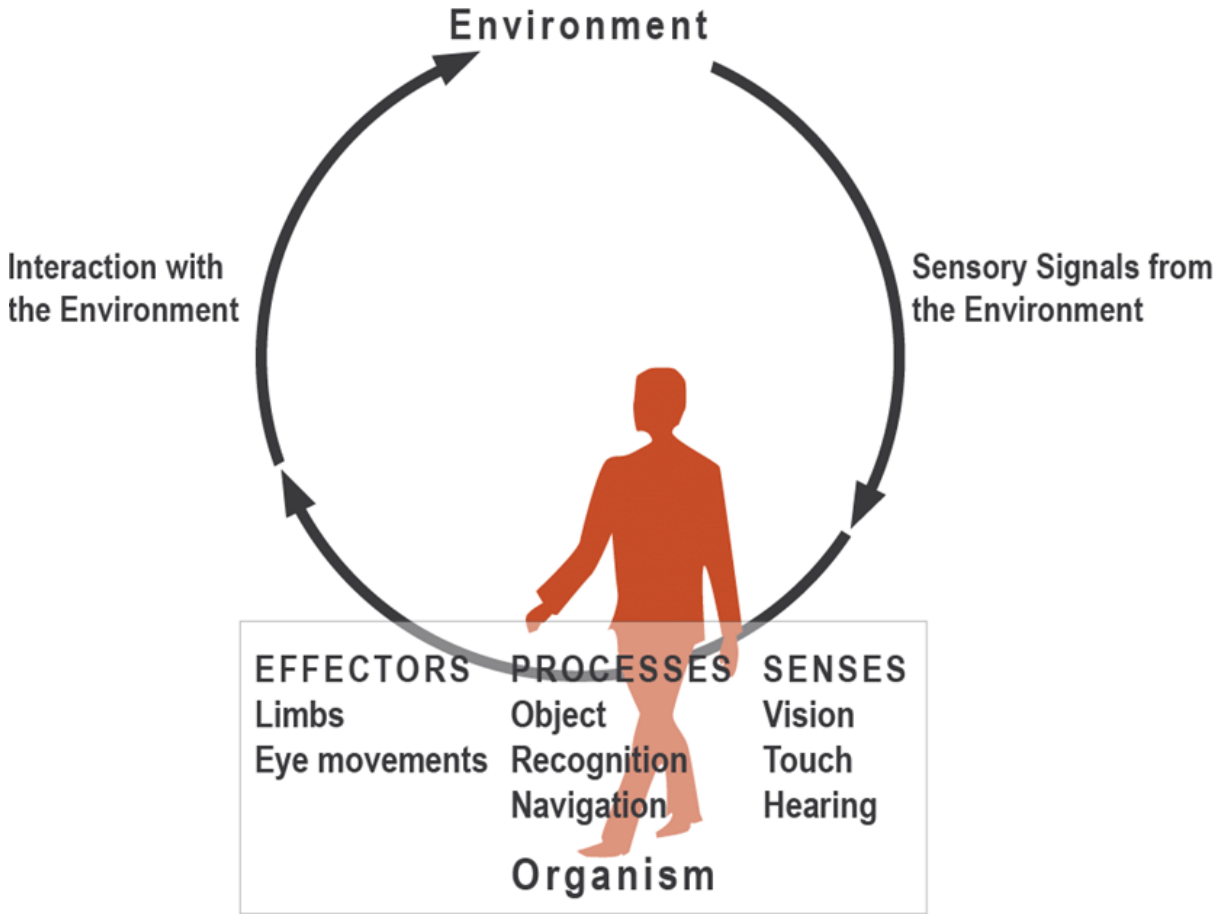
Motor system – control and its components

- locomotion + postural adjustments + periodical movement = motor activity
- motor action is typically a response to sensory perceptions
  - fight or flight, searching for shelter in rain, dance, smile, jerking away form painful object …
- Necessary components of proper motor control
  - volition, purpose, plan
  - coordination of signals to many muscle groups
  - proprioception and postural adjustments
  - sensory feed-back
  - unconscious processing
  - adaptability to changing conditions
    - i.e. growth, gain of weight (centre of mass), immobility of limb etc.



Functional Segregation and Hierarchical Organization

- the ease with which we make most of our movements point to enormous sophistication and complexity of the motor system
  - we have spent decades trying to make machines to perform simple tasks and human-like robots are nowhere near
- (1) Functional Segregation
  - motor system is divided into a **number of different areas** throughout the nervous system that control different aspects of movement (a **"divide and conquer" strategy**)
    - to understand the functional roles played by each area is necessary for understanding various motor disorders
- (2) Hierarchical Organization
  - higher-order areas can concern themselves with more global tasks regarding action, such as deciding when to act, devising an appropriate sequence of actions, and coordinating the activity of many limbs
  - they do not have to concern the activity of individual muscles, or coordinate movements with changes in posture
    - these low-level tasks are performed by the lower levels of the hierarchy

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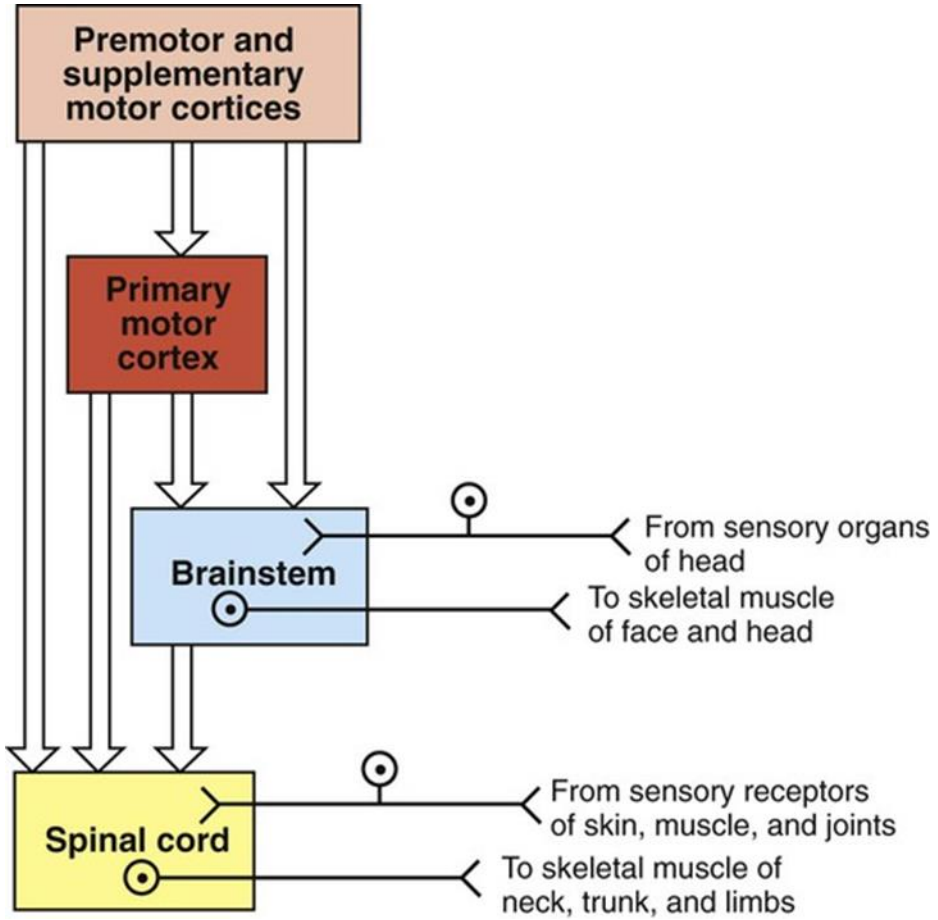
Hierarchical organisation of the motoric system

- 4 levels:
  - (1) the spinal cord
  - (2) the brain stem
  - (3) the motor cortex
  - (4) the association cortex
- It also contains two side loops, which interact with the hierarchy through connections with the thalamus :
  - (5) the basal ganglia
  - (6) the cerebellum



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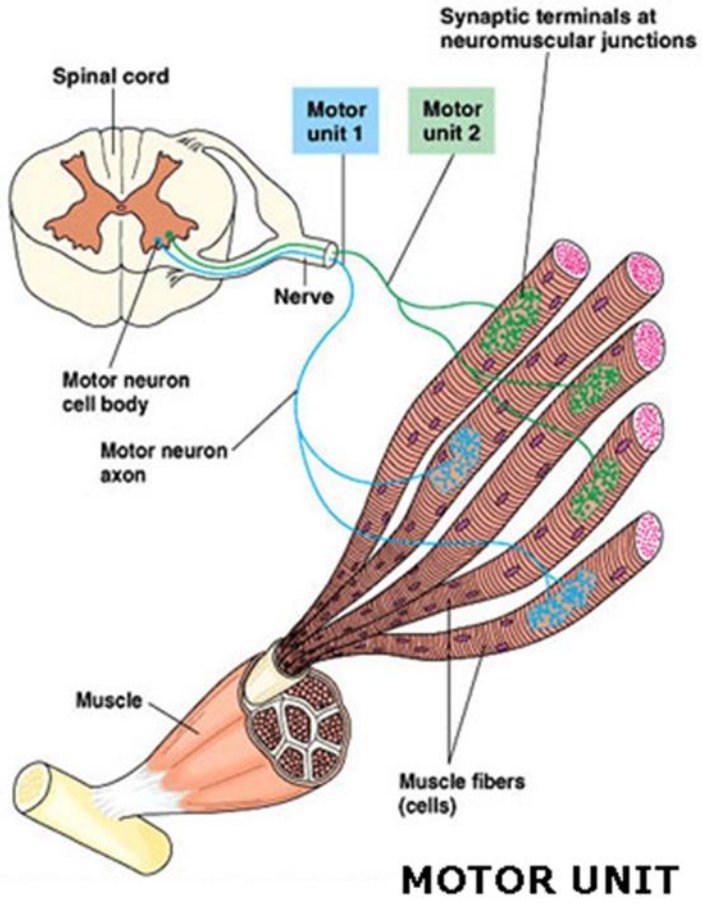
Level (1) spinal cord: α-motoneurons

- lower alpha-motoneurons (LMNs)
  - brainstem – for cranial muscles
  - spinal cord (ventral horns) – for neck, torso and limb muscles
- they release acetylcholine on neuromuscular junction and thus allow for muscle contraction
  - isometric
  - isotonic
- α-motoneurons are absolutely essential for ability to make a movement = the only communication with muscles
  - here all the signals for other systems and levels become integrated
- numerous inputs converge on α-motor neurons = **final common pathway**
- dendrites are connecting them with many other neurons – important for precision and adequacy of the movement
- **motor neuron pools** (or motor nuclei)
  - all of the motor neurons in a motor neuron pool innervate a single muscle
- **motor unit**
  - the combination of an individual motor neuron and all of the extrafusal muscle fibers that it innervates
    - each individual muscle fiber in a muscle is innervated by one motor neuron, a single motor neuron, however, can innervate many muscle fibers
  - the number of fibers innervated by a motor unit is called its **innervation ratio**
    - low (10-100) in muscles dedicated to delicate movements
      - e.g. digits of hands, facial mimic
    - high (≥1000) in muscles dedicated to gross movements
      - e.g. thigh
- α-motoneurons control muscle force



Organization of moto neurons in the spinal cord (anterior horns)

- the flexor-extensor rule
  - motor neurons that innervate flexor muscles are located posteriorly to motor neurons that innervate extensor muscles
- and the proximal-distal rule
  - motor neurons that innervate distal muscles (e.g., hand muscles) are located lateral to motor neurons that innervate proximal muscles (e.g., trunk muscles)

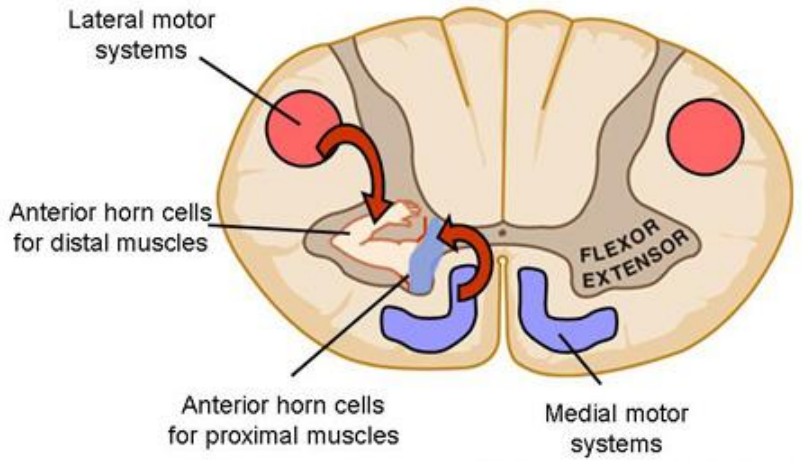
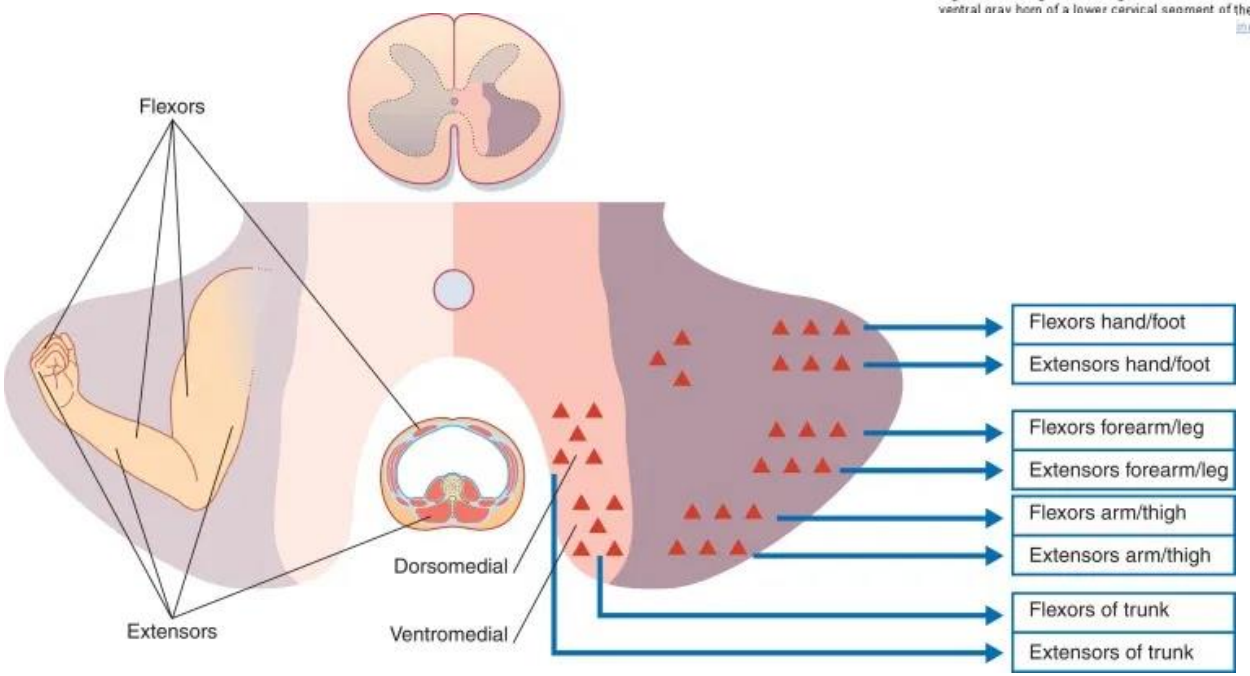


Figure 5-12. Diagram showing the functional localization of motor neuron groups in the ventral gray horn of a lower cervical segment of the spinal cord. In: Waxman SG. *Clinical* ine.com. Accessed January 3, 2010.



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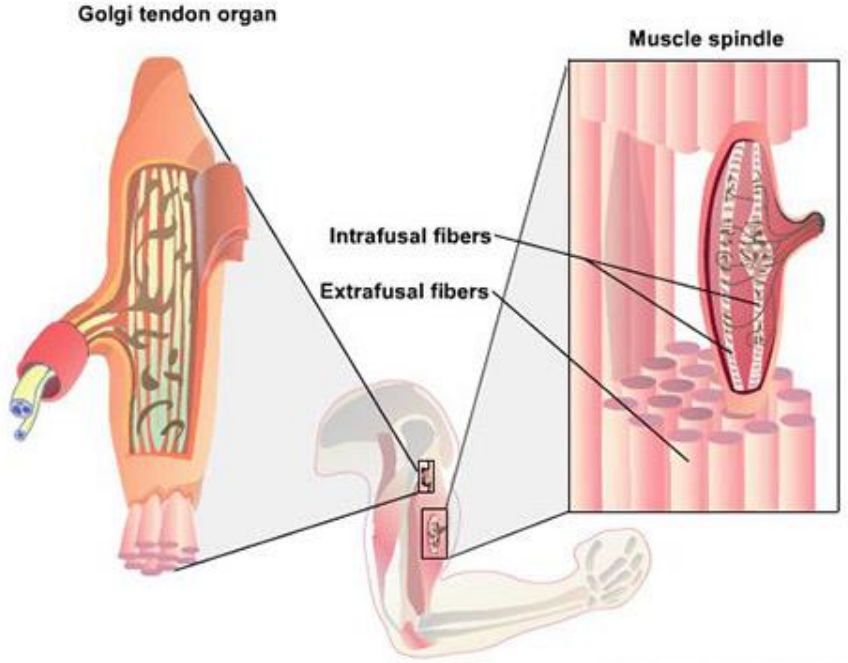
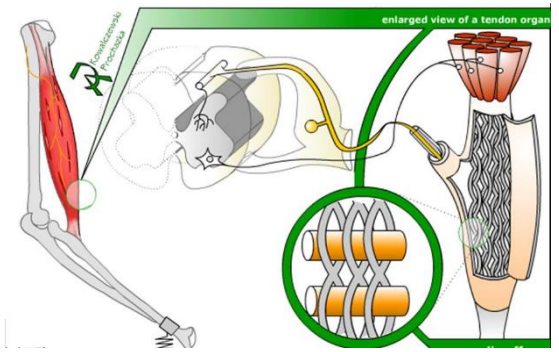
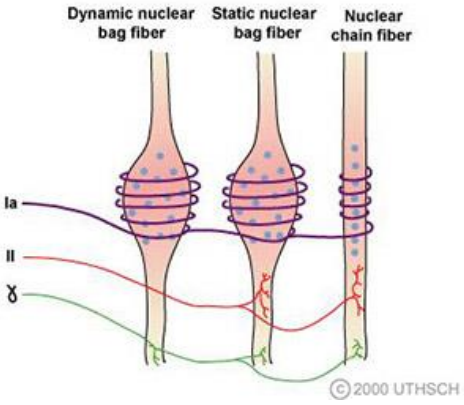
Level (1) spinal cord : Muscle Receptors and Proprioception

- **Proprioception** is the sense of the body's position in space based on specialized receptors that reside in the (A) muscles and (B) tendons
  - **(A) Muscle spindles** signal the **length** and the rate of **change** of length (**velocity**) of the muscle
    - collections of 6-8 specialized muscle fibers that are located within the muscle mass itself
    - they are formed by **intrafusal fibers** not participating in the active contraction (unlike extrafusal ones)
    - spindles are formed by different types of fibres
      - see figure
      - these fibres provide different information (length vs. velocity of its change) – via various afferents (Ia vs. II)
    - each muscle contains many muscle spindles
      - muscles that are necessary for fine movements contain more spindles than muscles that are used for posture or coarse movements
    - intrafusal fibres can contract though – innervation by γ-motoneurons
  - **(B) Golgi Tendon Organ** located between the muscle and the tendon signals information about the load or force being applied to the muscle = **inverse stretch reflex**
    - collagen capsule
    - afferents called group Ib fibers weave in between the collagen fibers being 'crushed' by movement and thus depolarized







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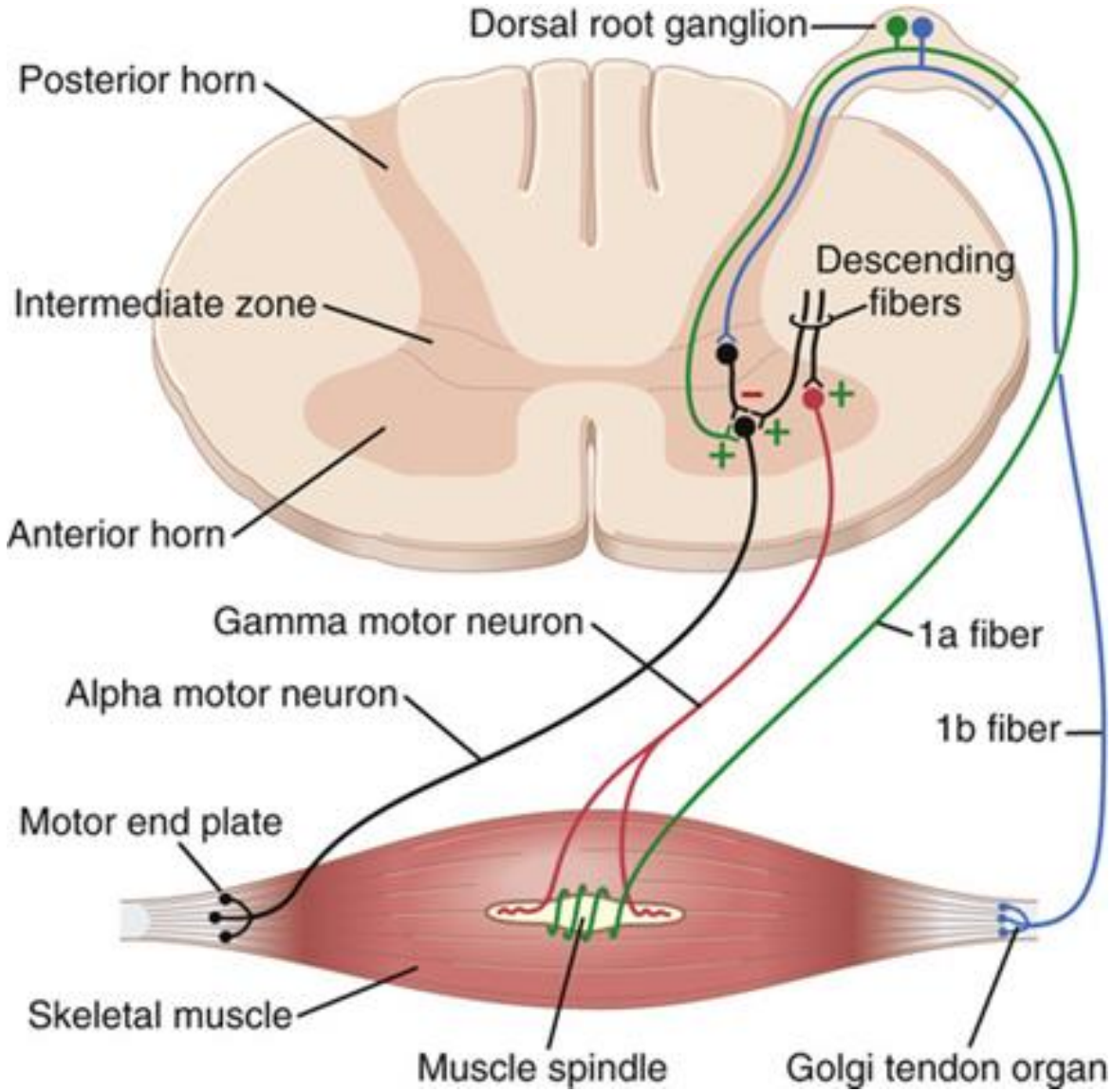
In summary



- **Muscle spindles** signal information about the length and velocity of a muscle
  - the properties of the various dynamic and static responses of muscle spindle afferents are related to **physiological tremor**
- **Golgi tendon organs** signal information about the load or force applied to a muscle

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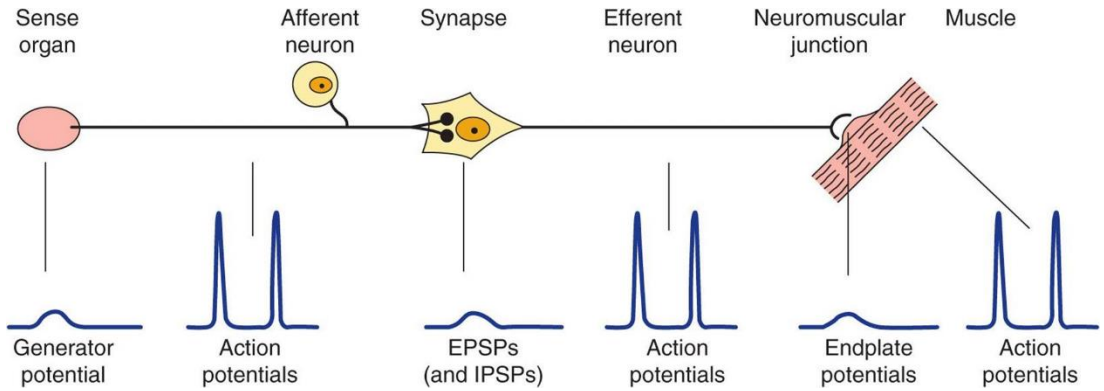
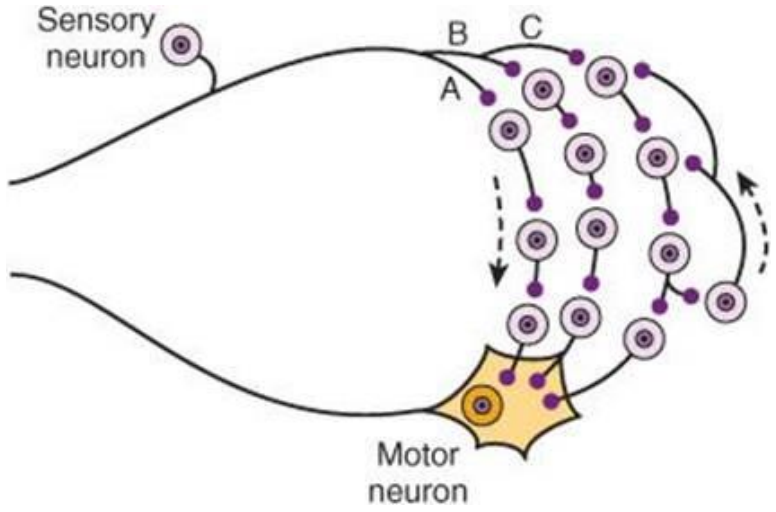
Level (1) spinal cord: spinal reflexes

- reflex is a basic functional unit of motor system
  - morphologically they rely on specialized neuronal circuits controlling the muscle function so that it can give rise to effective movements
  - without the spinal reflexes not even a simple movement would be possible
- reflex arch
  - 1) sensor (e.g. muscle spindle or Golgi tendon organ)
  - 2) afferent pathway
    - neurons of spinal ganglia entering the spinal cord via the dorsal roots
      - they split into two collaterals:
        - to the same spinal segment (monosynaptic)
        - afferents to other hierarchies
  - 3) centrum of the reflex
  - 4) efferent pathway – spinal motoneuron innervating the muscle
  - 5) effector – particular skeletal muscle(s)
- types of reflexes
  - monosynaptic
  - polysynaptic





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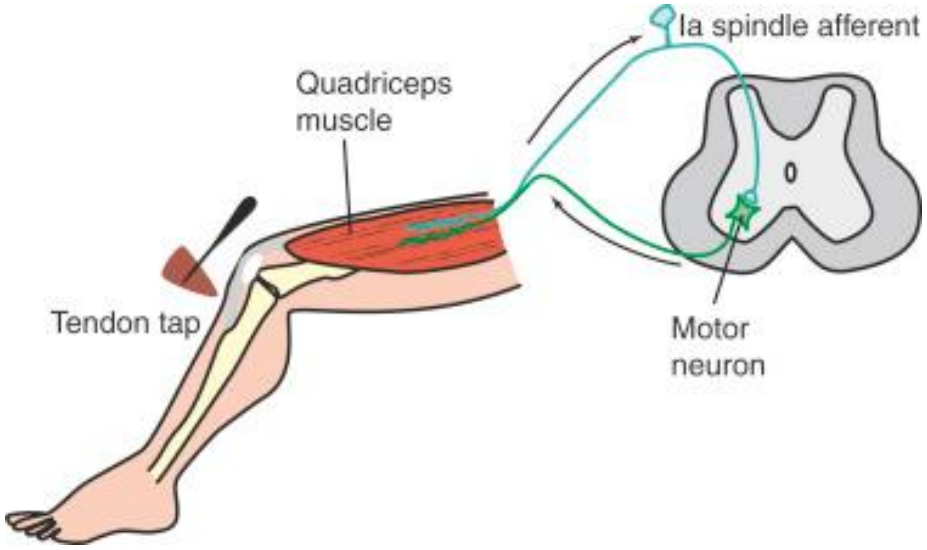
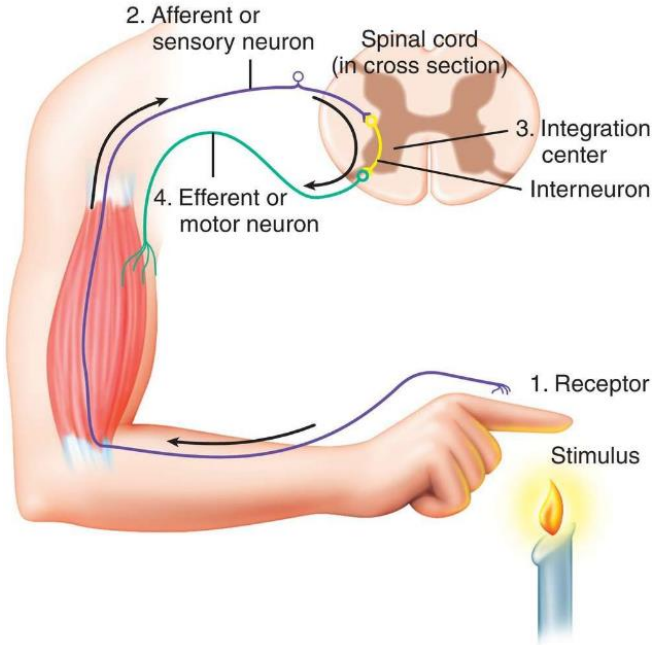
Level (1) spinal cord: spinal reflexes

- types of reflexes
  - monosynaptic
    - **stretch** or myotatic (e.g. patellar – knee jerk reflex) – sensor is the muscle spindle
  - polysynaptic – interneurons are interposed between the afferent and efferent neurons (often defensive)
    - flexor (**withdrawal reflex**) reflex – sensor is the nociceptor
      - activation of a-motoneuron of the particular flexor
      - inhibition of a-motoneuron of adjacent extensor (antagonist)
    - **crossed extensor response** reflex – follows the flexor one when stimulus is more intense
      - extension of the contralateral limb
      - the meaning is to better distribute the weight and to keep balance
        - evolutionary probably an old mechanism (now a rudiment) for optimizing a quadruped stance





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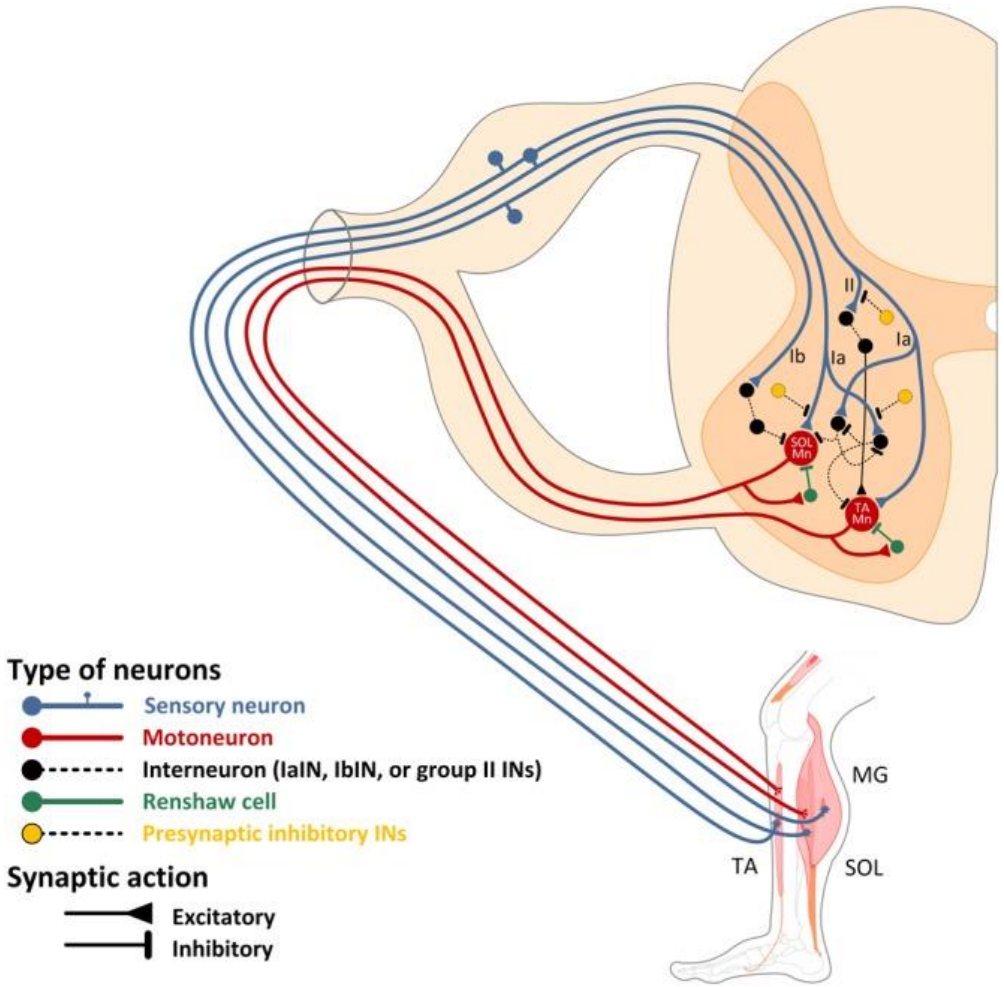
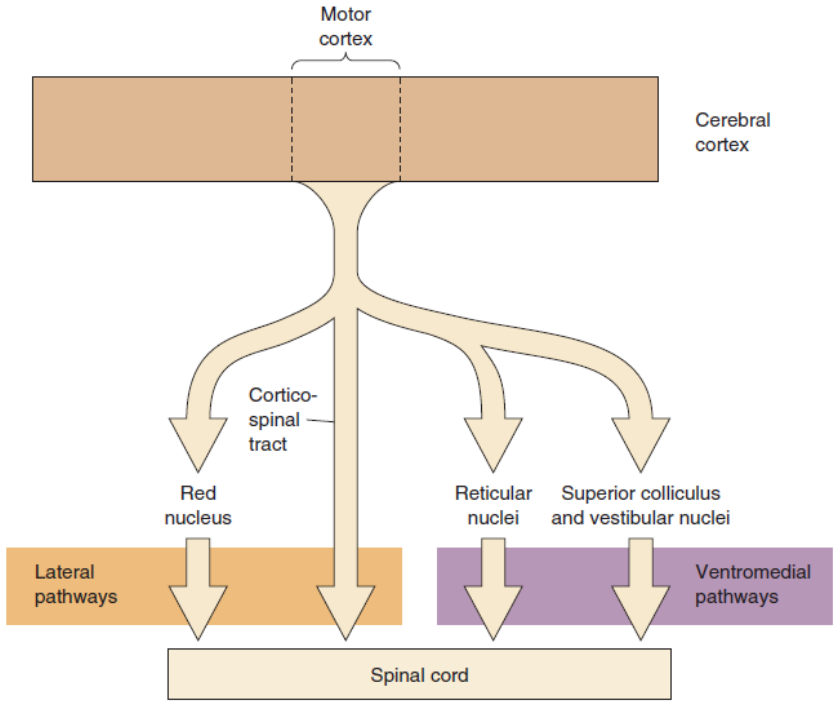
Level (1) spinal cord: role of interneurons



- interneurons constitute the majority of spinal neurons
- necessary for complex locomotor behaviors
  - left–right coordination to achieve optimal gaits
    - walking / running in humans
    - in other species walking / trotting / galloping, swimming, flying etc.
  - **flexor–extensor alternations**
- rhythm-generating and pattern-forming spinal circuits
- the four ventromedial descending pathways originating in the brain stem (see Level 2) terminate among the spinal interneurons controlling proximal and axial muscles
  - thez use information about balance, body position, and the visual environment to reflexively maintain balance and body posture



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Level (2) brainstem: Descending Motor Pathways

- Role of Descending Pathways on Spinal Circuits
  - **Voluntary movement** and some sensory-driven reflex actions are controlled by the descending pathways in order to be appropriate and effective
  - **Reflex modulation** - another critical function is to modulate/adapt the reflex circuits in the spinal cord
  - **Gamma motoneuron bias**
- Descending motor pathways are organized into two major groups
  - Lateral pathways control both proximal and distal muscles and are responsible for most voluntary movements of arms and legs. They include the
    - **lateral corticospinal tract**
    - rubrospinal tract
  - Medial pathways control axial muscles and are responsible for posture, balance, and coarse control of axial and proximal muscles. They include the
    - vestibulospinal tracts (both lateral and medial)
    - reticulospinal tracts (both pontine and medullary)
    - tectospinal tract
    - **anterior corticospinal tract**
- Parallel and Serial Processing
  - the flow of information through the motor system has both a serial organization (communication between levels) and a parallel organization (multiple pathways between each level)
  - this is critically important in understanding the various dysfunctions that can result from damage to the motor system
  - it allows to at least partly compensate for damage at certain parts of the control (e.g. corticospinal tract) and to recover voluntary motoric to some extent

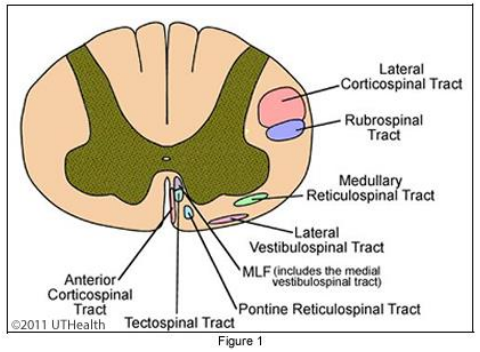
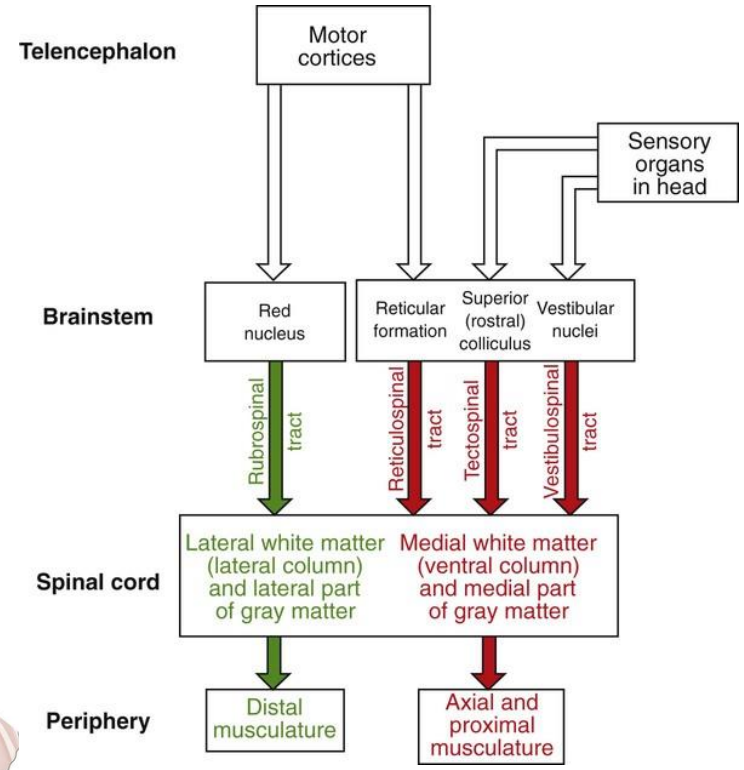
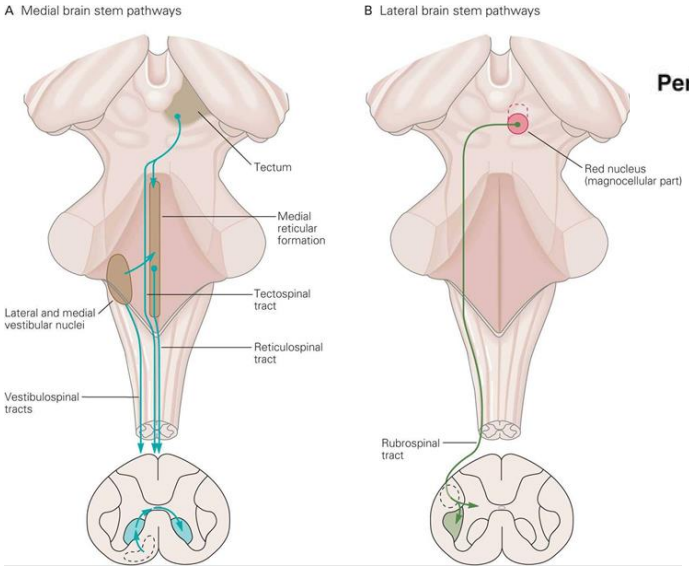


Figure 1





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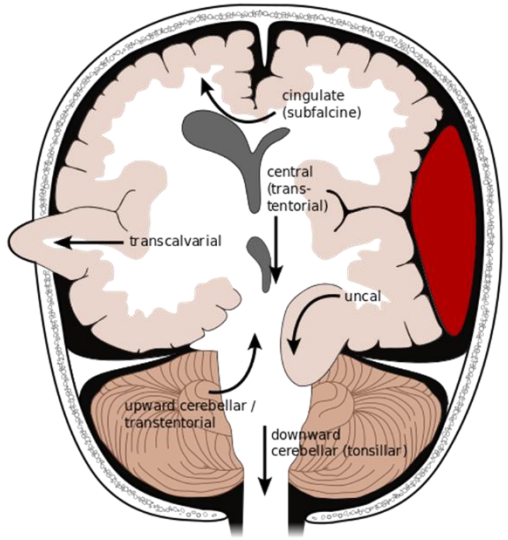
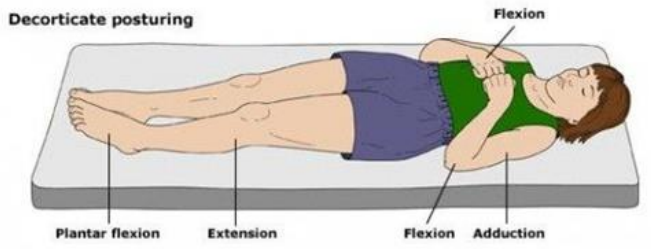
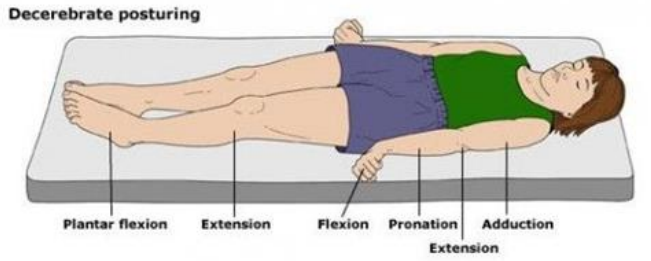
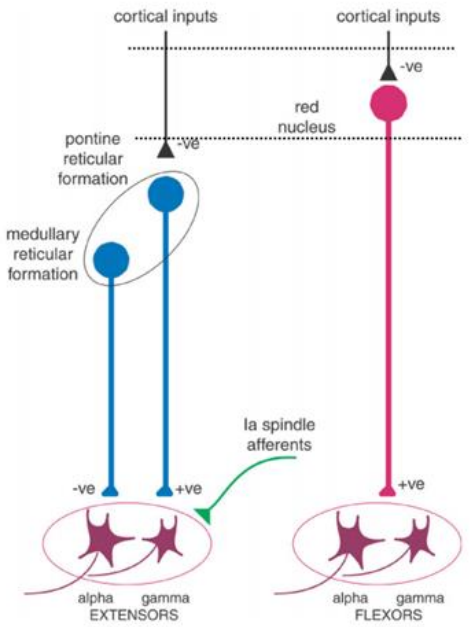
Medial and lateral descending brain stem pathways involved in motor control

- The rubrospinal tract
  - terminates primarily in the cervical and thoracic portions of the spinal cord, suggesting that it functions in upper limb but not in lower limb control
- **decerebration**
  - a complete transection of the brain stem interrupting all input from the cortex (CTS) and red nucleus (rubrospinal tract), primarily to distal muscles of the extremities
    - the rubrospinal tract excites flexor motor neurons and inhibits extensor motor neurons
  - leads to hyperactivity in extensor muscles in all four extremities which is called decerebrate rigidity together with coma, fixed and dilated pupils, absent eye movements and a Cheyne–Stokes respiratory pattern
  - causes: uncal herniation due to large tumors, hemorrhages, strokes or abscesses
- **decortication**
  - the rubrospinal tract excites flexor motorneurons and inhibits extensor motorneurons









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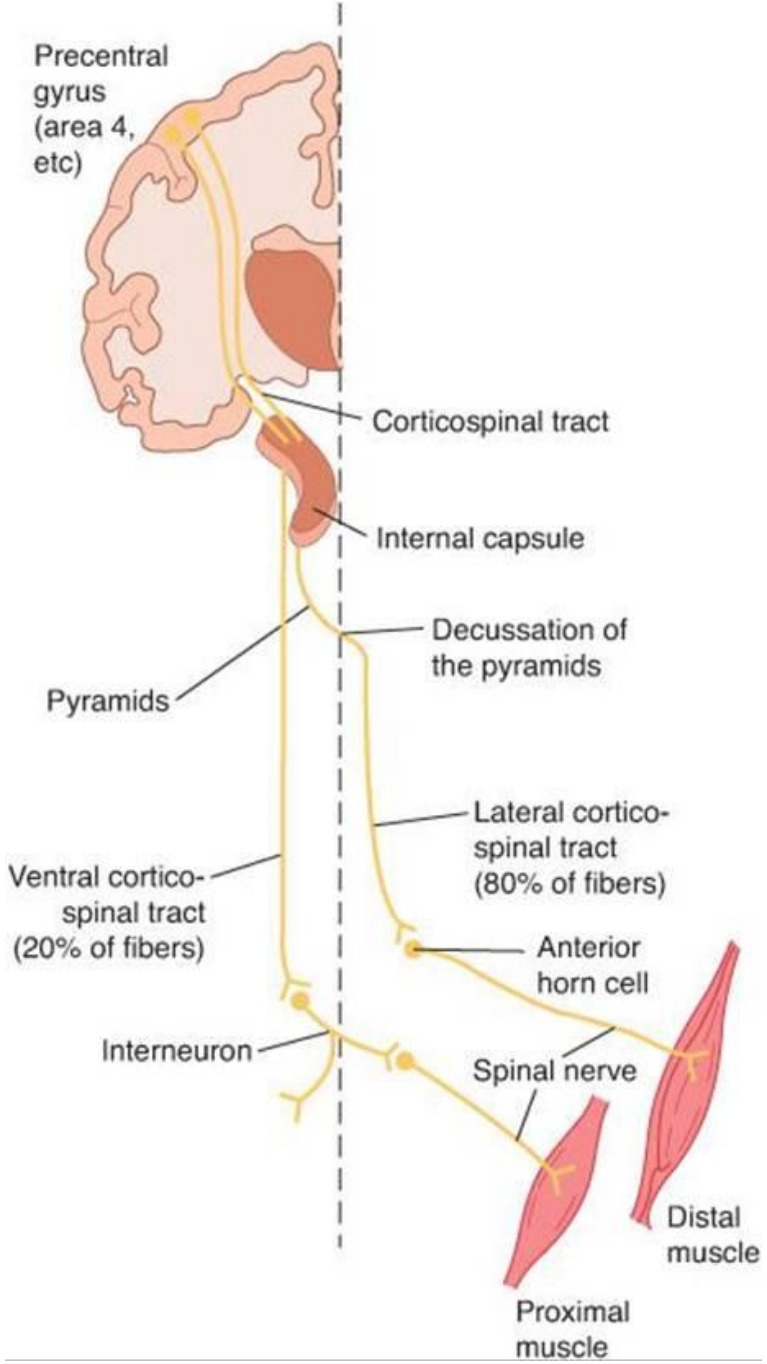
Corticospinal/corticobulbar tract

- The **corticospinal system** controls motor neurons and interneurons in the spinal cord
- The **corticobulbar system** controls brainstem nuclei that innervate cranial muscles
  - trigeminal, facial, and hypoglossal nuclei
  - not strictly contralateral manifestation
- CST originates in the motor cortex
  - the majority of CST axons originate from **pyramidal cells** located in the inferior part of cortical layer V in the primary motor (M1)
  - travels via capsula interna, crus cerebri (midbrain), **pyramids** of medulla oblongata – decussation (here it splits into two funiculi)
  - CST has approximately 1 million nerve fibres with an average conduction velocity of approximately 60m/s using glutamate as their transmitter substance
- **the primary pathway** that carries the motor commands that underlie voluntary movement in humans
  - the **lateral corticospinal tract** (90% of axons) is responsible for the control of the distal musculature
    - a particularly important function of the LCST is the fine control of the digits of the hand
  - the **anterior/ventral corticospinal tract** (10% of axons) is responsible for the control of the axial (trunk) and proximal musculature
- both the lateral and anterior corticospinal tracts are crossed pathways; they cross the midline at different locations, however



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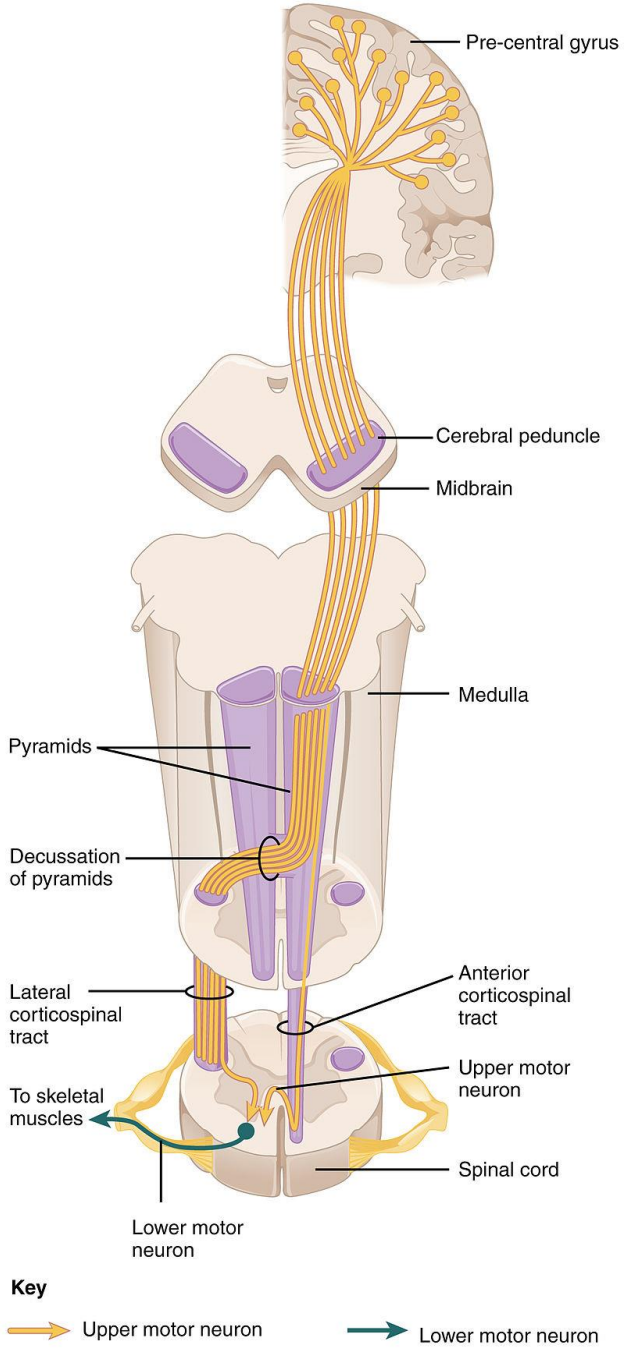
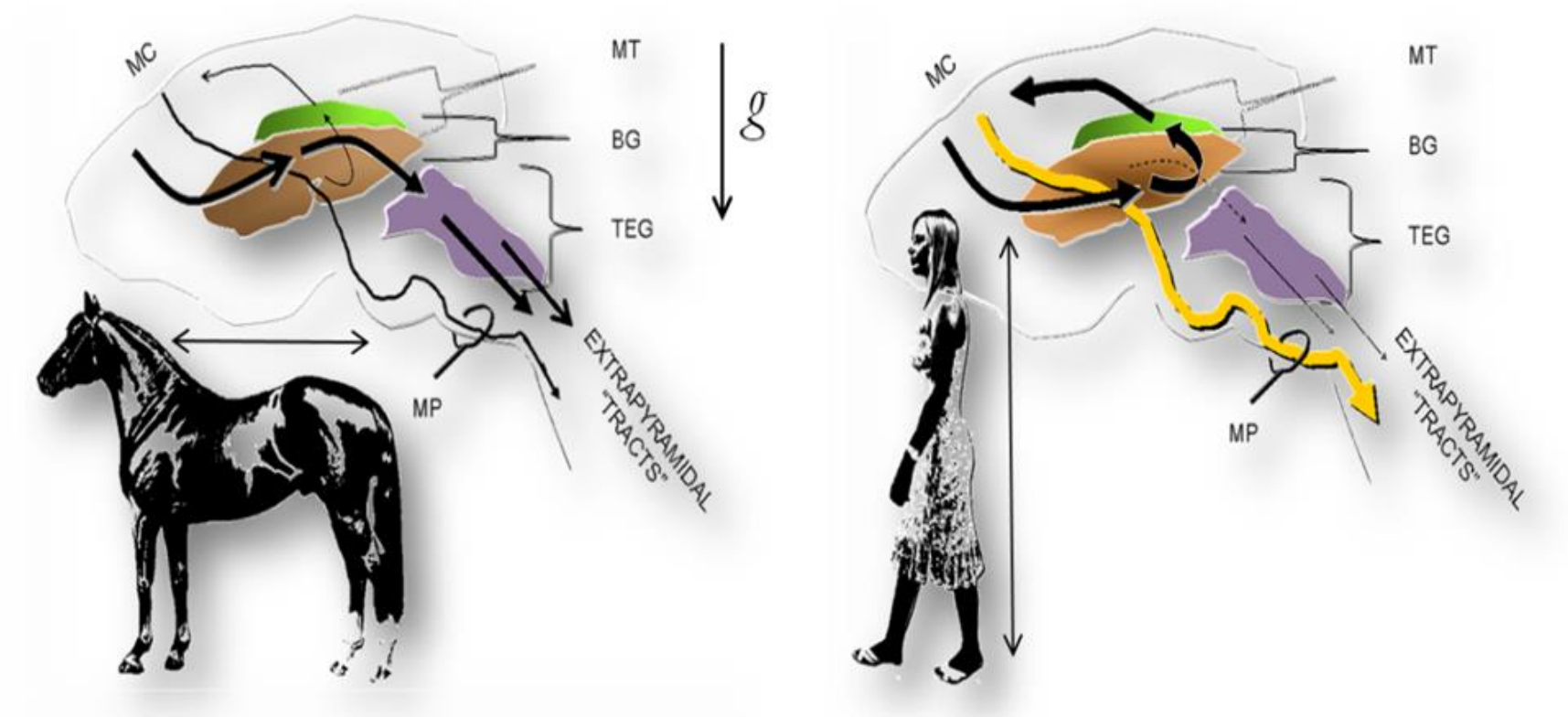
CST onto- and fylogenesis

- Humans neonatal brain being moderately myelinated and only 25% of its adult size
  - CST axons reach the lower part of the cervical spinal cord by 24 weeks postconception, and grey matter innervation begins a few weeks later
- The relative importance of CST to voluntary movement greatly varies across the species
  - humans > primates >> other mammalian vertebrates
    - non-mammalian vertebrates have essentially no CST
- The percentage of axons in CST that innervate a-motor neurons directly is greater in humans and nonhuman primates than in other mammals
  - presumably reflecting the increased manual dexterity of primates
  - in other species most of the CST connects with spinal interneurons
- therefore, damage to the CST results in a permanent loss of the fine control of the extremities most markedly in humans
  - while nearly undetectable in other mammals (e.g. cats or dogs)



Organization of the motor system in vertebrates and man

- In most vertebrates, including nonhuman primates, the extrapyramidal and pyramidal fiber systems run in parallel from the motor cortices (MC) to the motoneuron pools of the brainstem and spinal cord. The extrapyramidal system consists of a series of cortical projections interrupted at the basal ganglia (BG) and brainstem tegmentum (TEG) whence tegmentospinal projections originate (chiefly, reticulospinal, vestibulospinal, tectospinal and rubrospinal tracts). Right. The adoption of obligate erect bipedalism in humans was paralleled by a profound cerebral reorganization. These changes are reflected in an unprecedented increase in the ansa lenticularis fiber system. The ansa directs the projections from widespread cortical areas into the thalamic motor nuclei (mt), which project back to the motor cortices that give rise to the pyramidal tracts. The increase in the pyramidal tracts (MP), in turn, is paralleled by an unprecedented decrease of the descending motor (extrapyramidal) pathways. Note the perpendicular and parallel orientations of the quadrupedal and human body axes (arrows), respectively, in relation to gravity (g). mp: medullary pyramids.



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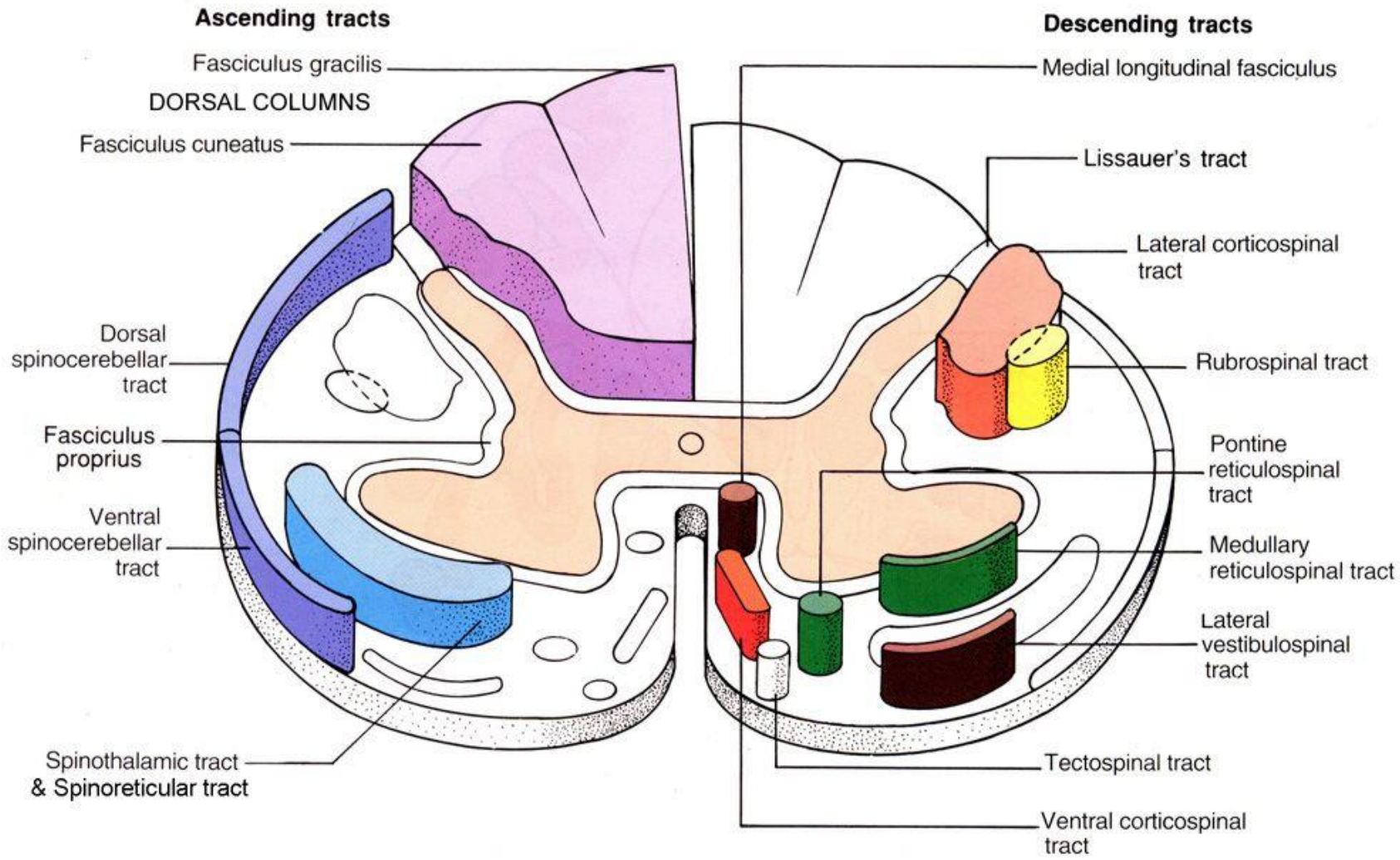
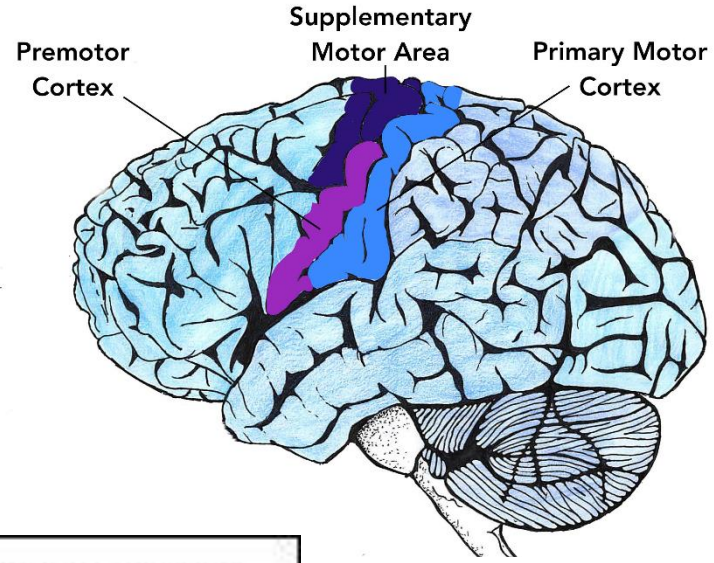
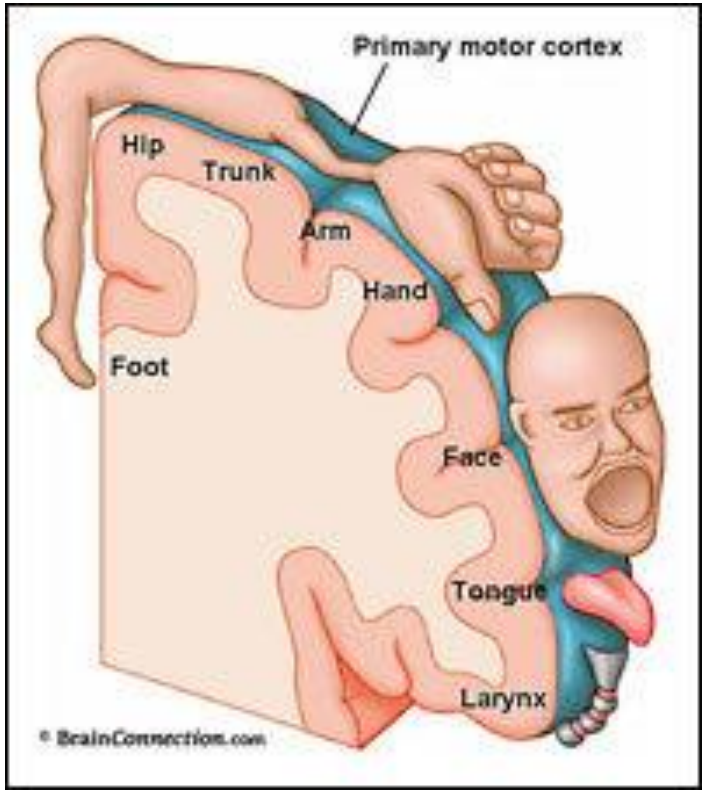
Overview of tracts in a spinal cord



Level (3): Motor cortex

- comprises three different areas of the frontal lobe
  - the **primary motor cortex** (Brodmann's area 4)
    - function: regulation of the onset, force, direction, extent and the speed of the movement (= regulation of the execution of movements rather than control of individual muscles)
  - the **premotor cortex**
    - function: more complex, task-related processing, selection of appropriate motor plans for voluntary movements (often based on visual stimuli or on abstract associations)
  - the **supplementary motor area**
    - function: programming complex sequences of movements and coordinating bilateral movements (based on remembered sequences of movements)
- electrical stimulation of these areas elicits movements of particular body parts
  - though different for each of the 3 areas
- they are somatotopically organized
  - motor cortex "**homunculus**"





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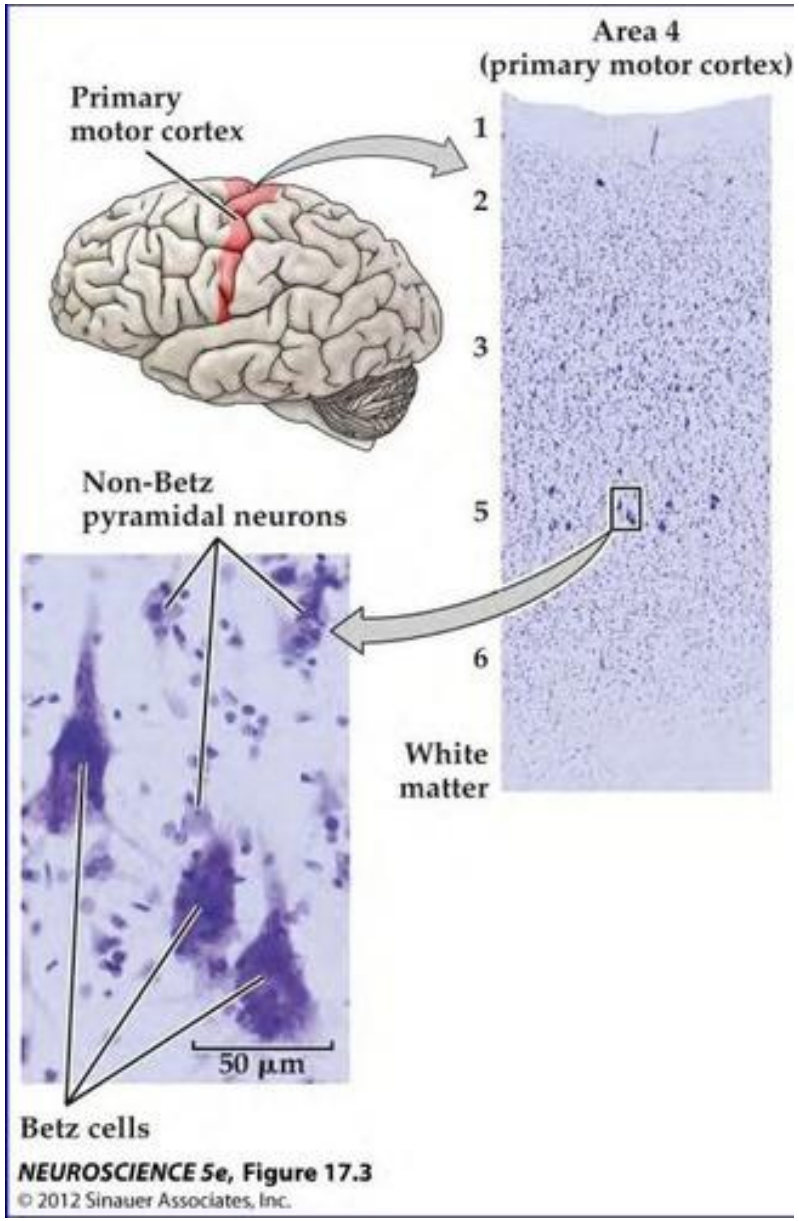
Cyto-architecture of the motor cortex

- brain cortex is very sensitive to hypoxia
  - motor cortex even more
- pre-/peri-/ and early post-natal development are vulnerable periods



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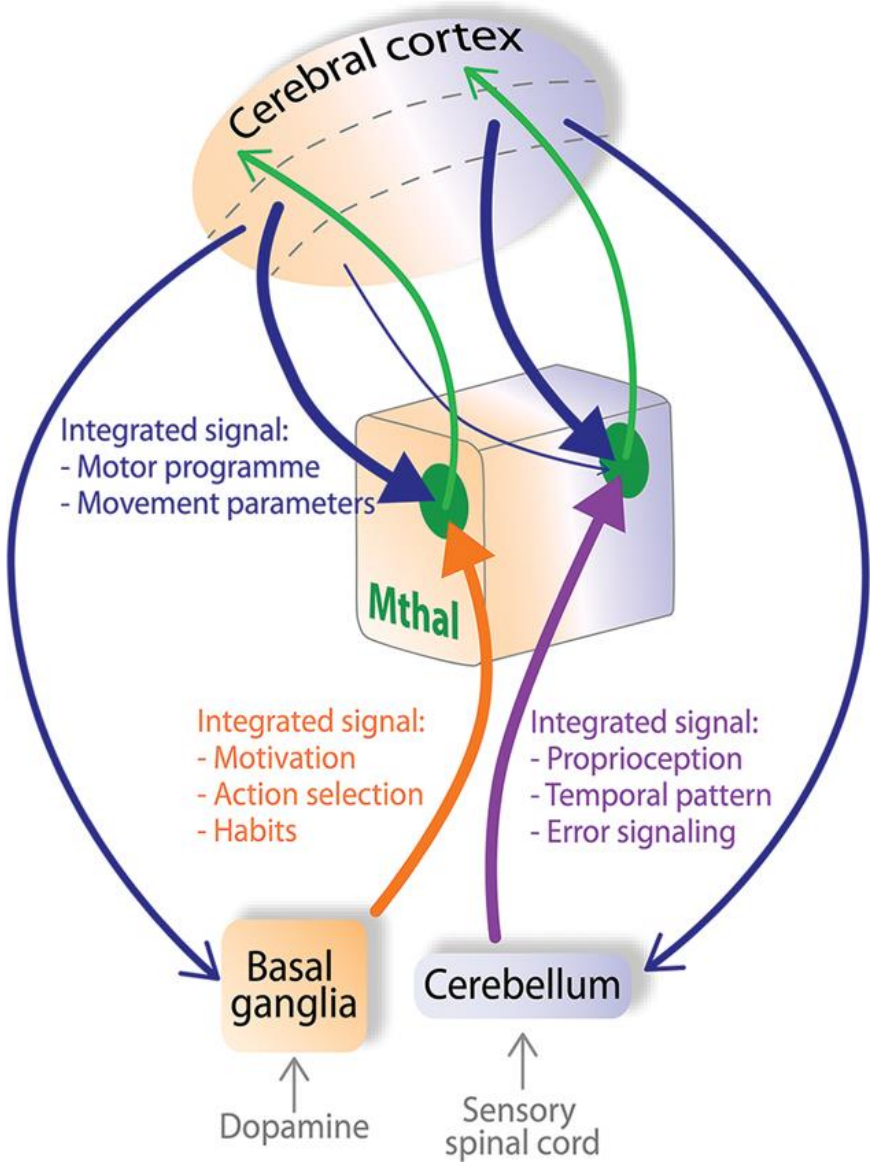
Cortical Afferents and Efferents and cytoarchitecture

- efferent pathways
  - directly to alpha motor neurons via the corticospinal tract
  - the corticorubral tract to modulate the rubrospinal tract
  - the corticotectal tract to modulate the tectospinal tract
  - the corticoreticular tract to modulate the reticulospinal tracts
  - the corticostriate tract to the caudate nucleus and putamen of the basal ganglia
  - the corticopontine tract and cortico-olivary tract to the cerebellum
  - the corticocortical pathways to other brain areas (bi-directional)
- afferent pathways
  - the corticocortical pathways from other brain areas (bi-directional)
  - indirectly via the corticothalamic pathways (from the cerebellum and basal ganglia)



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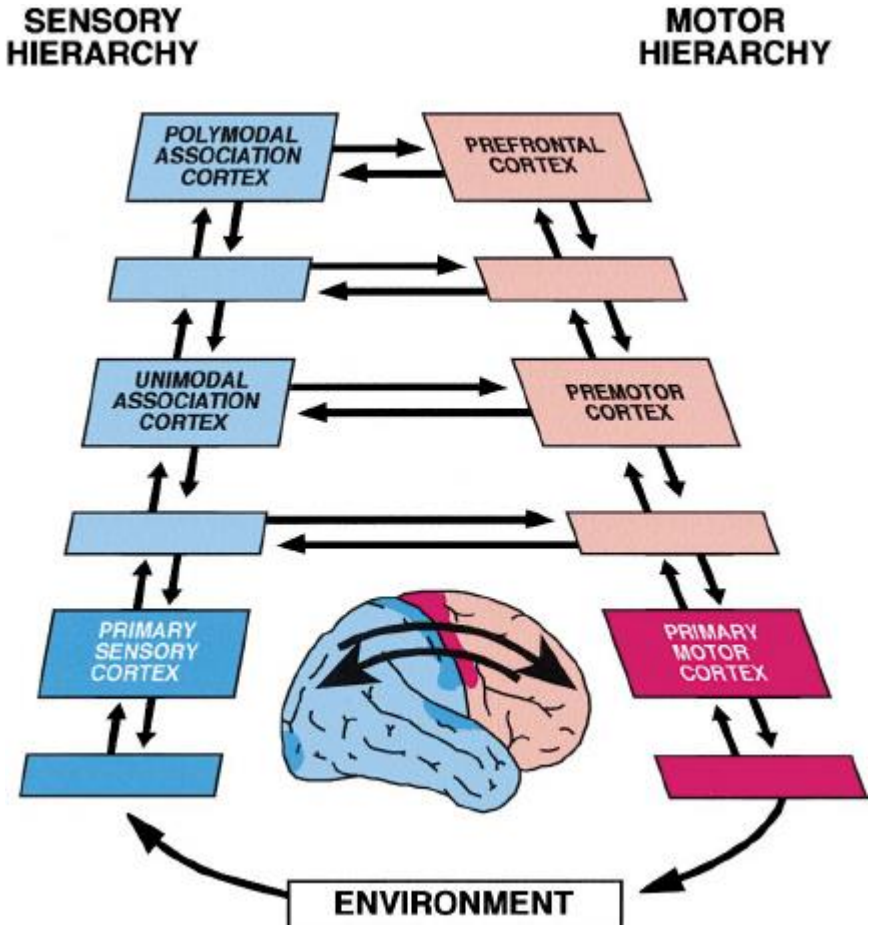
Level (4): Association cortex

- the **prefrontal cortex**
- the **posterior parietal cortex**
- disorders
  - apraxia
  - agnosia
  - aphasia



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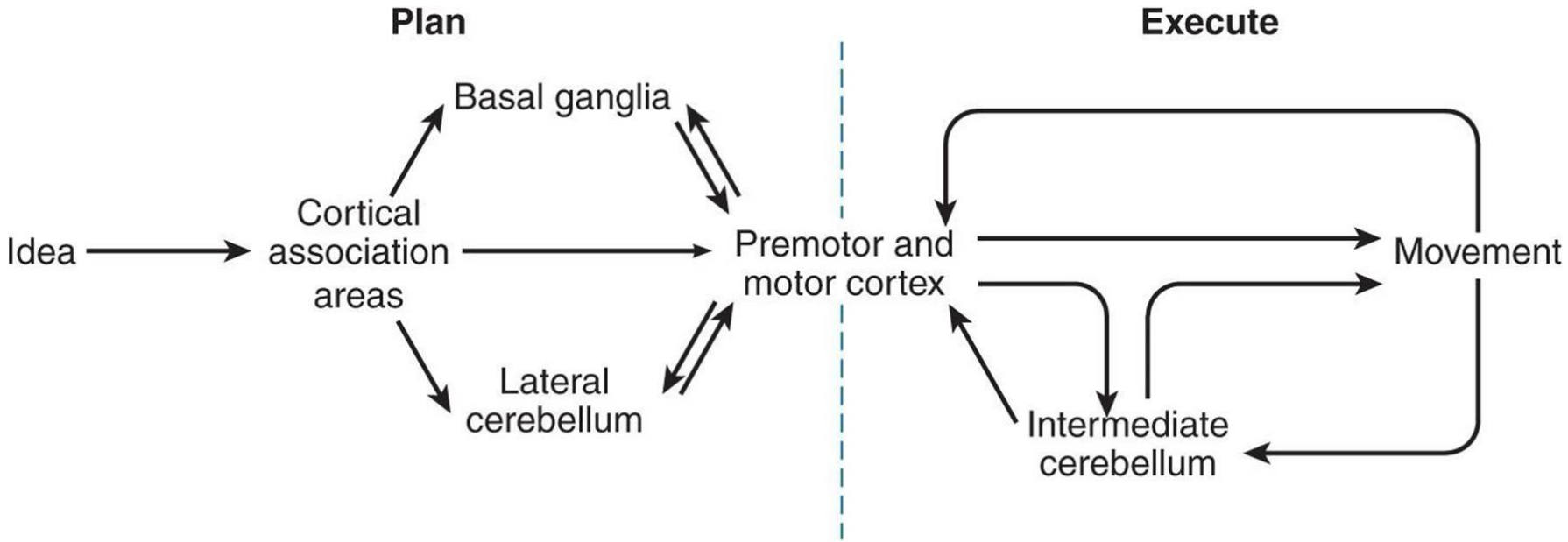
Levels (1-6): Control of voluntary movement



- Commands for voluntary movement originate in cortical association areas
- The cortex, basal ganglia, and cerebellum work cooperatively to plan movements
- Movement executed by the cortex is relayed via the corticospinal tracts and corticobulbar tracts to spinal motor neurons
- The cerebellum provides feedback to adjust and smooth movement

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Disorders of muscle tone and movement

- paralysis (UMND or LMND)
  - incl. spasticity or flaccidity
- basal ganglia and cerebellum disorders (i.e. extrapyramidal system)
  - incl. rigidity and abnormal movements
- abnormal electric activity of the brain
  - epilepsy
- disorders of neuromuscular junction
- skeletal muscle disorders
  - muscle atrophy
  - muscle dystrophy

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Palsy / paralysis

Upper and Lower moto neuron disease

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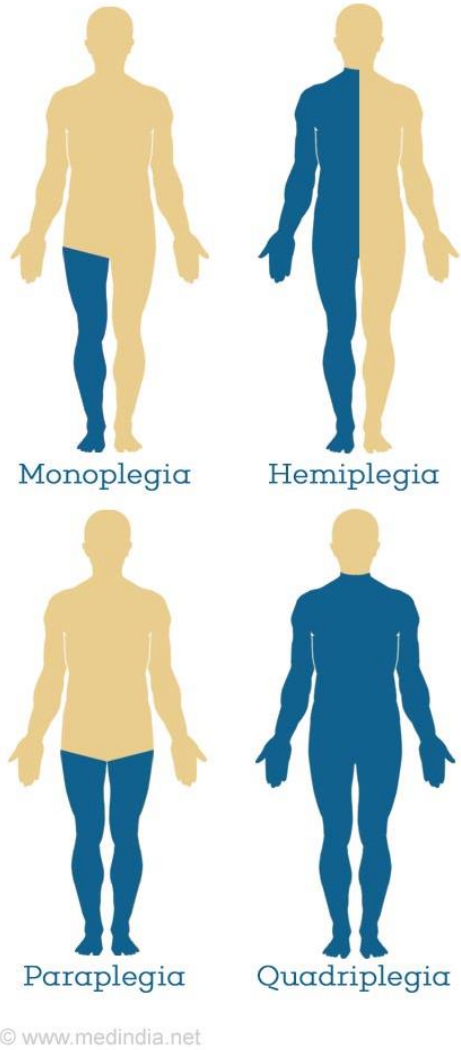
Paralysis (↓ voluntary muscle activity and weakness)

- loss of muscle function / weakness in part of your body due to **UMND** or **LMND** (= loss of the ability to move some or all of the body)
- degree/terminology
  - partial (some motor units) = **paresis**
  - complete (whole muscle) = **plegia**
- can be accompanied by a loss of feeling (sensory loss) in the affected area if there is sensory damage as well as motor
  - i.e. depending on aetiology
- paralysis always involves weakness And **changes of muscle tone**, which is different in UMN vs. LMN injury
  - **spastic paralysis** – lesion of UMNs (i.e. **central**) in the primary motor cortex, internal capsule, corticospinal and bulbar tracts)
    - ↑ muscle tone (**spasticity**)
      - loss of the control/inhibition of spinal stretch reflexes and gamma motoneurons
      - a **velocity-dependent increase in muscle tone** that manifests with resistance to movement
        - a clasp knife phenomenon
        - must be distinguished from rigidity! – extrapyramidal sign (a cog wheel phenomenon)
    - ↑ spinal reflexes (**hyperreflexia**) or even **clonus**
    - ↑ pathologic reflexes (= a deliberation phenomena) such as **Babinski**

  - **flaccid paralysis** – lesion of LMNs (i.e. **peripheral**) in the ventral spinal horns and ganglia of head nerves in brainstem)
    - ↓ muscle tone (**hypotonia**)
    - ↓ muscle mass (**atrophy**): muscle fibers deprived of necessary trophic factors
    - **fasciculations**: damaged LMN can produce spontaneous action potentials and muscle twitch
      - **fibrillations** with further degeneration of LMN – individual muscle fibres twitch
    - ↓ or no spinal reflexes (**hypofreflexia**)



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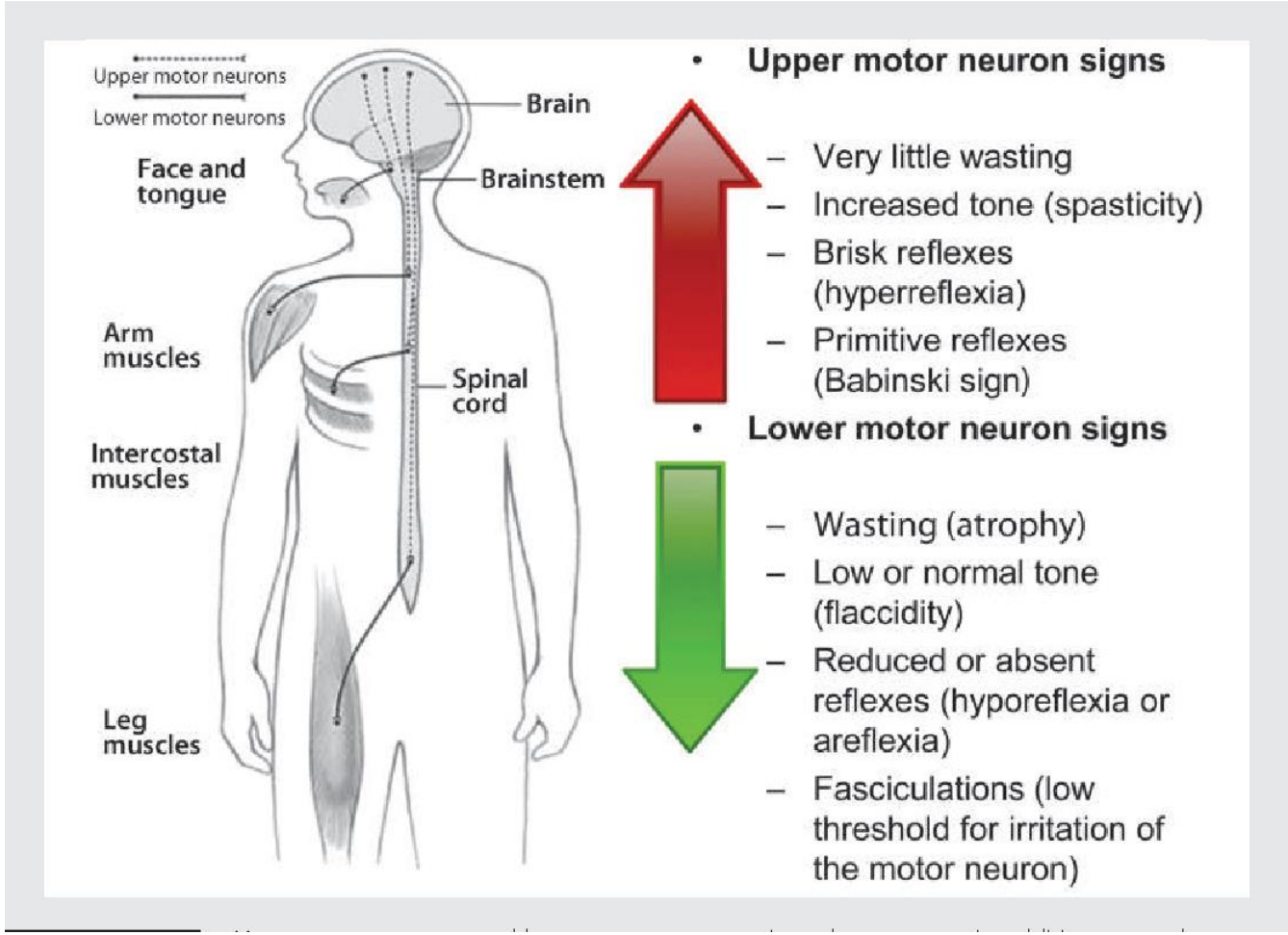
Etiology of paralysis

- UMND – spastic paralysis
  - generalised lesions of UMNs
    - amyotrophic lateral sclerosis
  - focal lesions of UMNs
    - ischemia
      - stroke
      - cerebral palsy
    - haemorrhage (stroke)
      - epidural or subdural
    - injury (head and spine)
    - central demyelinisation
      - multiple sclerosis
    - neuroinfection
    - brain tumours
- LMN – flaccid paralysis
  - spinal and peripheral nerve injury
  - ventral root lesions
    - hernia of the intervertebral disc, tumor, vertebral fracture, osteophyt, compression
  - spinal muscular atrophy
  - peripheral demyelinisation
    - Guillain Barre
  - infection
    - poliomyelitis (infantile paralysis)



Selected examples of paralyses due to UMND or LMND

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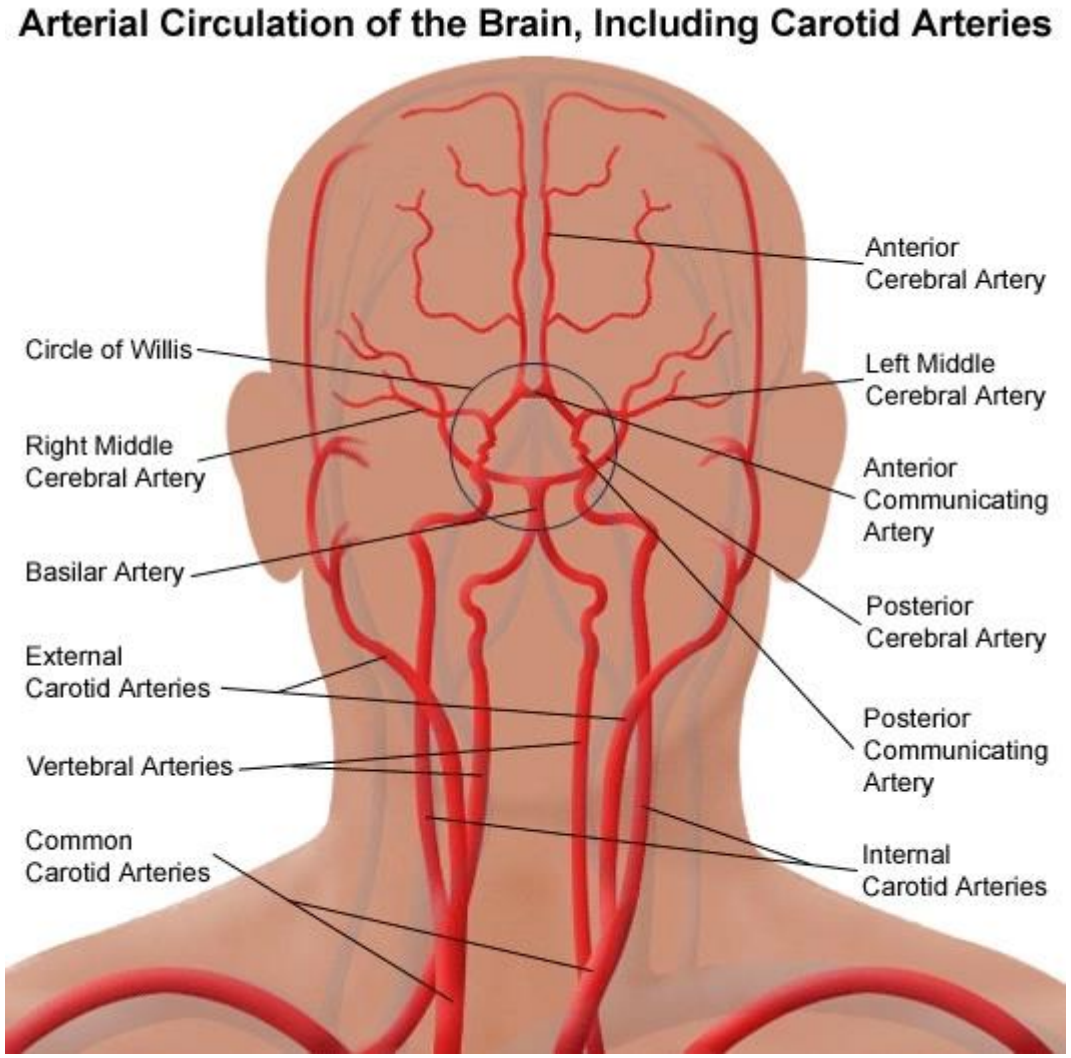
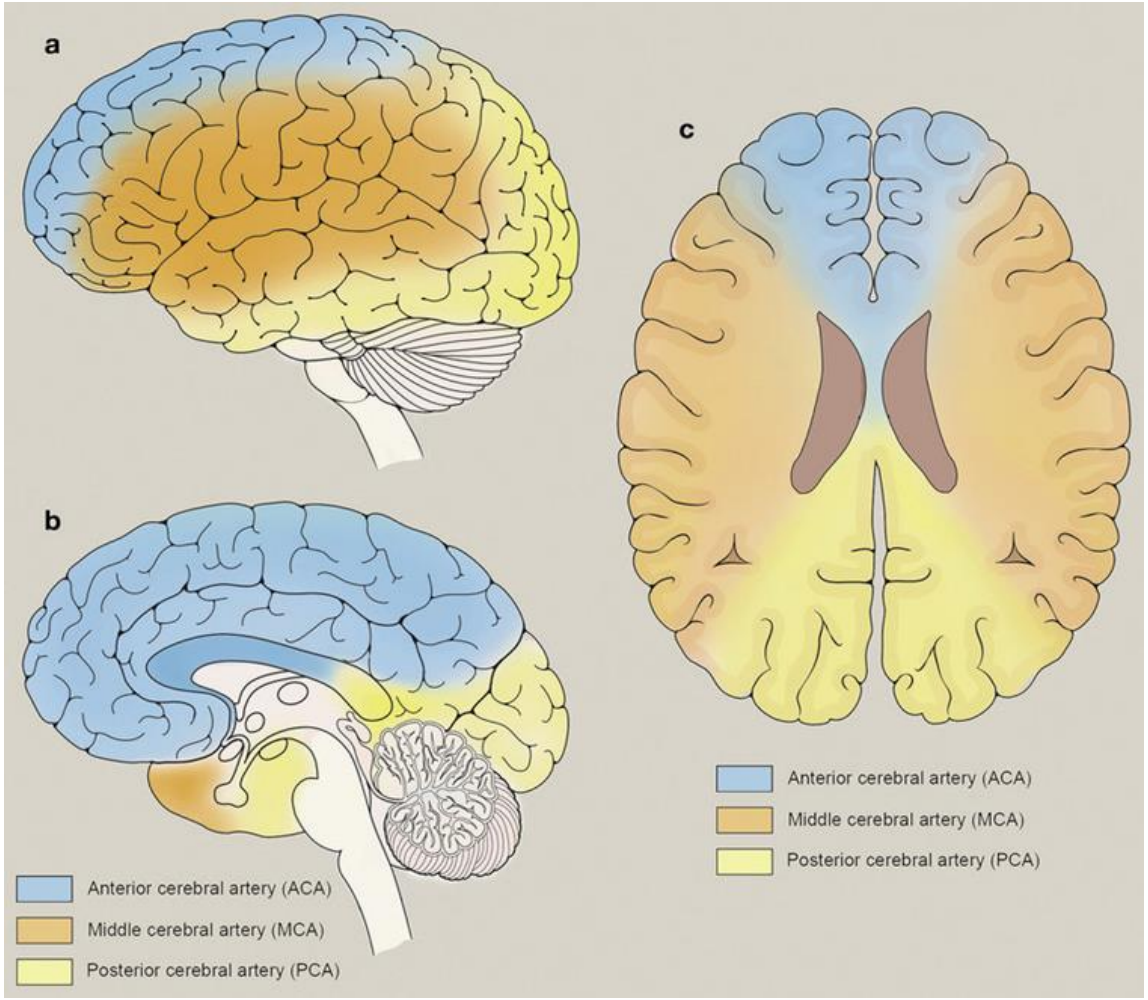
Example (1) - UMND: Stroke





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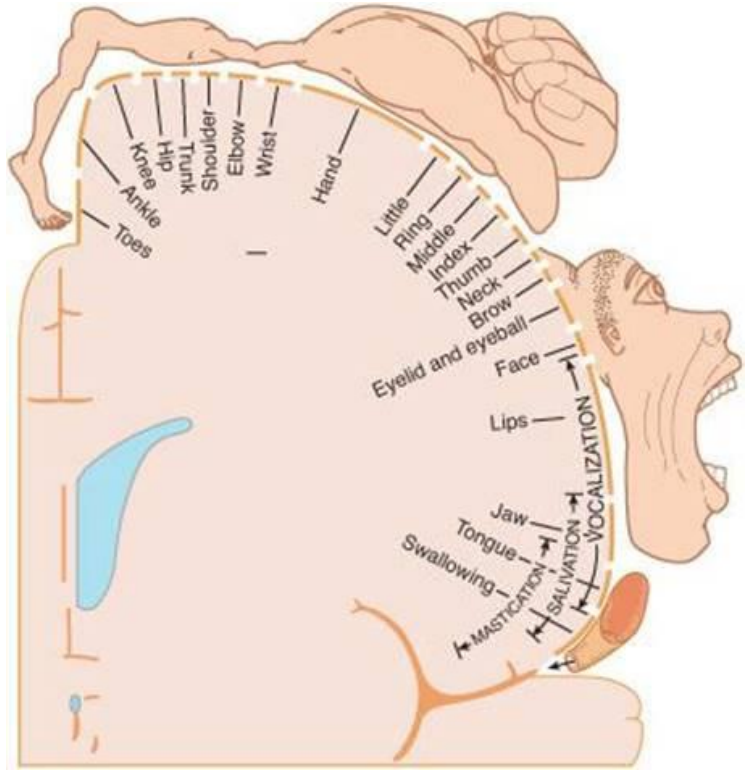
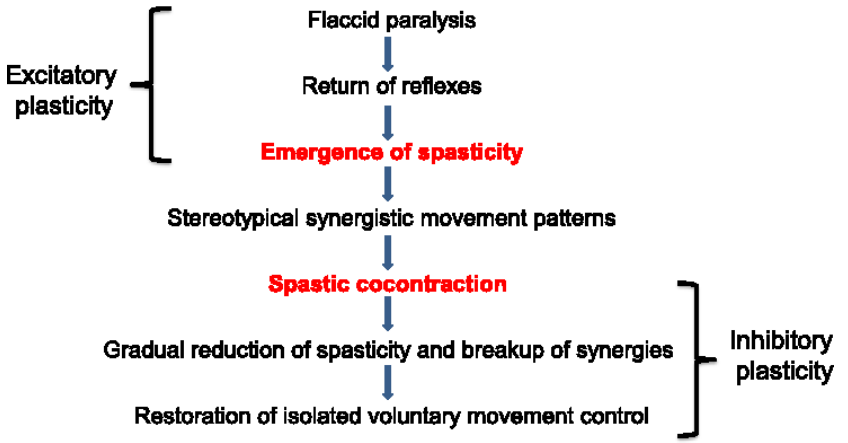
Example (1) - UMND: Stroke

- presentation of stroke syndrome depends on the side of the hemisphere affected!!!
  - see the motor homunculus to correlate with artery supply
- ACA infarction / stroke
  - motor deficits characteristically involving the lower extremity contralateral to the infarct site
- MCA infarction / stroke
  - the most common type (2/3 of cases) of cerebral vascular infarcts
  - MCA supplies the largest brain territory, infarcts are associated with many types of neurological deficits
  - MCA comprises
    - corticospinal tract, which is responsible for fine motor activity of the hands, a
    - corticoreticulospinal tract, which is involved in postural control and locomotor function, and therefore, motor weakness is one of the most disabling sequelae of a middle
- posterior circulation





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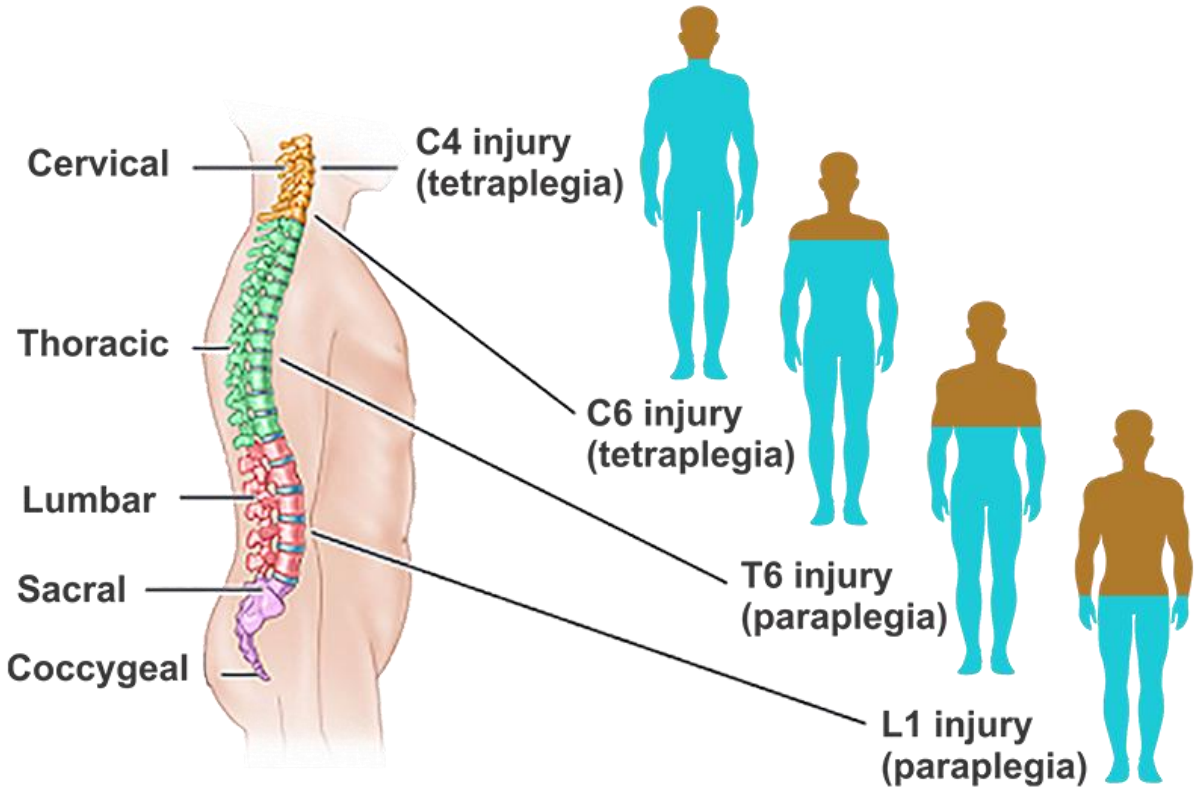
Example (2) - UMND: Spinal cord injury (SCI)

- leading causes are vehicle accidents, violence, and sports injuries
- the mean age of patients is ~33 years old
  - men outnumber women with a nearly 4:1 ratio
- approx. 52% of SCI cases result in quadriplegia and about 42% lead to paraplegia
- immediately after the injury there is a spinal shock (approx. 2 weeks)
  - depression of all the functions
  - subsequently reflex responses return and become hyperactive (knee jerk or withdrawal reflexes)
- below the lesion SCI affects
  - motor functions
  - spinal reflexes
  - afferent sensation
  - vegetative functions



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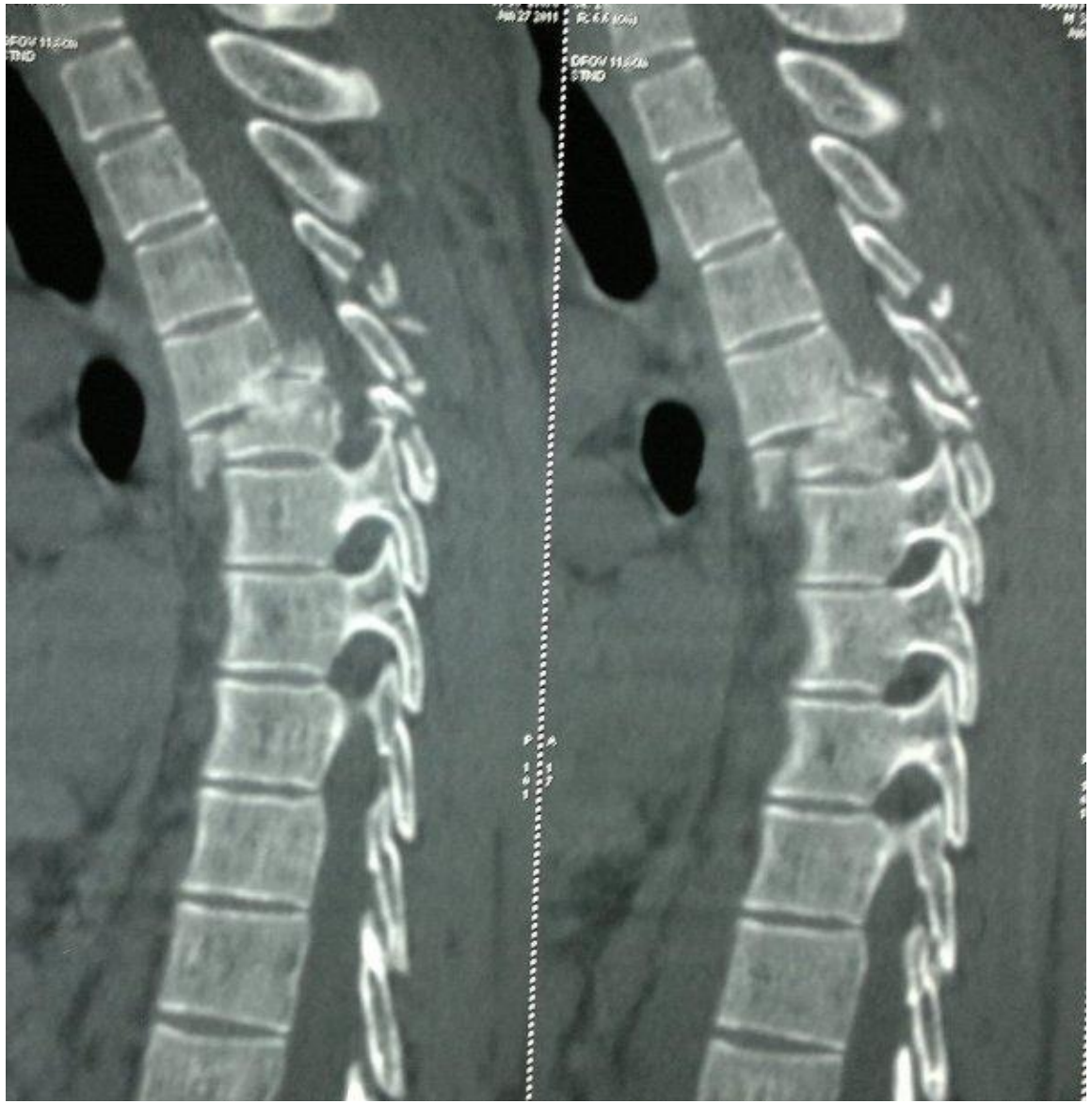
Example (2) - UMND: Spinal cord injury (SCI)



- (A) complete transversal lesion
  - immediately after injury – spinal shock
    - no muscle tension, no reflexes, no perception, blood pressure instability (neurogenic shock), loss of thermoregulation, loss of function over the rectum, urinary bladder and bowels
  - later spastic paralysis, hyperreflexia, loss of perception
    - C1 - C4 – acute respiratory failure
    - below C5 + upper Th
      - quadriplegia
      - loss of sensation
      - spontaneous ventilation (intact innervation of diaphragm)
      - complete loss of vegetative sympathetic function (hypotension)
      - loss of caudal parasympathetic function (defecation and urination reflexes)
    - lower Th, L and S
      - paraplegia
      - loss of sensation
      - loss of caudal parasympathetic function (defecation and urination reflexes)
  - normal ovary cycle and pregnancy possible (no pain during the labour though)
  - erection and ejaculation possible after tactile stimulation
- (B) lateral spinal hemisection (Brown-Sequard syndrome)
  - paralysis and loss of proprioception on the site of lesion
  - loss of pain and thermoreception on the contralateral site

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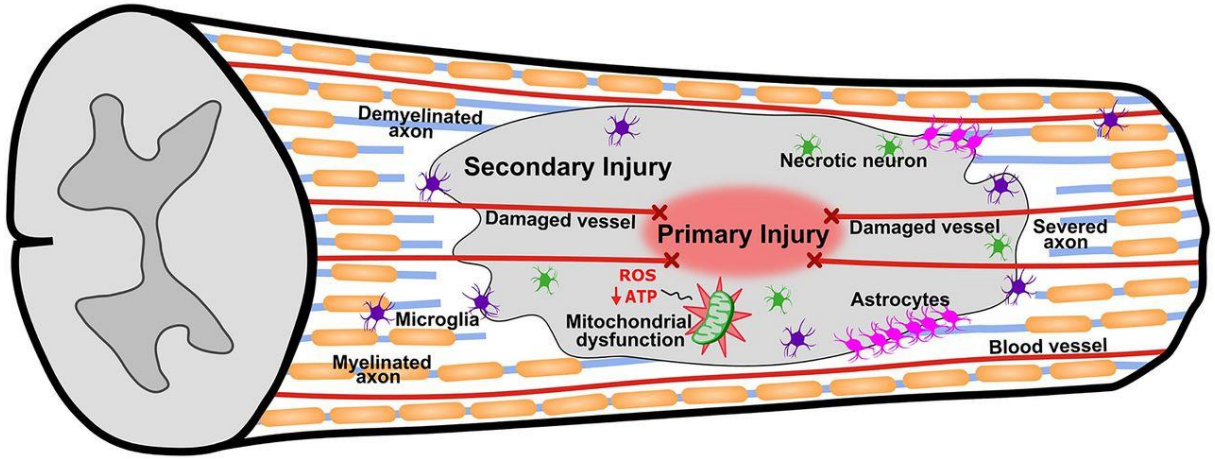
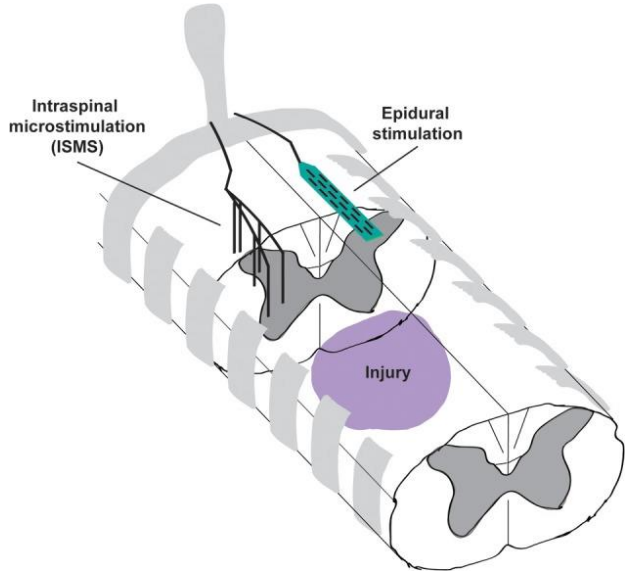
Current and future management of SCI

- SCI represents a great therapeutic management challenge
  - a negative nitrogen balance due to immobilization
  - body weight compresses the circulation causing decubitus ulcers to form
  - healing is poorly and prone to infection because of body protein depletion
  - Ca2+ is released in large amounts from skeleton and tissues leading to hypercalcemia, hypercalciuria, and formation of calcium stones in the urinary tract
  - combination of stones and bladder paralysis cause urinary stasis, which predisposes to urinary tract infection, the most common complication of SCI
- spinal cord regeneration?
  - administration of neurotrophins shows some promise in experimental animals
  - embryonic stem cells at the site of injury
  - electronic devices mimicking stimulation by UMN





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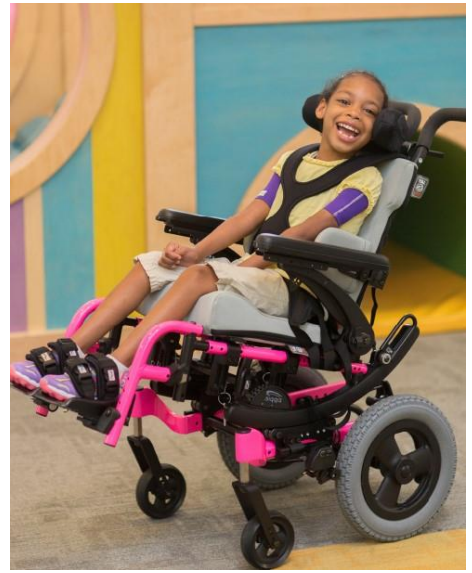
Example (3) - UMND: Cerebral palsy (CP)

- non-progressive neurological disorders that occur due to the exposure of the (developing) brain to hypoxia
  - before or during childbirth (70–80% of cases)
    - toxins, infections
    - pre-term deliveries
    - perinatal asphyxia
  - during early childhood
    - up to 3yrs of age
  - adulthood
    - cardiac arrest
    - hemorrhage
    - stroke
- symptoms of CP
  - motor symptoms
    - spasticity, ataxia, deficits in fine motor control, and abnormal gait (crouched or “scissored gait”)
  - sensory deficits
    - loss of vision and hearing as well as learning difficulties and seizures
- CP subtypes
  - spastic CP – classical UMND, typical and most prevalent
    - spasticity, hyperreflexia, clonus, and a positive Babinski sign
  - dyskinetic CP - due to damage of extrapyramidal motor areas (see further)
    - abnormal involuntary movements (chorea and athetosis)
  - mixed CP
  - hypotonic CP
    - truncal and extremity hypotonia, hyperreflexia, and persistent primitive reflexes



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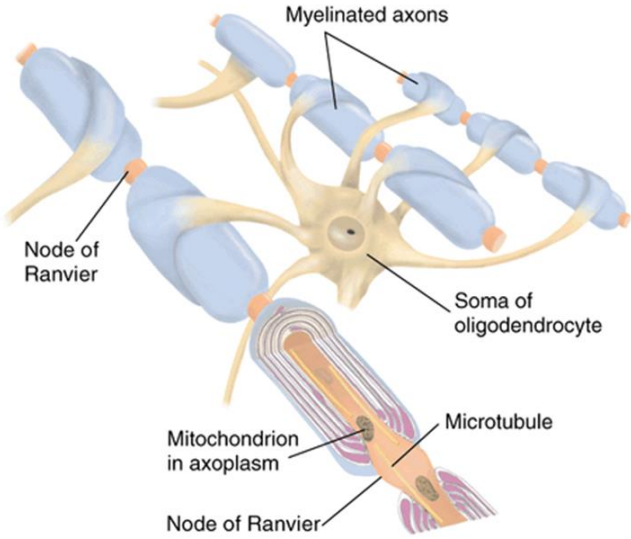
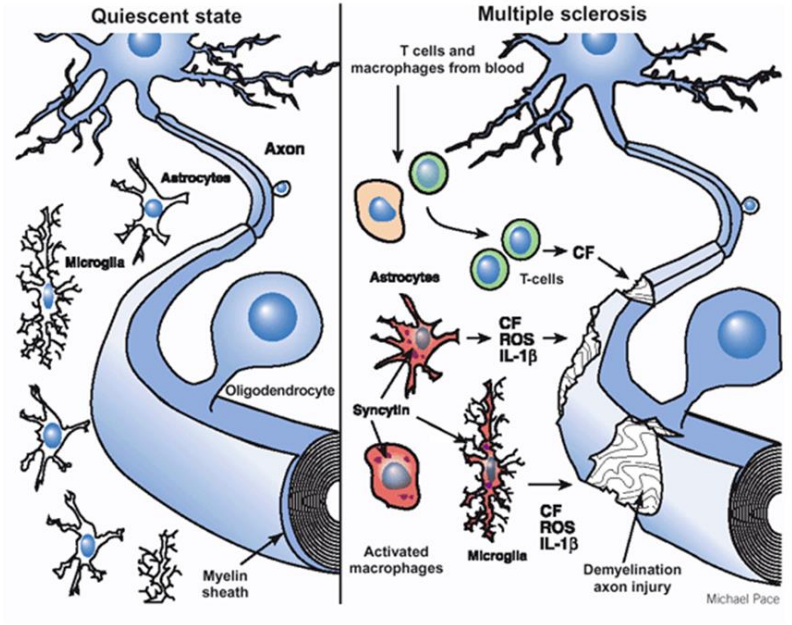
Example (4) - UMND: Demyelinisation - multiple sclerosis

- young adults (20 – 45), 2x more women, moderate regions of the Northern hemisphere
- etiology
  - genetic predisposition (MHC genes)
  - environmental triggers
    - infection, vitamin D, …
- pathogenesis
  - myelin produced by oligodendrocytes permits rapid conductance
  - loss of myelin results in conduction abnormalities (decreased velocity to block)
  - impaired BBB allows immune cells to enter the CNS
  - autoimmune injury (auto-agressive T-cell and macrophage mediated) of the oligodendrocytes (ODCs)
  - active destruction of ODCs and myelin results in the formation of sharp-edged demyelinated patches in CNS - **plaques**
  - initial inflammation follows in the formation of the scar (sclerosis)





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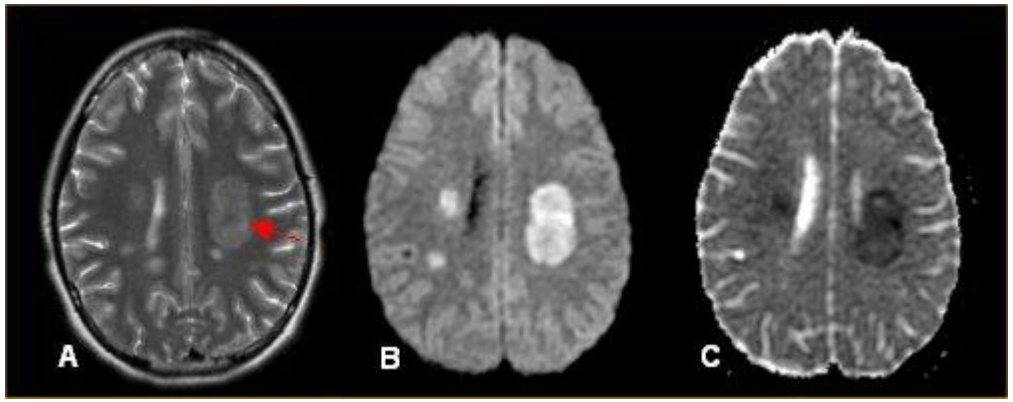
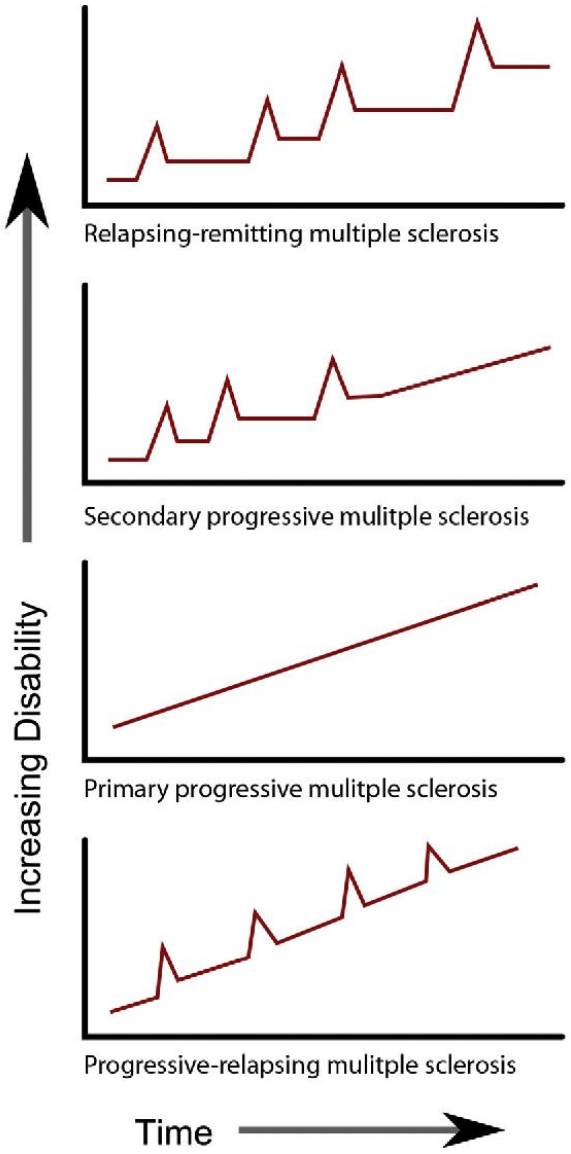
Example (4) - UMND: Demyelinisation - multiple sclerosis

- symptoms
  - predilection for optic nerve (vision impairment), periventricular white matter, brain stem (swallowing and speech), cerebellum (gait and coordination), corticospinal tract (muscle strength), spinothalamic tract (vibration sensation)
  - psychological manifestation (fatigue, mood swings, depression, euphoria, loss of memory) reflects involvement of the white matter of the cerebral cortex
  - periodical exacerbations and remission with subsequently less complete restoration of the neural function
- disease course
  - relapsing-remitting (85%)
  - secondary progressive
  - primary progressive



- **Guillain-Barre syndrome**
  - post-inflammation peripheral polyneuropathy due to demyelinisation (Schwan cells)



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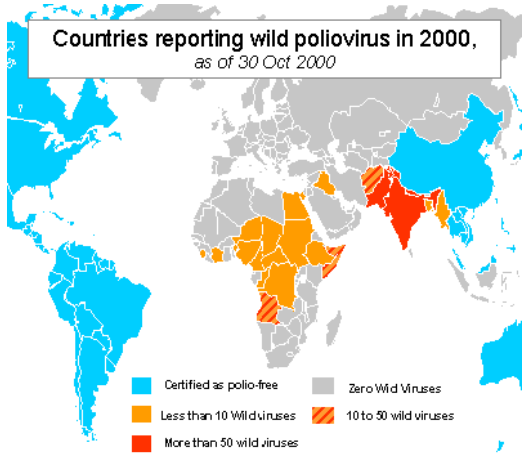
Example (5) - LMND: Polio and the beauty of vaccination



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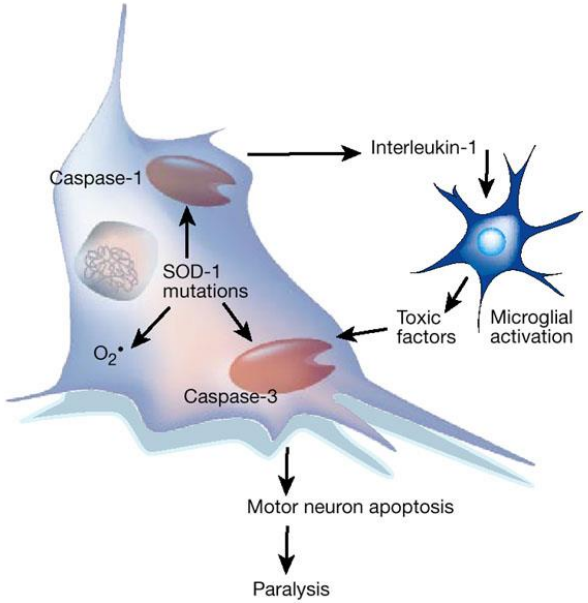
Example (6) – L+UMND: Amyotrophic Lateral Sclerosis

- synonym Lou Gehring disease
- fatal and incurable neurodegenerative disorder arising from a progressive loss of motoneurons in the spinal cord, brainstem and motor cortex
  - 1) LMNs of the ventral spinal horns
  - 2) motor nuclei of the brain stem
    - esp. n. hypoglossus
  - 3) UMNs of the motor cortex
- sensory, vegetative and some motor neurons (occulomotory) as well as intellect capacities are spared
- symptoms
  - early symptoms of ALS often include increasing muscle weakness, especially involving the arms and legs, speech, swallowing or breathing
  - later on, increasing impairment of moving, swallowing (dysphagia), and speaking or forming words (dysarthria)
- muscle weakening and paralysis irrevocably lead to cell death with 3-5 years following the appearance of the first symptoms
- onset typically between the ages of 40 and 70, more common in men than in women
- etiology
  - ~90% of ALS cases are sporadic
    - apparently at random with no clearly associated risk factors, negative family history of the disease
  - ~10% are familial
    - >100 distinct mutations in the ubiquitously expressed enzyme Cu/Zn superoxide dismutase (SOD1, chrom. 21) have been identified in approximately 20% of familial cases of ALS
- pathogenesis – just hypotheses
  - ROS toxicity – damage of axonal transport ?
  - exotoxicity – activation of glutamate-gated channels ?
  - autoimmunity ?



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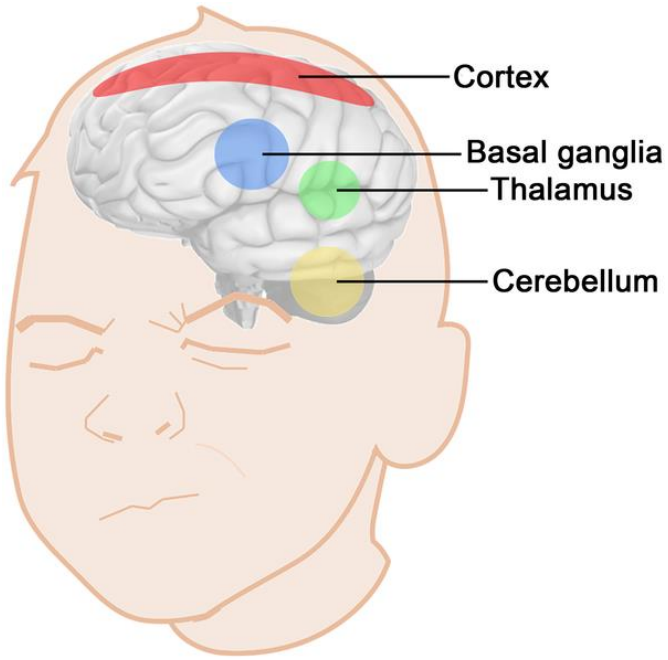

Extrapyramidal motor system

The two brain structures considered as “side loops” in the motor hierarchy:

- Level (5) basal ganglia
- Level (6) cerebellum

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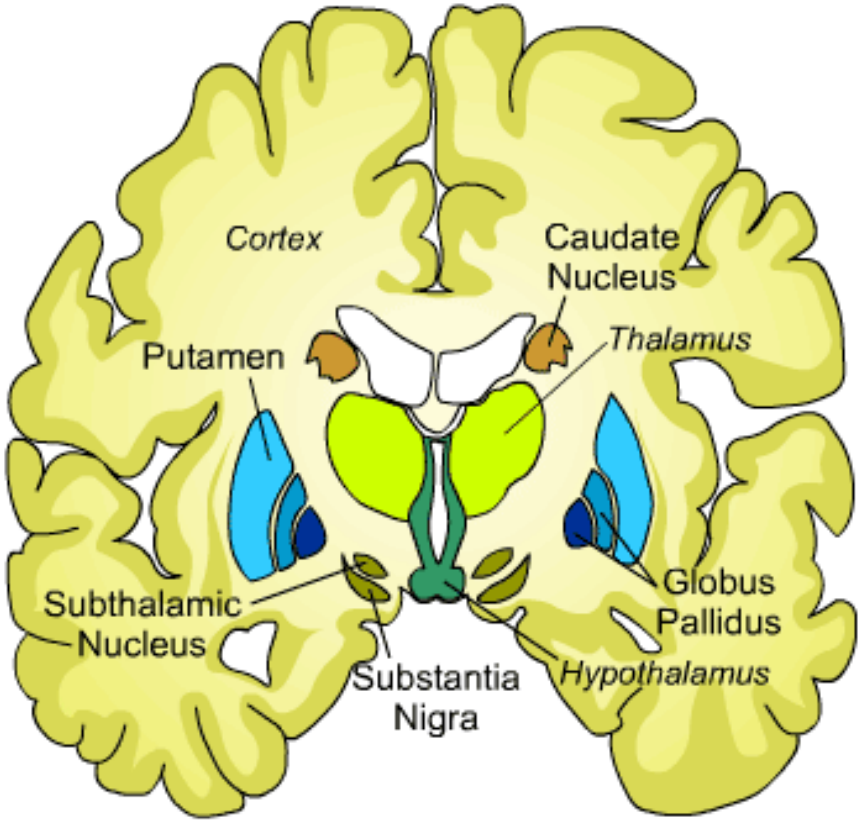
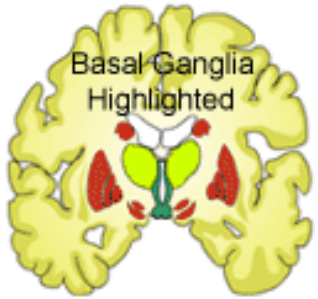
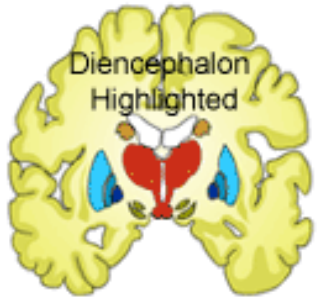
Level (5): basal ganglia







forebrain	telencephalon	**n. accumbens**
		caudate nucleus (striatum)
		putamen (striatum)
		globus pallidus (lentiform nucleus; devided to internal segments (GPe and GPi))
	diencephalon	**subthalamic nucleus**
midbrain	mesencephalon	**substantia nigra**

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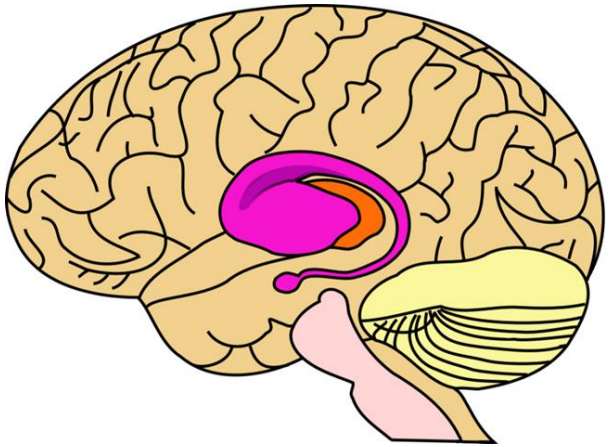
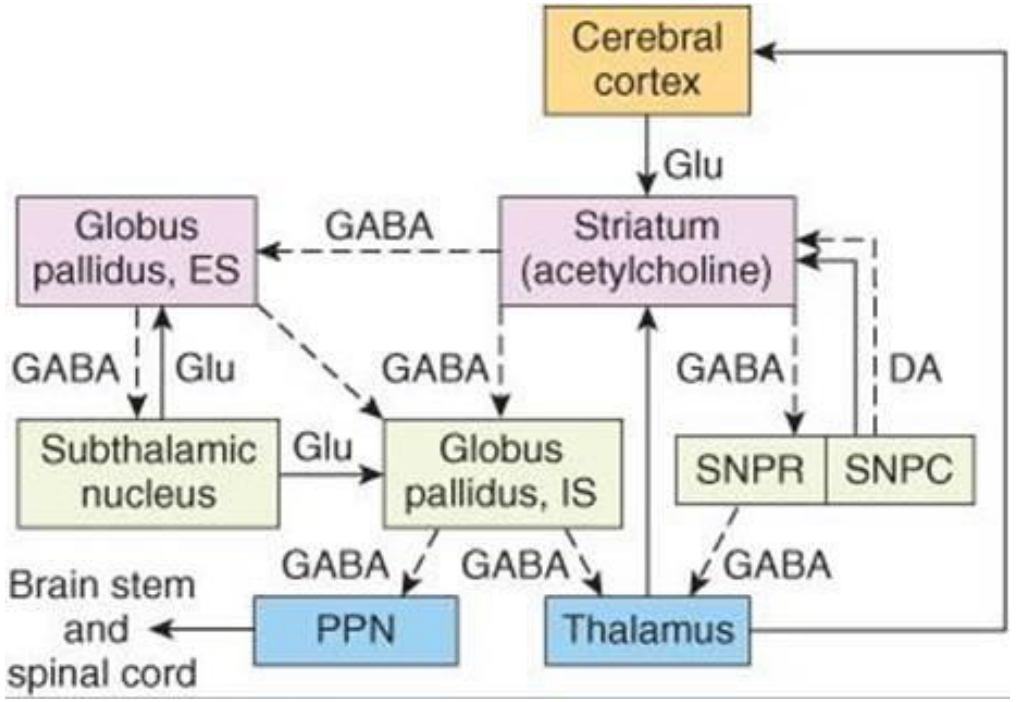
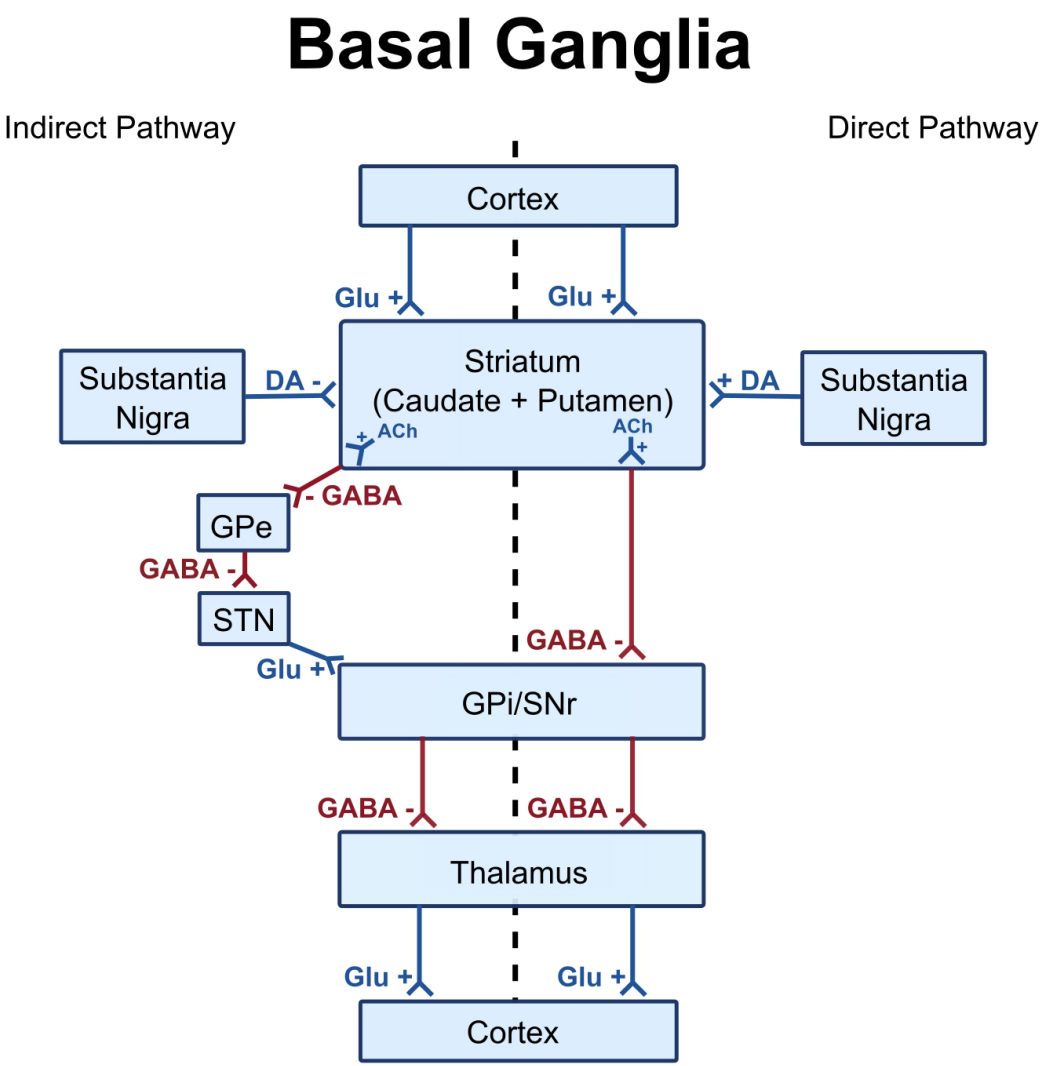
Basal ganglia – connections



- There are two main inputs to the BG (both excitatory - glutamate) terminating in the striatum
  - from a wide region of the cerebral cortex (**corticostriate pathway**)
  - from intralaminar nuclei of the thalamus (**thalamostriatal pathway**)
- The two major outputs of the BG (both are inhibitory GABAergic) projecting to the thalamus
  - from GPi
    - to a number of thalamic structures by way of two fiber tracts: the **ansa lenticularis** and the **lenticular fasciculus**
  - from substantia nigra pars reticulate
    - to the **superior colliculus**, which is involved in eye movements, as well as to the VA/VL thalamic nuclei
- The connections within the BG include
    - more detail explanation of the balance between the BG pathays on the next slide
  - a dopaminergic **nigrostriatal projection** from the substantia nigra pars compacta to the striatum
  - GABAergic projection from the striatum to substantia nigra pars reticulate
  - inhibitory projection from the striatum to both GPe and Gpi
  - the subthalamic nucleus receives an inhibitory input from GPe, and in turn the subthalamic nucleus has an excitatory (glutamate) projection to both GPe and GPi



Two pathways process signals in the basal ganglia

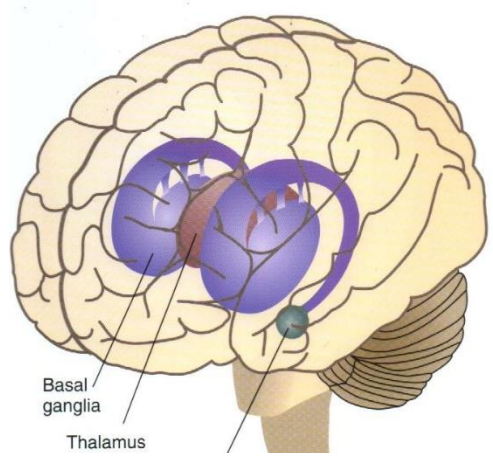


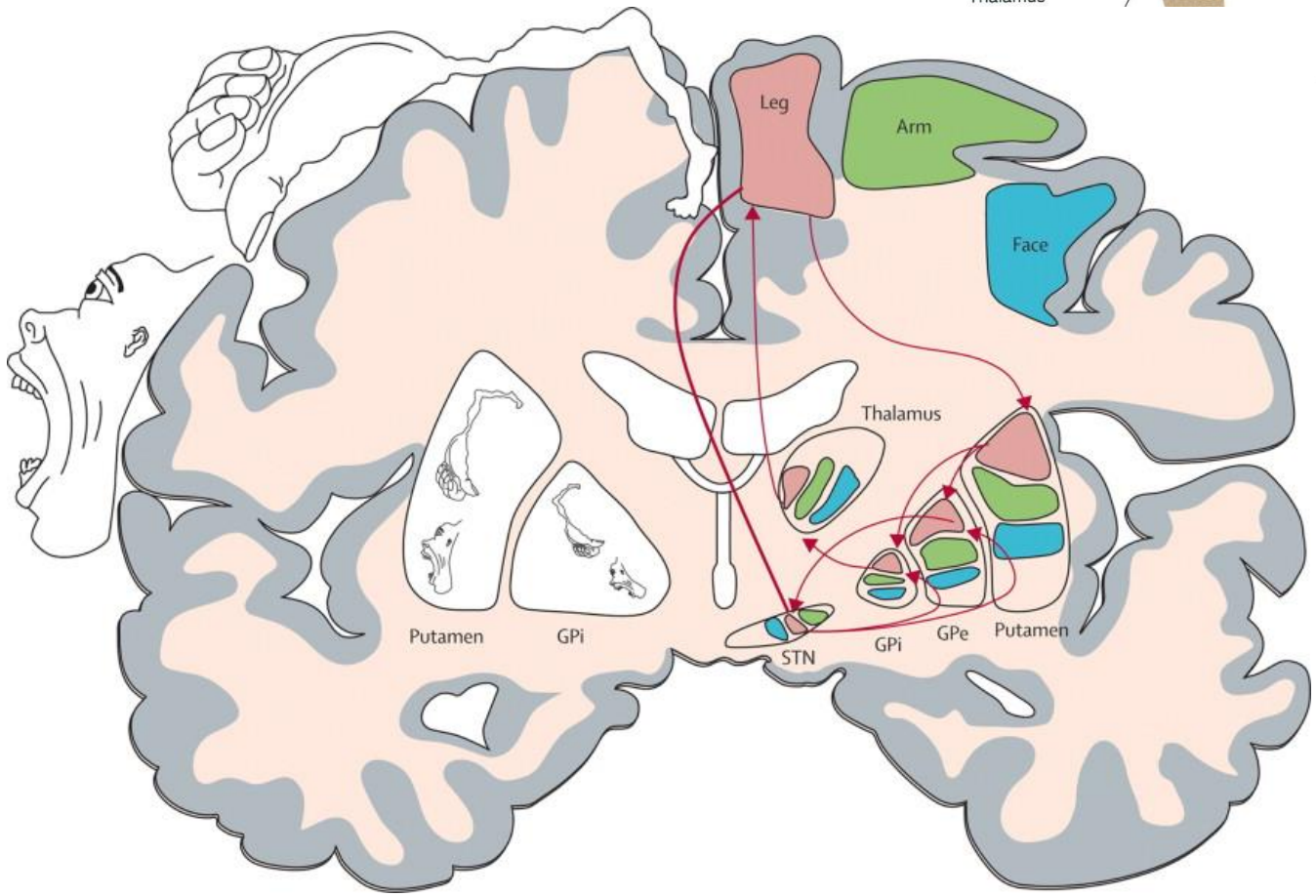
- These two pathways have opposite net effects on thalamic target structures
  - the normal functioning of the basal ganglia apparently involves a proper balance between the activity of these two pathways
- the direct pathway
  - the net effect is the cortex exciting (positive feedback loop)
  - direct pathway striatal neurons have D1 dopamine receptors, which depolarize the cell in response to dopamine
- the indirect pathway
  - the net effect is to inhibit the cortex (negative feedback loop)
  - indirect pathway striatal neurons have D2 dopamine receptors, which hyperpolarize the cell in response to dopamine
- **nigrostriatal projection** from the substantia nigra pars compacta to the striatum is an important pathway in the modulation of the direct and indirect pathways via **dopamine**
  - it amplifies the effect of direct and deepens the inhibition of indirect pathway on cortex
  - see Parkinson´s disease as an example/confirmation

Moises Dominguez

Basal ganglia – function

- (A) motor functions
  - voluntary movements are not initiated in the BG (they are initiated in the cortex); however, proper functioning of the BG appears to be necessary in order for the motor cortex to relay the appropriate motor commands to the lower levels of the hierarchy
    - control of cortical activity
      - selection form learned and stereotypical movements (motor programmes)
    - movement coordination, precision and balance
  - influence and modulate the activity of motor cortex and the descending motor pathways in ways that cause distinct symptoms when different BG structures are damaged
    - disorders of BG comprise motor disturbances, not paralysis
      - tremor
      - involuntary movements
      - changes of muscle tone
      - slowness/too high rapidity of movement
  - BG are connected with cortical structures as well as with afferent system (from thalamus) and between each other
    - see further
  - somatotopic organisation similar to motor cortex
- (B) cognitive functions
  - there are a number of cortical loops through the BG that involve prefrontal association cortex and limbic cortex
  - BG are involved in selecting and enabling various cognitive, executive, or emotional programs that are stored in these other cortical areas
  - BG appear to be involved in certain types of learning





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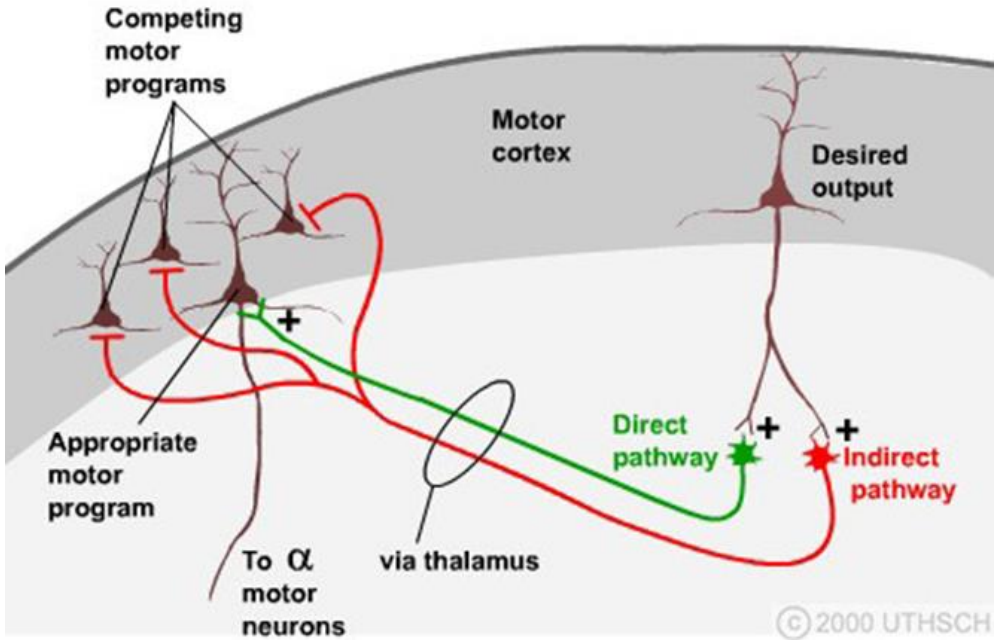
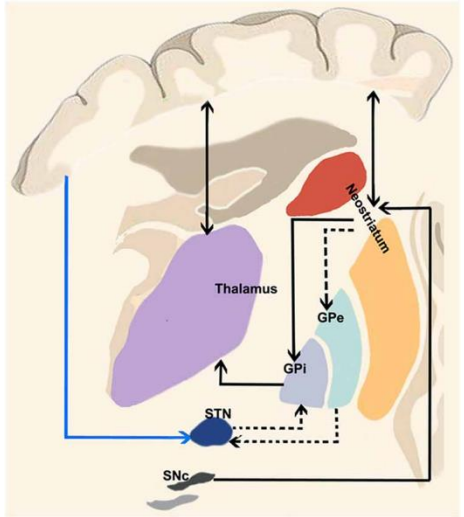
BG select/modulate motor programs stored in the motor cortex

- The basal ganglia and motor cortex form a processing loop whereby the basal ganglia enables the proper motor program stored in motor cortex circuits via the direct pathway and inhibits competing motor programs via the indirect pathway
- The proper motor programs are selected based on the desired motor output relayed from cortex
- BG may have a major role in learning what motor acts result in rewards for the organism
  - enhance the firing of cortical motor programs that produce rewarding outcomes
  - connections with the limbic system and other structures





Extrapyramidal syndromes

- (1) hypokinetic
  - hyperfunction of the BG inhibitory loop (inhibition of cortical function)
    - slow beginning of the movement
    - reduced range and force
    - resting tremor
    - muscle rigidity ("cog-wheel" phenomenon)
      - resistance to passive movement of the limb
  - Parkinson disease
- (2) dyskinetic
  - excessive, involuntary motor activity due to the reduced BG inhibitory loop
    - chorea
    - athetosis
    - ballism
    - dystonia
    - tardive dyskinesia (drug induced)
  - Huntington disease
  - Wilson disease
    - degeneration of the putamen, a part of the **lenticular nucleus**
    - motor disturbances include "wing-beating" tremor or **asterixis, dysarthria,** unsteady gait, and rigidity
  - hemiballism

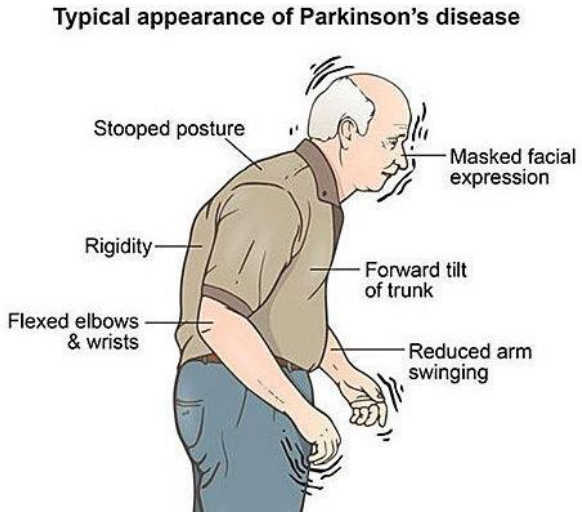
Table 20.15
Changes in the major neurotransmitter profile in Parkinson's and Huntington's diseases

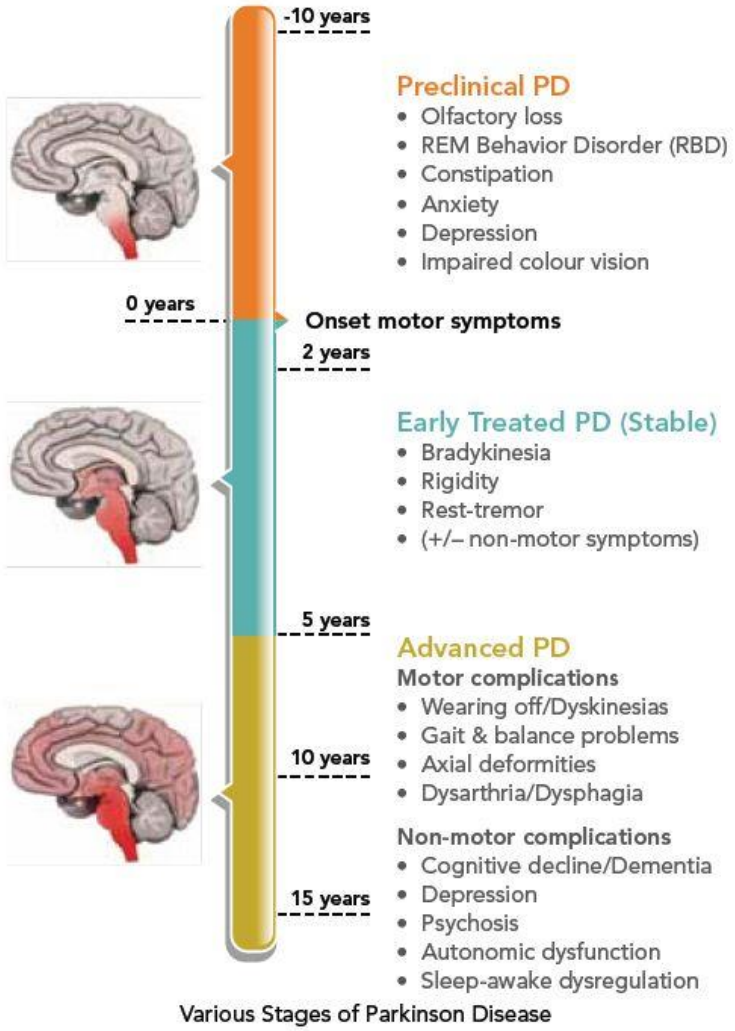
Condition	Site	Neurotransmitter
Parkinson's disease	Putamen	Dopamine ↓ 90% Norepinephrine (noradrenaline) ↓ 60% 5-HT ↓ 60%
	Substantia nigra	Dopamine ↓ 90% GAD + GABA ↓↓
	Cerebral cortex	GAD + GABA ↓↓
Huntington's disease	Corpus striatum	Acetylcholine ↓↓ GABA ↓↓ Dopamine: normal GAD + GABA ↓↓

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

Parkinson´s disease (dysfunction of the „direct pathway“)

- degenerative condition due to the lost of cells producing dopamine (SNr)
  - progressive destruction of the nigrostriatal pathway with subsequent reduction of the dopamine in striatum
  - because the nigrostriatal pathway excites the direct pathway and inhibits the indirect pathway, the loss of this input tips the balance in favour of activity in the indirect pathway
    - GPint neurons are abnormally active, keeping the thalamic neurons inhibited
    - without the thalamic input, the motor cortex neurons are not as excited, and therefore the motor system is less able to execute the motor plans in response to the patient's volition
- usually occurs over the age of 50
- characterized by slowness or absence of movement (bradykinesia or akinesia), rigidity, and a resting tremor (especially in the hands and fingers)
- etiology
  - idiopathic – degeneration of the substantia nigra
    - autooxidation of catecholamines during melanin synthesis?
  - cerebral vascular disease
  - toxic (e.g. CO poisoning)
  - early-onset – genetic
    - mutations in the α-synuclein and parkin gene
- symptoms
  - tremor
  - rigidity
  - bradykinesia (slow movements)
  - loss of postural reflexes
  - speech and swallowing problems
  - loss of facial mimics
  - dementia (late in 20% patients)
  - vegetative dysbalances





Various Stages of Parkinson Disease

- treatment – restoration of the dopaminergic system
  - L-DOPA + other drugs prolonging the dopamine half live (cathechol-O-methyltransferase (COMT) inhibitors)
  - deep brain stimulation

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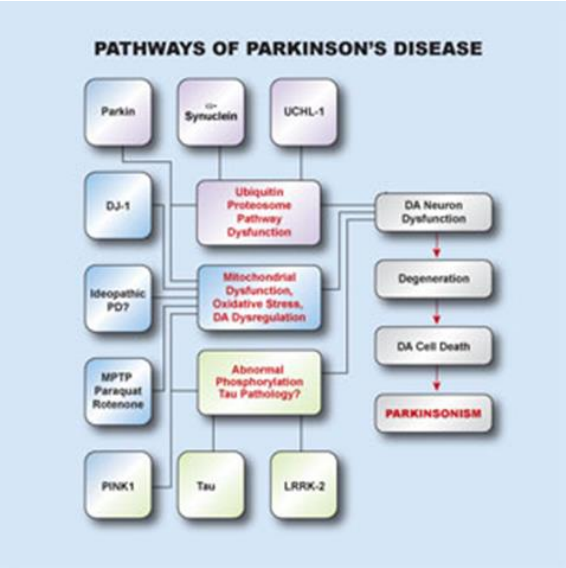
Etiopatogeneze PD

- familial forms – implicated genes indicate likely etiopathogenesis
  - (1) impaired intracellular protein homeostasis
    - dysfunction of ubiquitin-proteasome system
      - PINK-1 (parkin) = ubiquitin E3 ligase
    - misfolding of proteins and their aggregation (α-synuclein $\rightarrow$ Lewy bodies)
  - (2) mitochondrial dysfunction (LRRK2)
    - defect of complex 1
      - experimentally by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
    - oxidative stress (DJ-1 – antioxidant enzyme)
  - (4) role of dopamin metabolis
    - formation of ROS
  - (5) others
    - iron homeostasis
    - Ca metabolism

LOCUS	CHROMOSOME LOCATION	GENE	INHERITANCE PATTERN
PARK1/PARK4	4q21-q23	*alpha-synuclein*	AD
PARK2	**6q25.2-q27**	***parkin***	**AR**
PARK3	2p13	unknown	AD
PARK5	**4p14**	**UCH-L1**	**AD**
PARK6	1p35-p36	PINK1	AR
PARK7	1p36	DJ-1	AR
PARK8	12p11.2-q13.1	LRRK2	AD
PARK10	1p32	unknown	unclear
PARK11	2q36-2q37	GIGYF2	unclear
unknown	5q23.1-q23.3	*Synphilin*-1	AD
unknown	2q22-q23	NR4A2	AD



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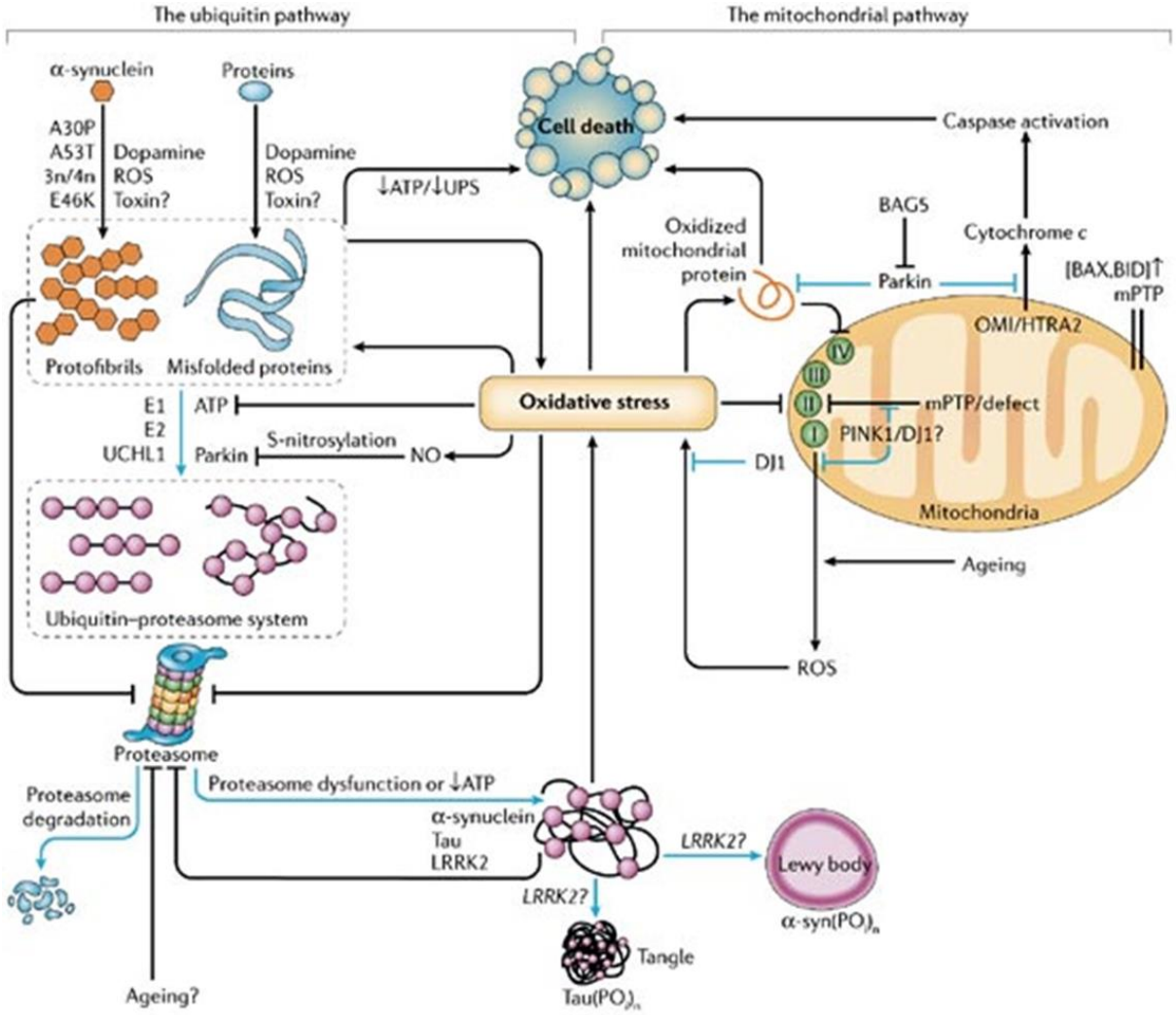
Neurodegeneration pathways in Parkinson's disease



- The discovery of Mendelian inherited genes has enhanced our understanding of the pathways that mediate neurodegeneration in Parkinson's disease.
- One main pathway of cell toxicity arises through a-synuclein, protein misfolding and aggregation.
  - These proteins are ubiquitinated and initially degraded by the ubiquitin–proteasome system (UPS), in which parkin has a crucial role. However, there is accumulation and failure of clearance by the UPS over time, which leads to the formation of fibrillar aggregates and Lewy bodies. Synuclein protofibrils can also be directly toxic, leading to the formation of oxidative stress that can further impair the UPS by reducing ATP levels, inhibiting the proteasome, and by oxidatively modifying parkin. This leads to accelerated accumulation of aggregates. Phosphorylation of a-synuclein-containing or tau-containing aggregates might have a role in their pathogenicity and formation, but it is not known whether leucine-rich repeat kinase 2 (LRRK2) mediates this.
- Another main pathway is the mitochondrial pathway.
  - There is accumulating evidence for impaired oxidative phosphorylation and decreased complex I activity in Parkinson's disease, which leads to reactive oxygen species (ROS) formation and oxidative stress. In parallel, there is loss of the mitochondrial membrane potential. This leads to opening of the mitochondrial permeability transition pore (mPTP), release of cytochrome c from the intermembrane space to the cytosol, and activation of mitochondrial-dependent apoptosis resulting in caspase activation and cell death. There is evidence that recessive-inherited genes, such as phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1), Parkinson's disease (autosomal recessive, early onset) 7 (DJ1) and HtrA serine peptidase 2 (HTRA2, also known as OMI), might all have neuroprotective effects against the development of mitochondrial dysfunction, although the exact site of their action remains unknown. Parkin has also been shown to inhibit the release of cytochrome c following ceramide-induced stress, and is itself modified by the interacting protein BCL2-associated athanogene 5 (BAG5).
- Dysfunction of both pathways leads to oxidative stress, which causes further dysfunction of these pathways by feedback and feedforward mechanisms, ultimately leading to irreversible cellular damage and death.
  - I–IV, mitochondial electron transport chain complexes I–IV; -syn$(PO_4)_n$, phospho--synuclein; A30P, alanine to proline substitution at -synuclein amino acid residue 30; A53T, alanine to threonine subsitution at -synuclein residue 53; E_1, ubiquitin activating enzyme; E_2, ubiquitin conjugating enzyme; E46K, glutamic acid to lysine substitution at -synuclein residue 46; NO, nitric oxide; 3n/4n, 3 or 4 copies of a-synuclein; Tau$(PO_i)_n$,Tau $(PO_i)_n$, phospho-Tau; UCHL1, ubiquitin carboxyl-terminal esterase L1.

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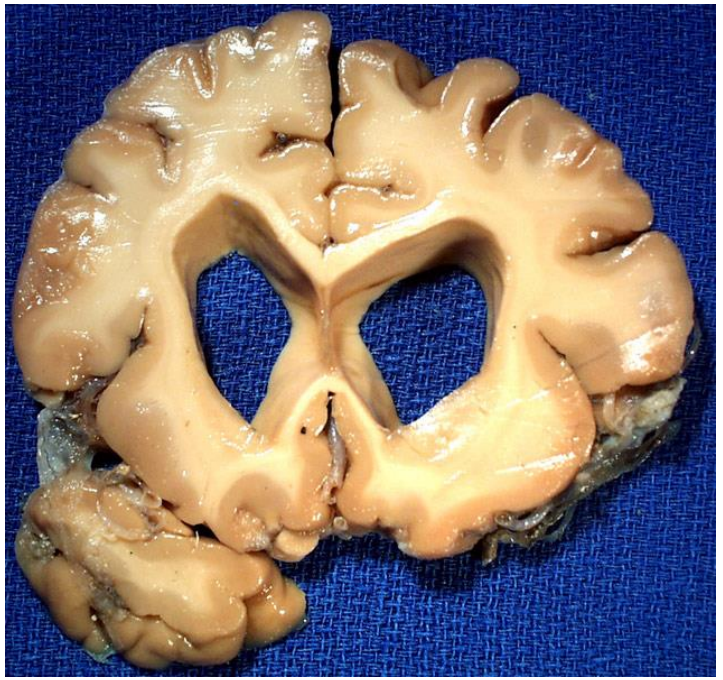
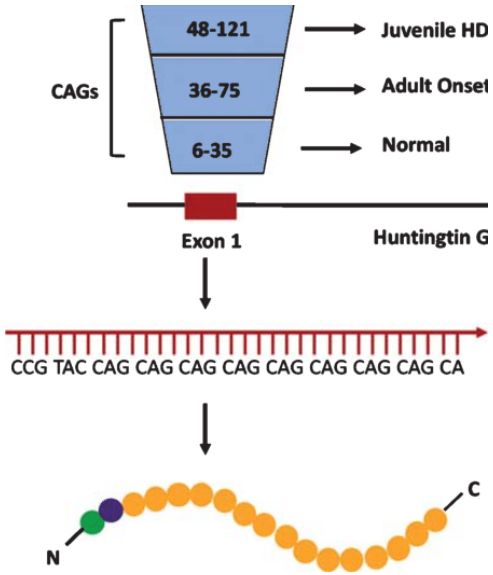
Huntington's disease (chorea)

- prevalence 4-10/100 000 in Caucasoid population
- manifestation
  - onset of symptoms typically between 35 – 50 yrs of age, but it depends on genetics
  - dead after 15 - 20 let from diagnosis (~12% commit suicide)
- progressive neurodegeneration due to a **loss of (GABA-ergic) neurons of striatum** and then in **cortex**
  - GPe de-inhibited and leads to dyskinesia symptoms/movements - chorea
- etiopathogenesis
  - genetics - expansion of CAG (= glutamine) trinucleotide repetition in exon 1 (in total67 exons) of the genu encoding huntingtin (ch. 4p16.3)
    - htt is 350kDa protein encoded by gene with normal number of CAG repetitions 6 - 35
    - in HD there are 36 – 121 repetitions
      - late manifestation when CAG <60
      - early manifestation CAG >60
      - but in subjects with 36-40 repetitions < 100% penetrance !!
    - the number of repetitions increases with generations in paternal transmission **– phenomenon of anticipation**
  - misfolded htt is contained in inclusion bodies, mutant htt negatively affects critical gene expression and thus function of striatum and cortes
- symptoms
  - early – clumsiness, loss of balance, involuntary movements, lack of concentration, depression, irritability
  - late – chorea, dyskinesia, dysarthria, cognitive impairment to dementia
  - DEA
- MORPHOLOGICALLY a generalised brain atrophy (by 25-30%)





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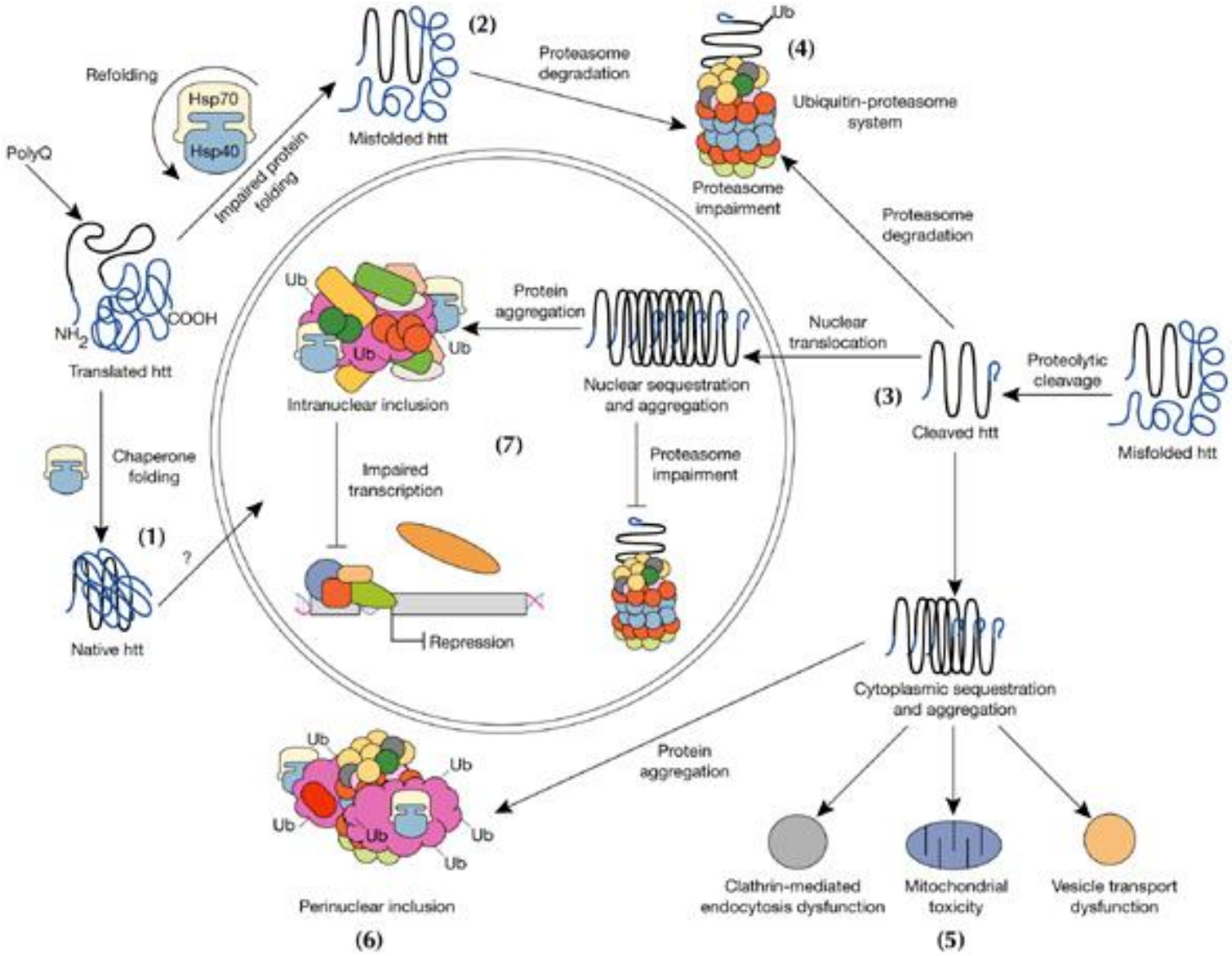
HD - huntingtin



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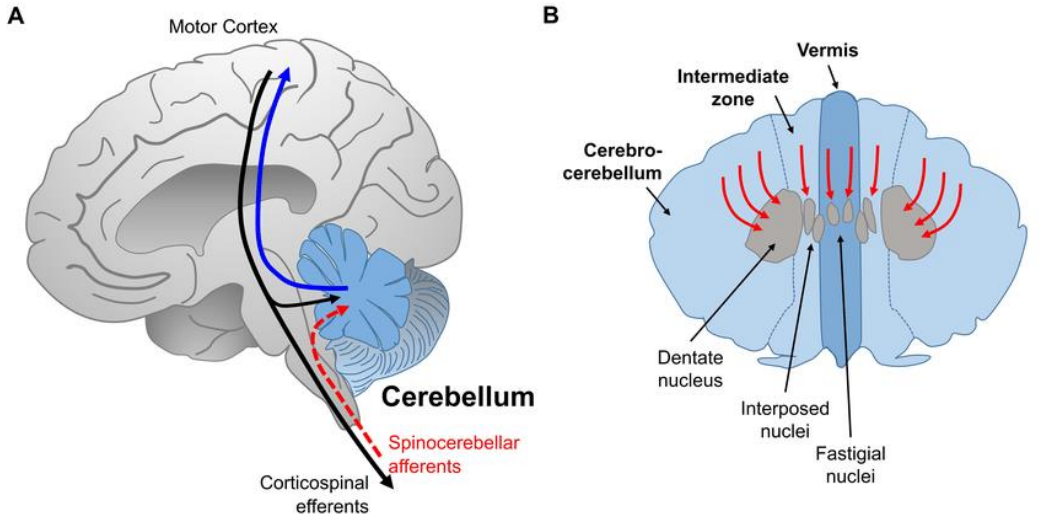
Level (6): cerebellum

- although the cerebellum accounts for approximately 10% of the brain's volume
  - it contains over 50% of the total number of neurons in the brain!!!
  - its surface area is about 75% of that of the cerebral cortex
- does not initiate motor activity, rather, the cerebellum modifies the motor commands of the descending pathways to make movements more adaptive and accurate
- major functions
  - maintenance of balance and posture
    - subsequent balance disorders require postural strategies to compensate for this problem (e.g., a wide-based stance)
  - coordination of voluntary movements
  - motor learning
  - cognitive functions
- damage to cerebellum produces movement disorders not associated with the visual control (persist with closed eyes)
  - vestibulocerebellar disorders
    - fixation of gaze when moving a head
  - cerebellar ataxia
    - gait
    - adiadochokinesis
    - dysmetria
  - cerebellar tremor

- Friedrich ataxia
  - FA (similar to HD) is one of an increasing number of human genetic diseases affecting the nervous system that are characterized by **trinucleotide repeat** expansion
    - all in exons with exception of Friedrich ataxia
    - frataxin gene – mitochondrial dysfunction
    - neurological symptoms combined with sensory loss and cardiomyopathy



Disease	Expanded Trinucleotide Repeat	Affected Protein
Huntington disease	CAG	Huntingtin
Spinocerebellar ataxia, types 1, 2, 3, 7	CAG	Ataxin 1, 2, 3, 7
Spinocerebellar ataxia, type 6	CAG	α_{1A} subunit of Ca^{2+} channel
Dentatorubral-pallidoluysian atrophy	CAG	Atrophin
Spinobulbar muscular atrophy	CAG	Androgen receptor
Fragile X syndrome	CGG	FMR-1
Myotonic dystrophy	CTG	DM protein kinase
Friedreich ataxia	GAA	Frataxin

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Dementia

Definition, signs, types and mechanisms

Alzheimer's disease

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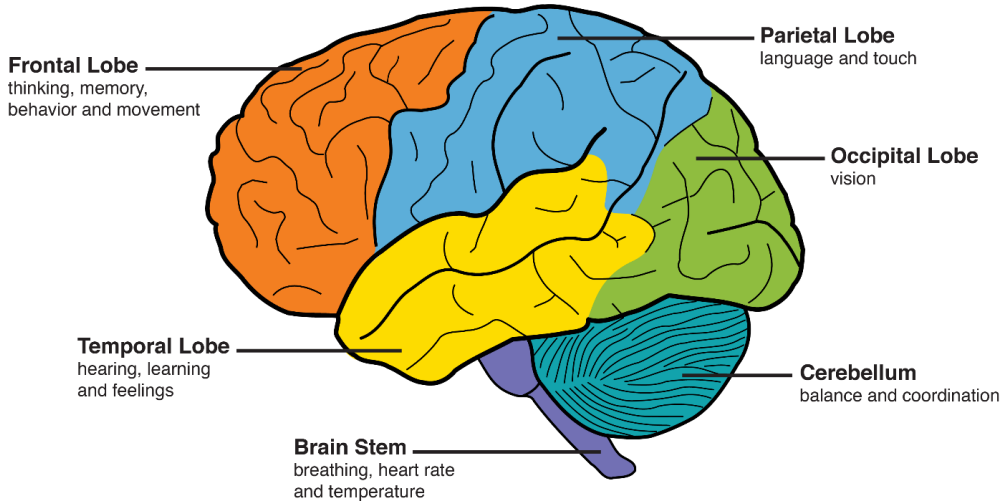
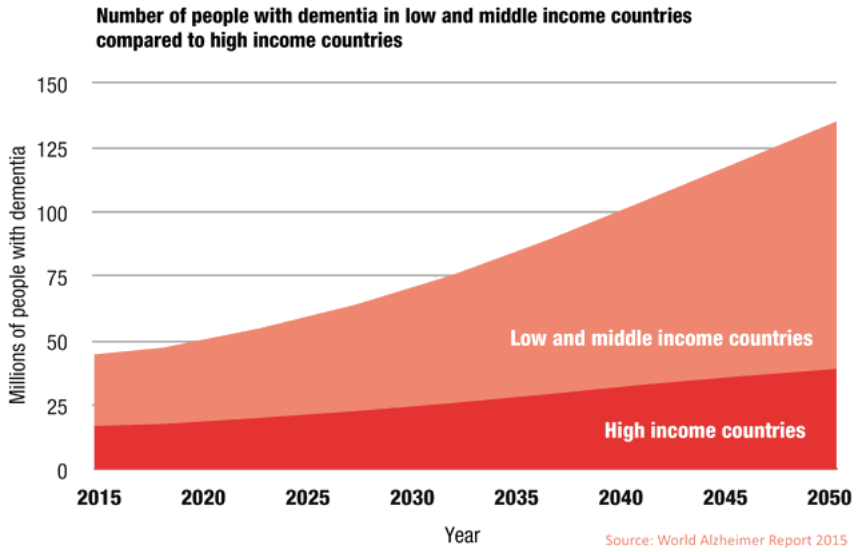
Dementia as a consequence of neurodegeneration

- general term for any disease that causes a long-term and gradual change in **ability to think** and remember (**memory**) and is severe enough to impair a person's daily functioning
  - while some mild changes in cognition are considered a part of the normal aging process, dementia is not
  - consciousness is usually not affected
- symptoms – might differ in different aetiologies of dementias
  - memory loss
  - trouble planning and organizing, doing familiar tasks
  - impaired visual-spatial orientation
  - poor judgment, trouble and making decisions
  - confusion or agitation
  - changes in personality and mood
  - later problems with walking, swallowing, apathy, frequent falls
- time course of dementia:
  - cognitive functions impaired
  - impaired behaviour and emotions
  - impaired daily activities (eating, dressing, hygiene, sleep etc.)
  - mortality – mute, incontinent, bed ridden, feeding failure, aspiration pneumonia
- prevalence
  - about 3% of people between the ages of 65–74 have dementia
  - 19% between 75 and 84
  - nearly half of those over 85 years of age
- Diagnosis is usually based on history of the illness and cognitive testing with medical imaging
  - the mini mental state examination is one commonly used cognitive test





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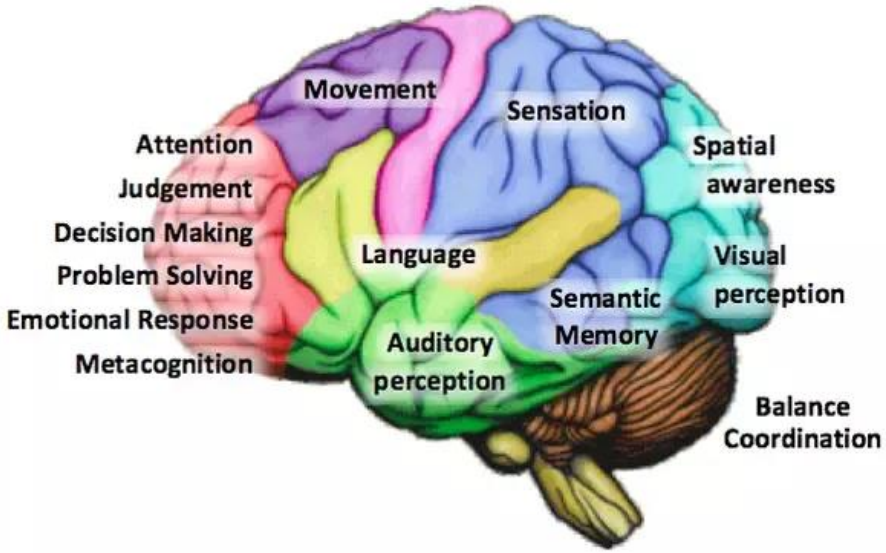
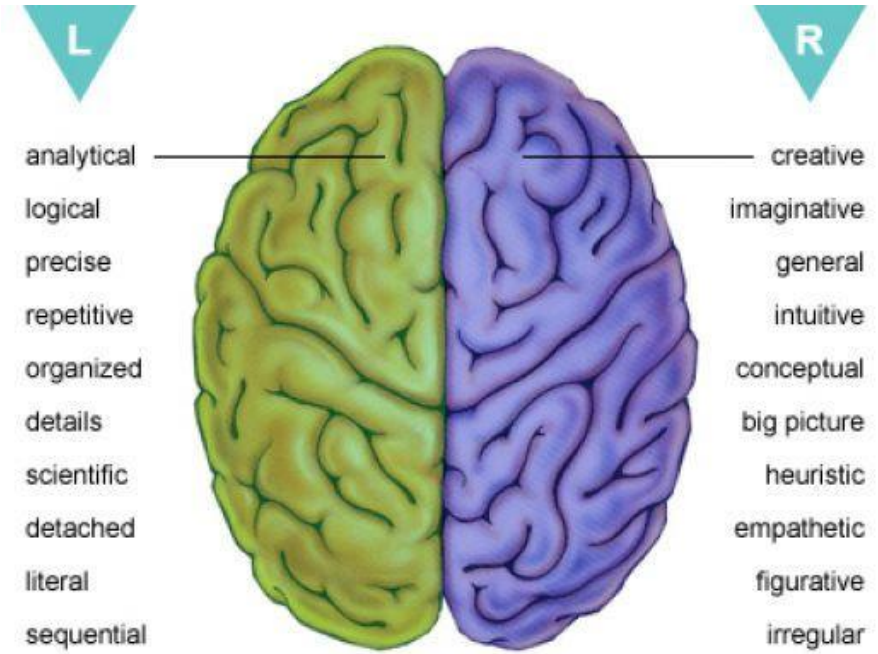
Cognitive functions

- cognitive functions are inherent features of CNS aiming to recognize and understand both external and internal environment and to properly react to it
- categories
  - memory
    - declarative – can be expressed by words (related to hippocampus)
      - semantic – what we learned
        - affected in FTD
      - episodic – what we experienced (defines our identity)
        - affected by AD, WKD
    - non-declarative –– difficult to express (related to hippocampus, basal ganglia, cerebellum and neocortex)
      - emotional memory, conditional reflexes, procedural memory (incl. motor programmes)
        - affected in PD
  - attention, concentration
  - executive functions (planning, decision making, problem solving) incl. emotions and self-regulation
  - speech, expression, understanding
  - spatial orientation
- disorders
    - complex severe – in dementia
    - mild cognitive impairment – aging
    - temporary - delirium
    - isolated amnestic syndromes - strokes





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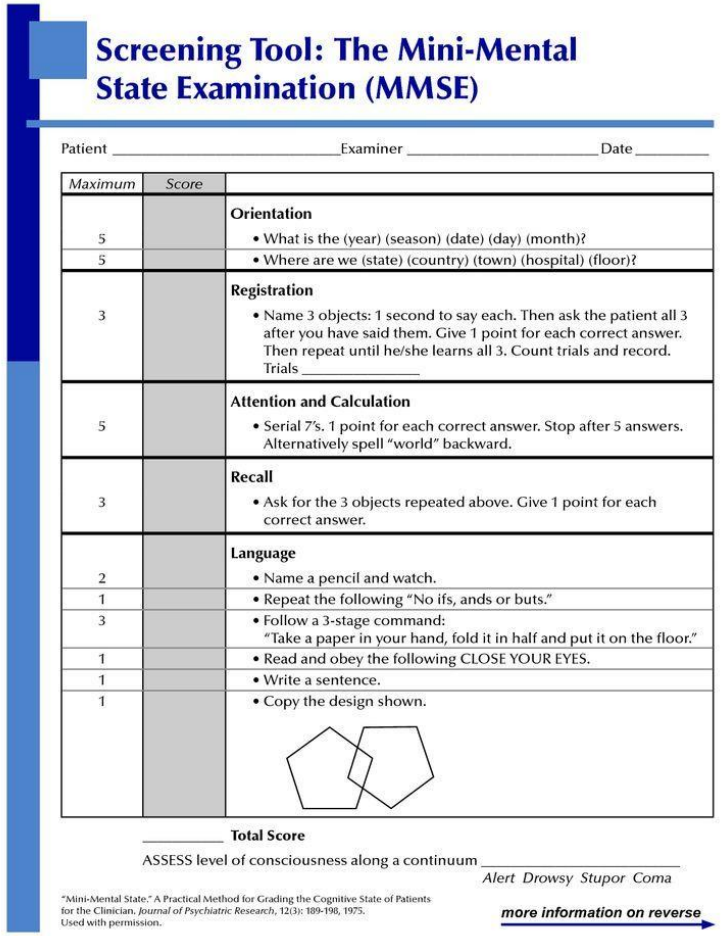
Types and aetiologies of dementia

- Alzheimer's disease (60%)
  - typical hippocampal atrophy
- Vascular dementia (25%)
  - not gradual but abrupt or stepwise
    - with or without stroke in personal history
      - focal neurological deficits
    - emotional instability, impulsivity, depression,
- Dementia with Lewy bodies (15%)
  - dementia develops together with motor symptoms
  - visual hallucination!
- Parkinson's disease
  - dementia develops relatively late after motor symptoms
- Frontotemporal dementia
  - socially inappropriate behaviour (disinhibition)
  - apathy
- Huntington disease
- Creutzfeld Jacob disease
  - spongiform encefalopathy
- normal pressure hydrocephalus
- Wernicke-Korsakoff Syndrome
  - severe shortage of thiamine (vitamin B-1) in the body. It most commonly happens in people who are long-term heavy drinkers
- NOTE: unrecognised and untreated depression can mimic dementia



Screening Tool: The Mini-Mental State Examination (MMSE)

Patient _____ Examiner _____ Date _____

Maximum	Score	
		Orientation
5		• What is the (year) (season) (date) (day) (month)?
5		• Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3		• Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5		• Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3		• Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2		• Name a pencil and watch.
1		• Repeat the following "No ifs, ands or buts."
3		• Follow a 3-stage command: "Take a paper in your hand, fold it in half and put it on the floor."
1		• Read and obey the following CLOSE YOUR EYES.
1		• Write a sentence.
1		• Copy the design shown.

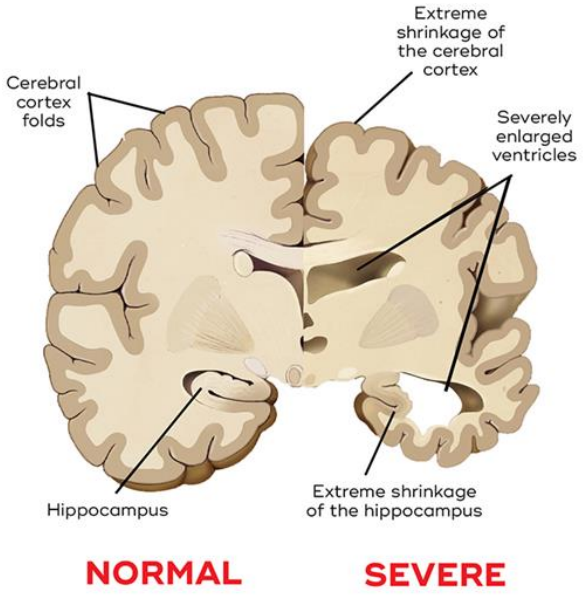
_____ **Total Score**

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

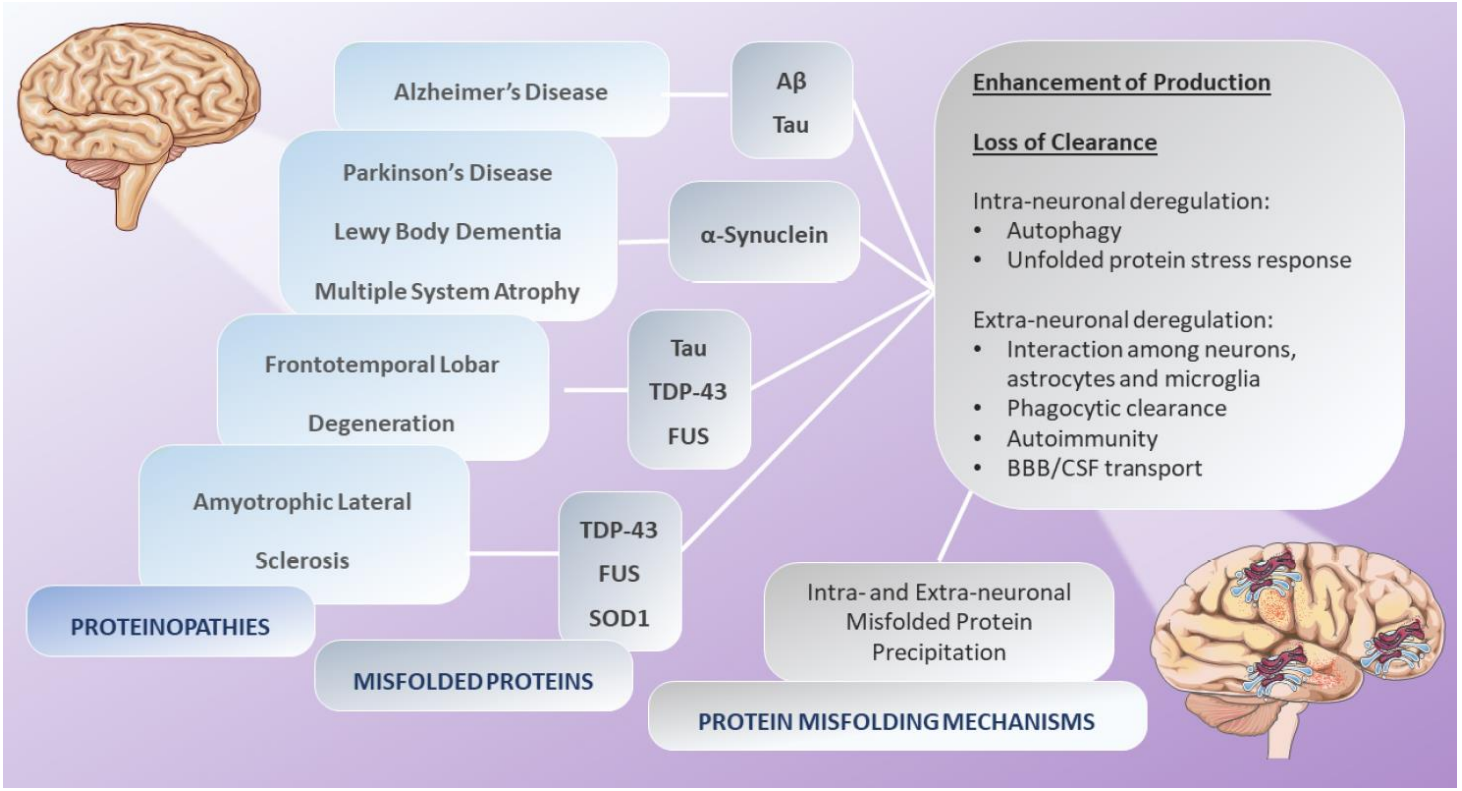
"Mini-Mental State." A Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used with permission.

more information on reverse



Neurodegenerative diseases as proteinopaties

- mechanisms of neurodegeneration in general
  - build-up of proteins in the brain that interferes with the brain functions
    - different protein build-up in different types of dementia though
      - beta-amyloid and tau in AD, alpha-synuclein in DLW, prions in CJD
- neurodegeneration could therefore be consider as a proteinopathy
  - cumulated protein in toxic doses or mutated is prone to misfolding and aggregation
  - resistance or concomitant dysfunction in systems degrading the proteins
    - ubiquitin-proteasom
    - autophagy
- ER stress (UPR) and apoptosis



- In most neurodegenerative disorders, proteins that are unstructured in healthy brains, undergo modifications in their structural folding, forming small oligomeric or large fibrillary aggregates. These changes lead to their self-association, elongation and intra- and extra-neuronal precipitation. The molecular mechanisms resulting in misfolded protein conformational changes tend to be the same in all the proteinopathies and may include different mechanisms, such as post-translational modifications, the loss of protein clearance or the enhancement of protein production

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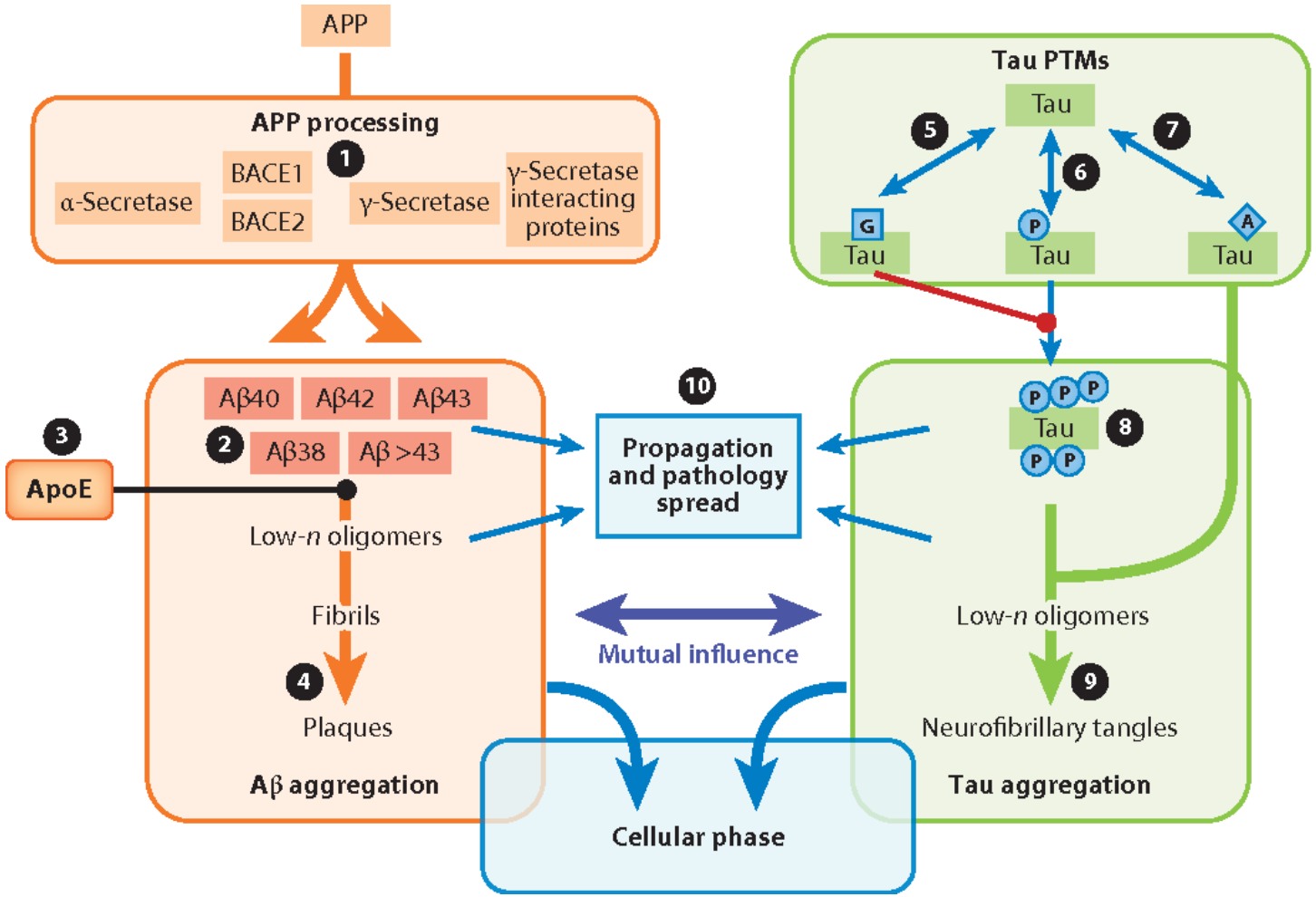
AD = beta-amyloid and Tau-proteinopathies



- The amyloid cascade hypothesis posits that Aβ aggregation is the starting point of a series of events ultimately leading to AD.
- Aβ originates from the sequential cleavage of APP by BACE1 and γ-secretase.
- Gradual formation of Aβ low-*n* oligomers and their buildup into dynamic, higher-order aggregates impacts synaptic function first and leads progressively to tau hyperphosphorylation, aggregation, and intracellular deposition; elicits neuroinflammation; and ultimately leads to neurodegeneration and dementia.
- Although these steps are proposed to proceed in a mostly linear timeline, researchers increasingly appreciate the fact that Aβ and tau pathology may well start and proceed independently, eventually feeding into each other

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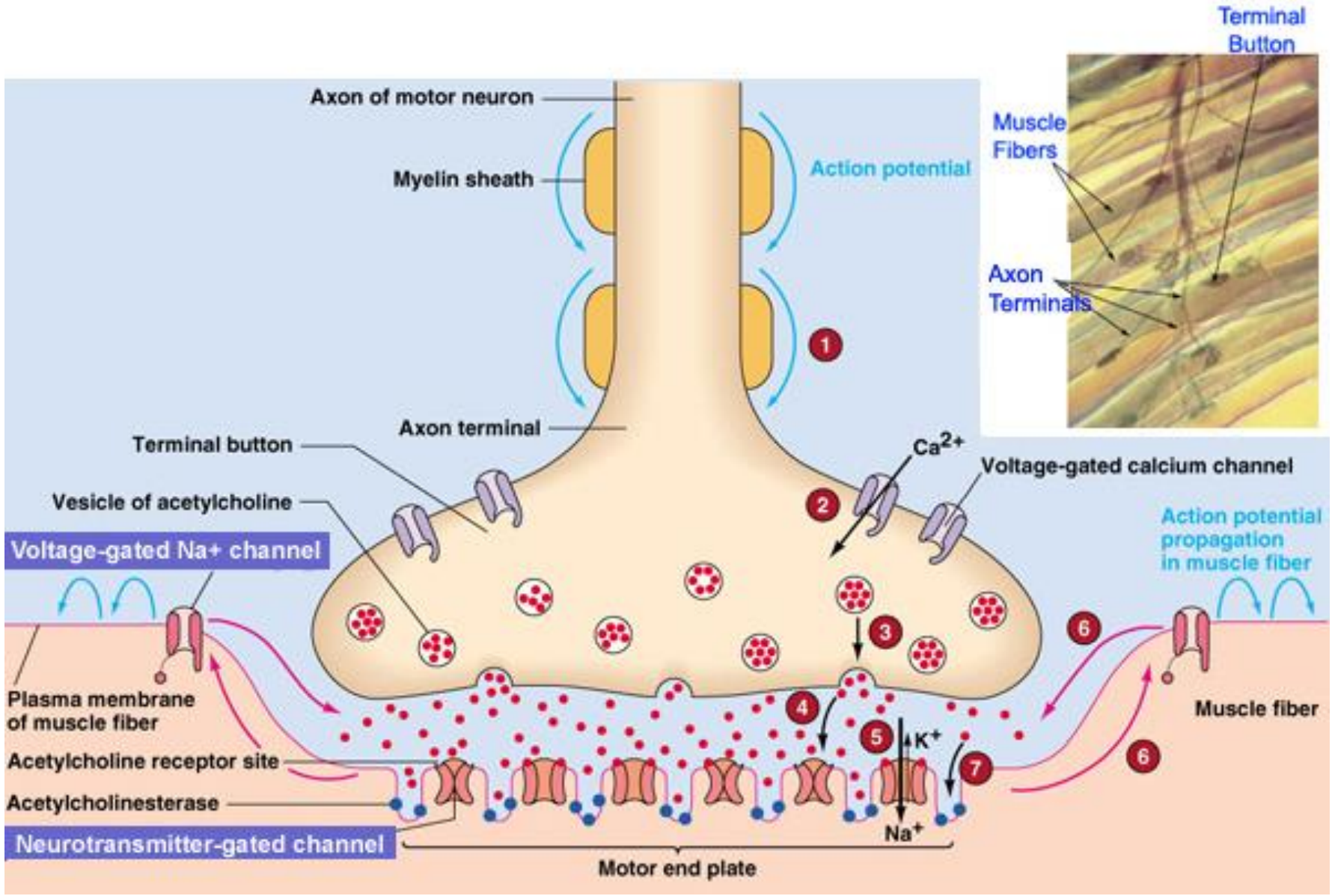
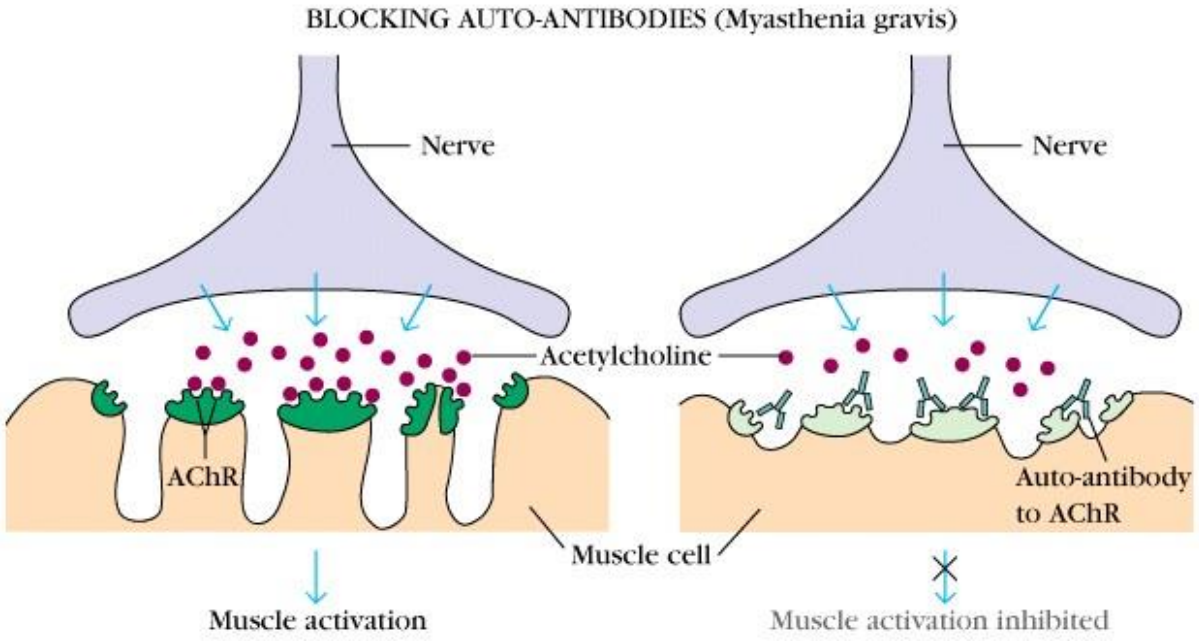
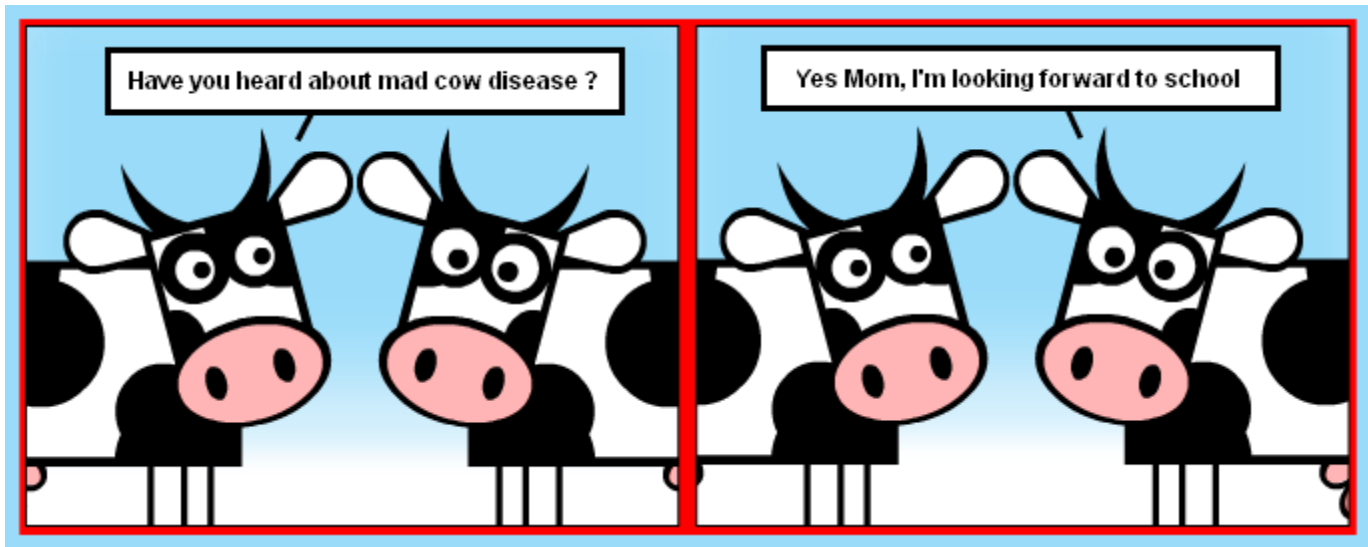
Disorders of neuromuscular junction



Disorders of neuromuscular junction

- drug effects
  - curare-type
    - block Ach receptor activation
  - botulotoxin type
    - affect Ach release (irreversibly)
  - organophosphates
    - block Ach-esterase
- myasthenia gravis
  - onset between 20 – 30 yrs, 2x more women
  - etiology
    - unknown
    - in 75% cases MG associated with thymoma or thymus hyperplasia
  - pathogenesis - autoimmune
    - production of blocking Ab against Ach receptors
    - autoantibodies also induce complement-mediated degradation of the AchR, resulting in progressive weakening of the skeletal muscles
  - symptoms
    - muscle weakness (ptosis, diplopia, chewing, speech, respiration)
    - fatigue
- Lambert-Eaton syndrome
  - blockade of presynaptic Ach release
  - paraneoplastic (lung carcinoma)




Have you heard about mad cow disease ?
Yes Mom, I'm looking forward to school

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