Pathophysiology of nervous system I: motoric function and its disorders

Organisation of nervous system

Neurons, synapses, neurotransmitters

Neuromuscular junction and its disorders (myasthenia syndromes)

Muscles diseases (muscular dystrophy)

Proprioception and spinal reflexes

Hierarchy of the motoric control systems

Paralysis

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

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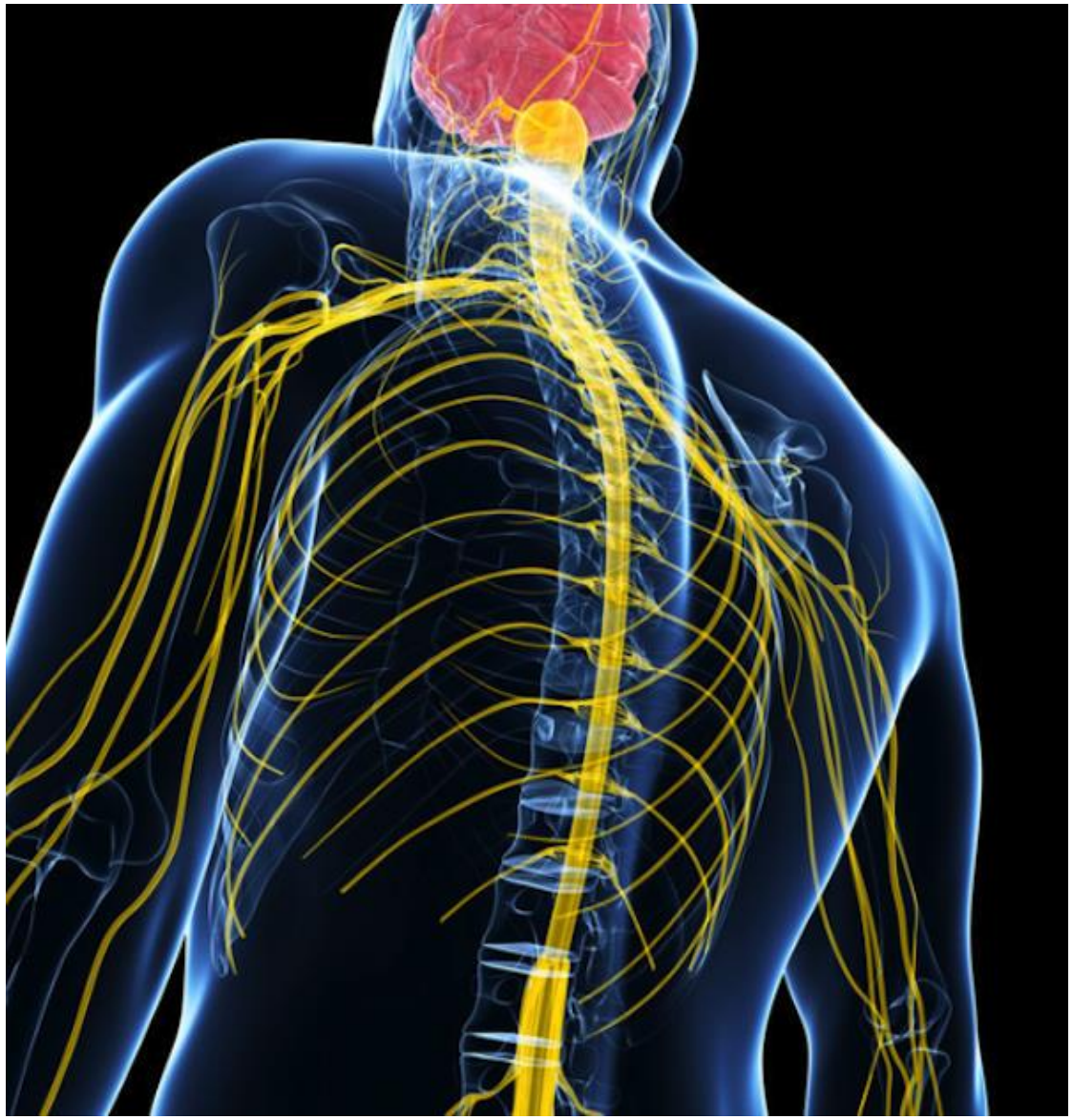
Anatomy and physiology of NS



- **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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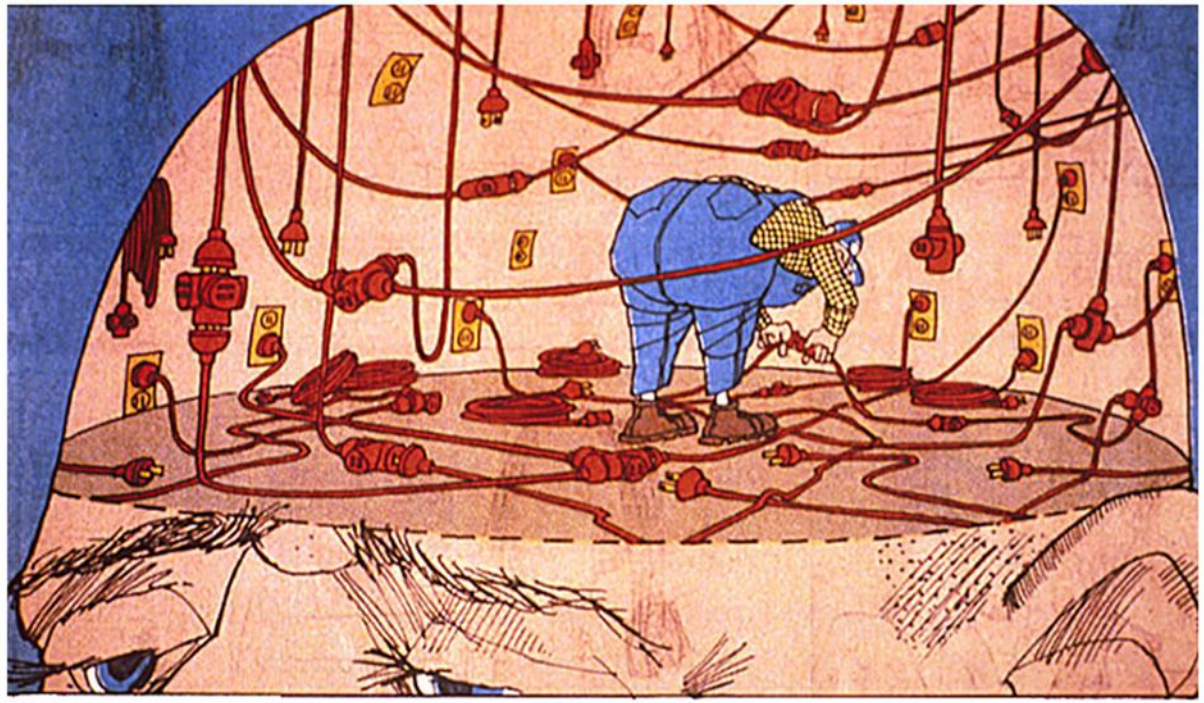
Functions of nervous system (NS)



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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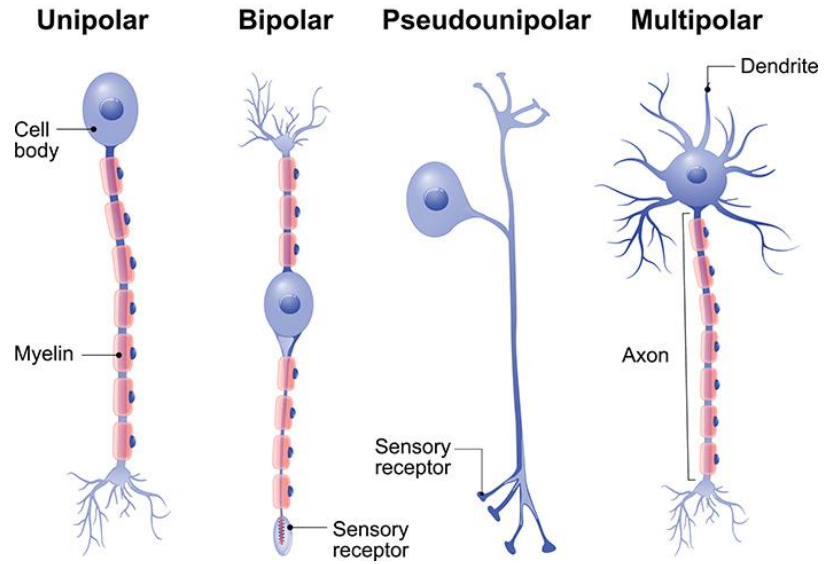
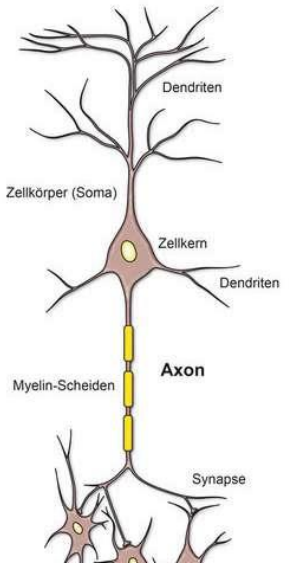
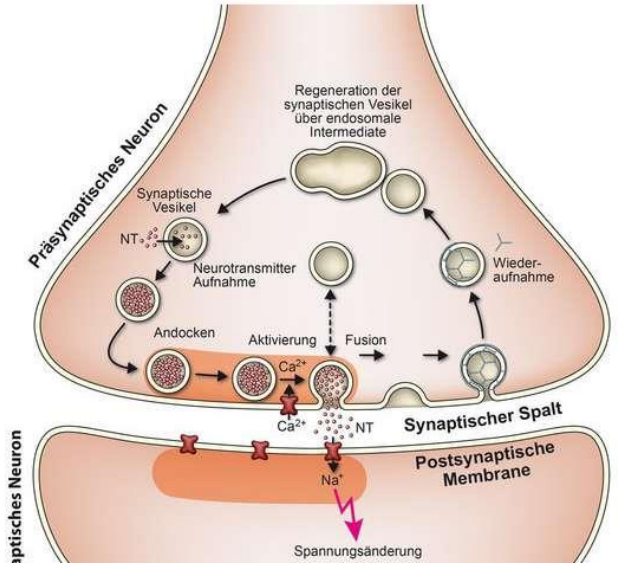
Buňky NS - neuron jako funkční jednotka

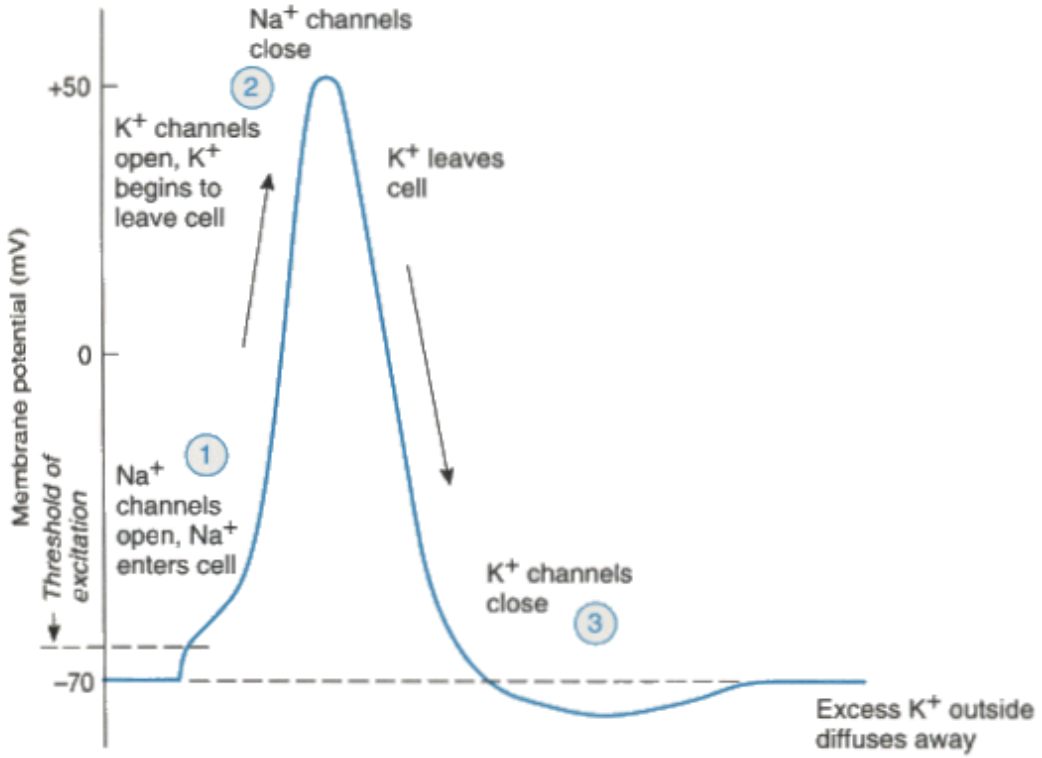
- vysoká variabilita neuronů podle specifity, velikosti a typu
  - jeden α-motoneuron v předních rozích míšních v hrudní oblasti má axonální délku více než 1 m a inervuje několik set až tisíc svalových fibril a vytváří motorickou jednotku
  - jiné neurony mají délku pod 100 µm a končí na jednotlivých tělech jiných neuronů

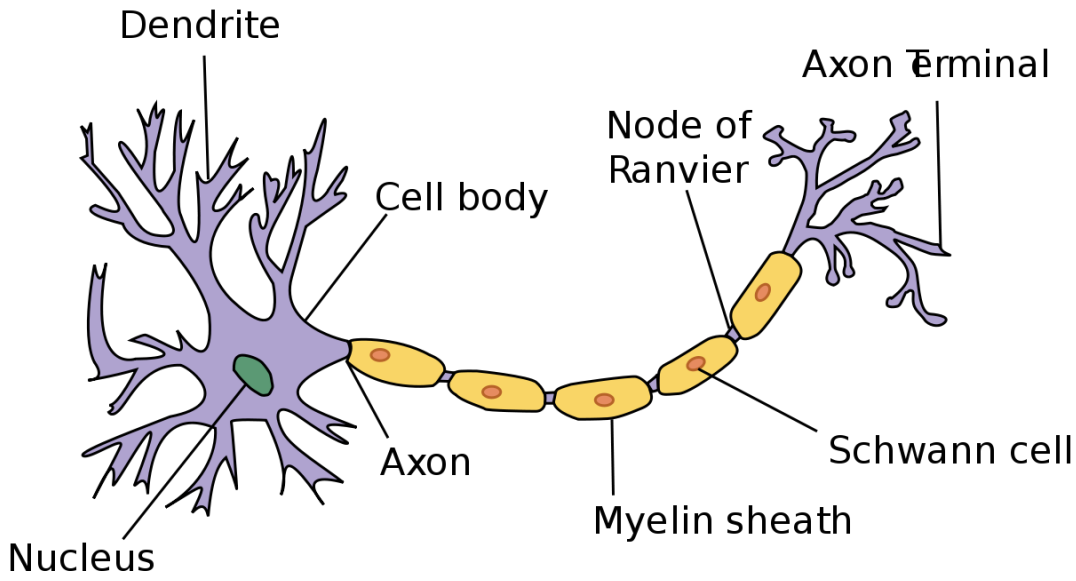


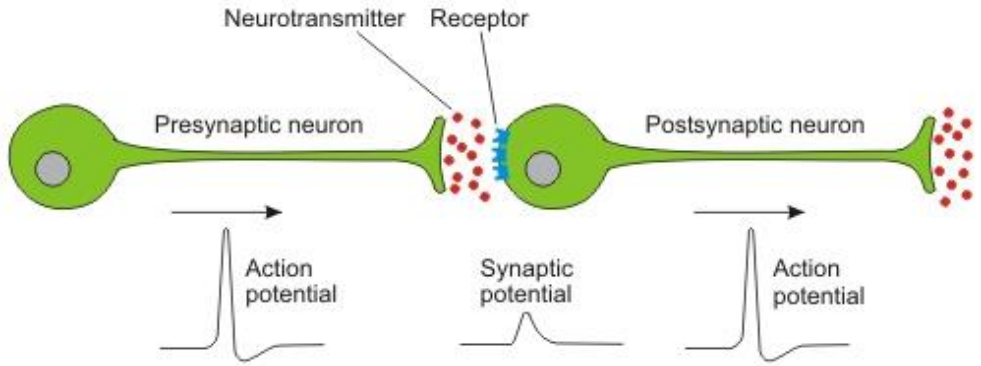




Neurons/action potential/nerve transmission







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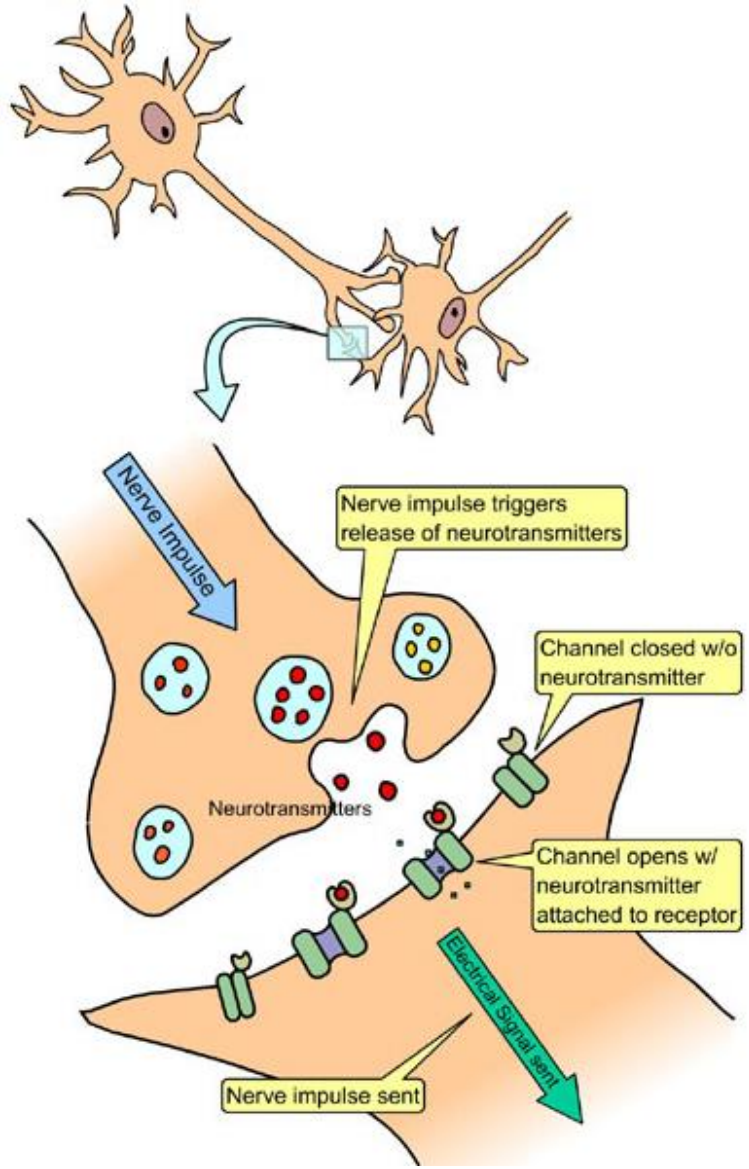
Synapses/neurotransmitters

- 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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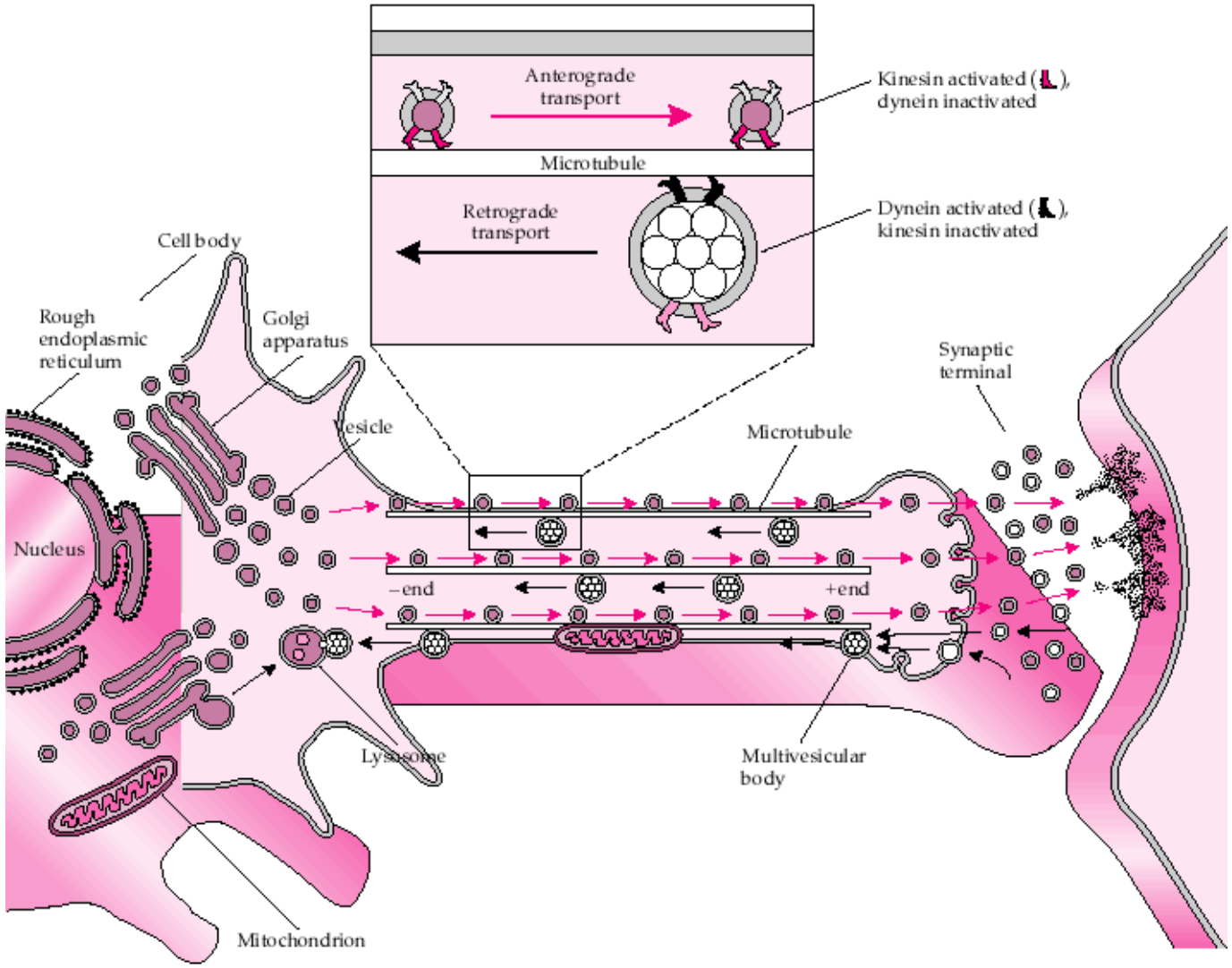
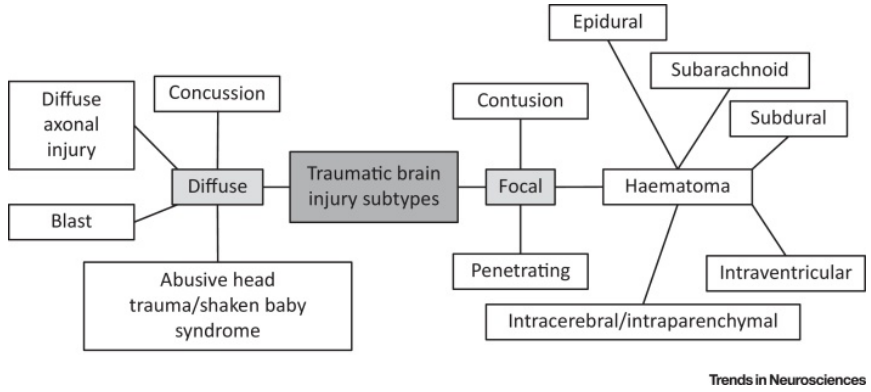
Axonal transport



- 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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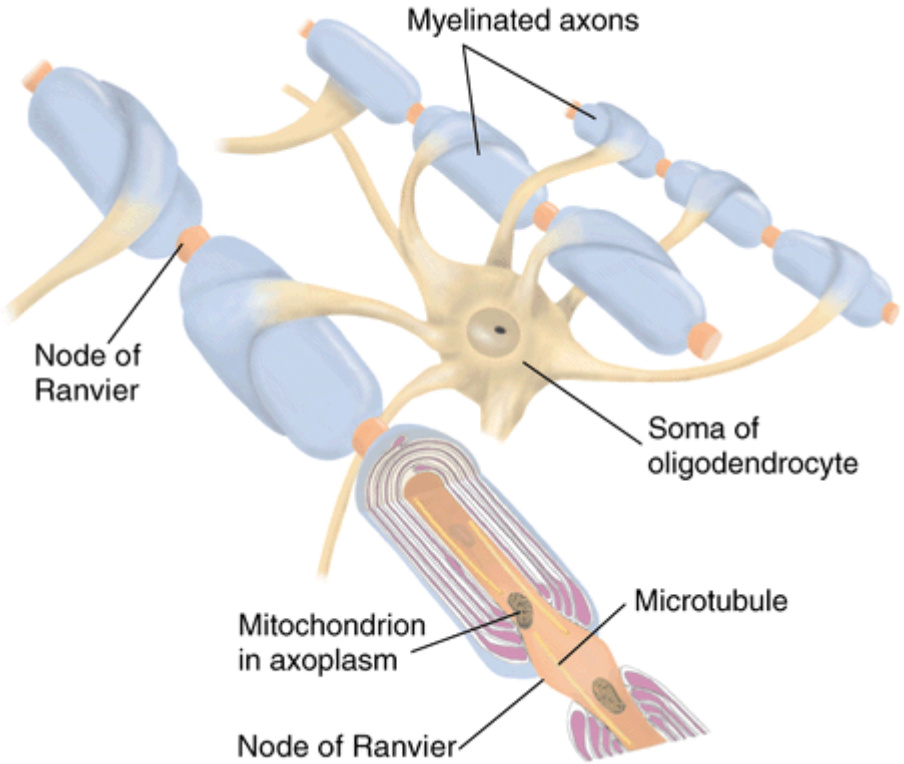
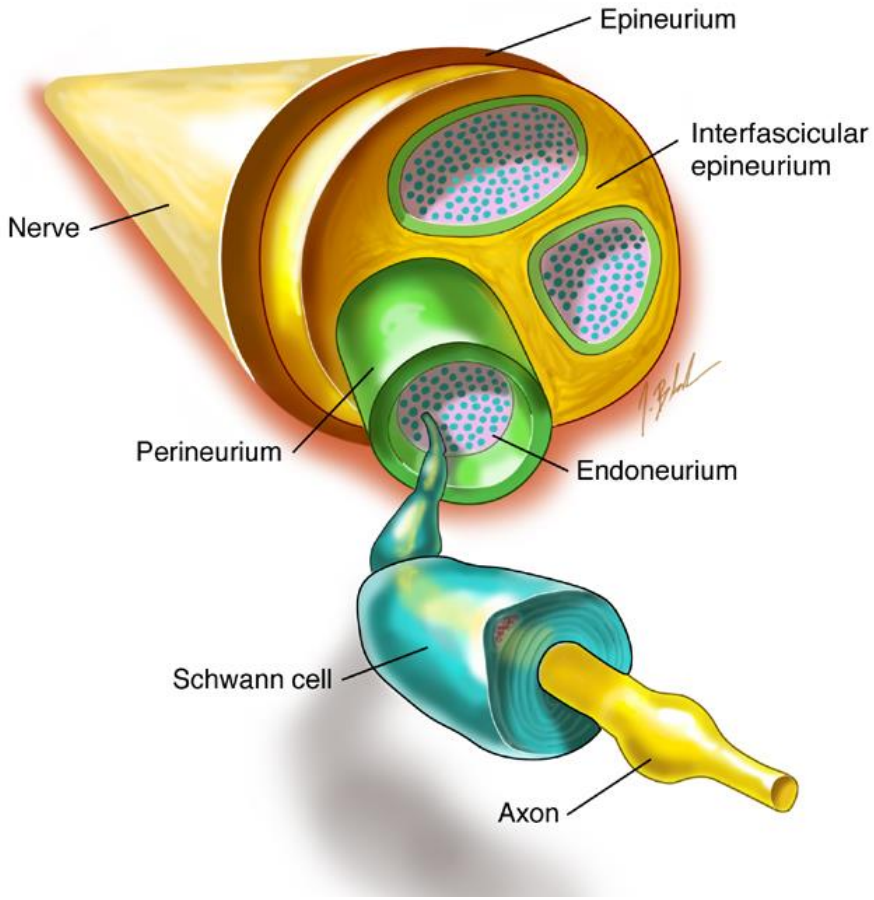
Myelin and nerve structure





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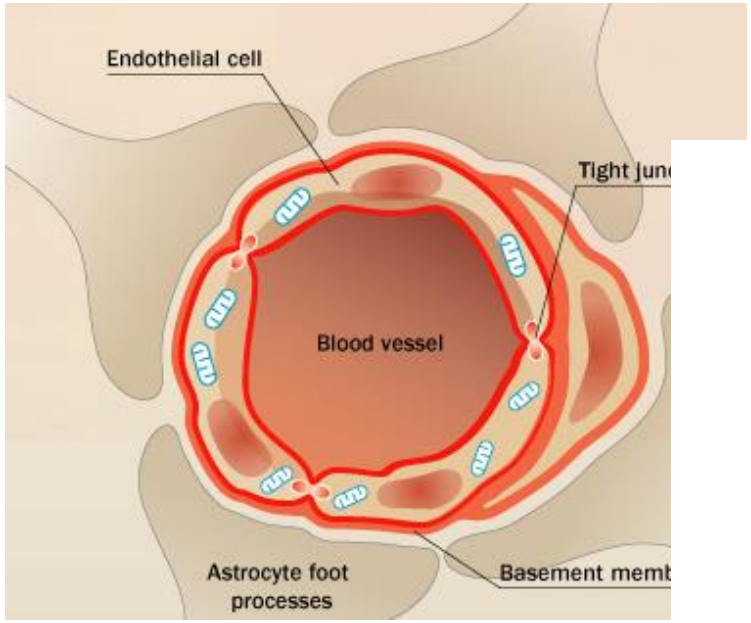
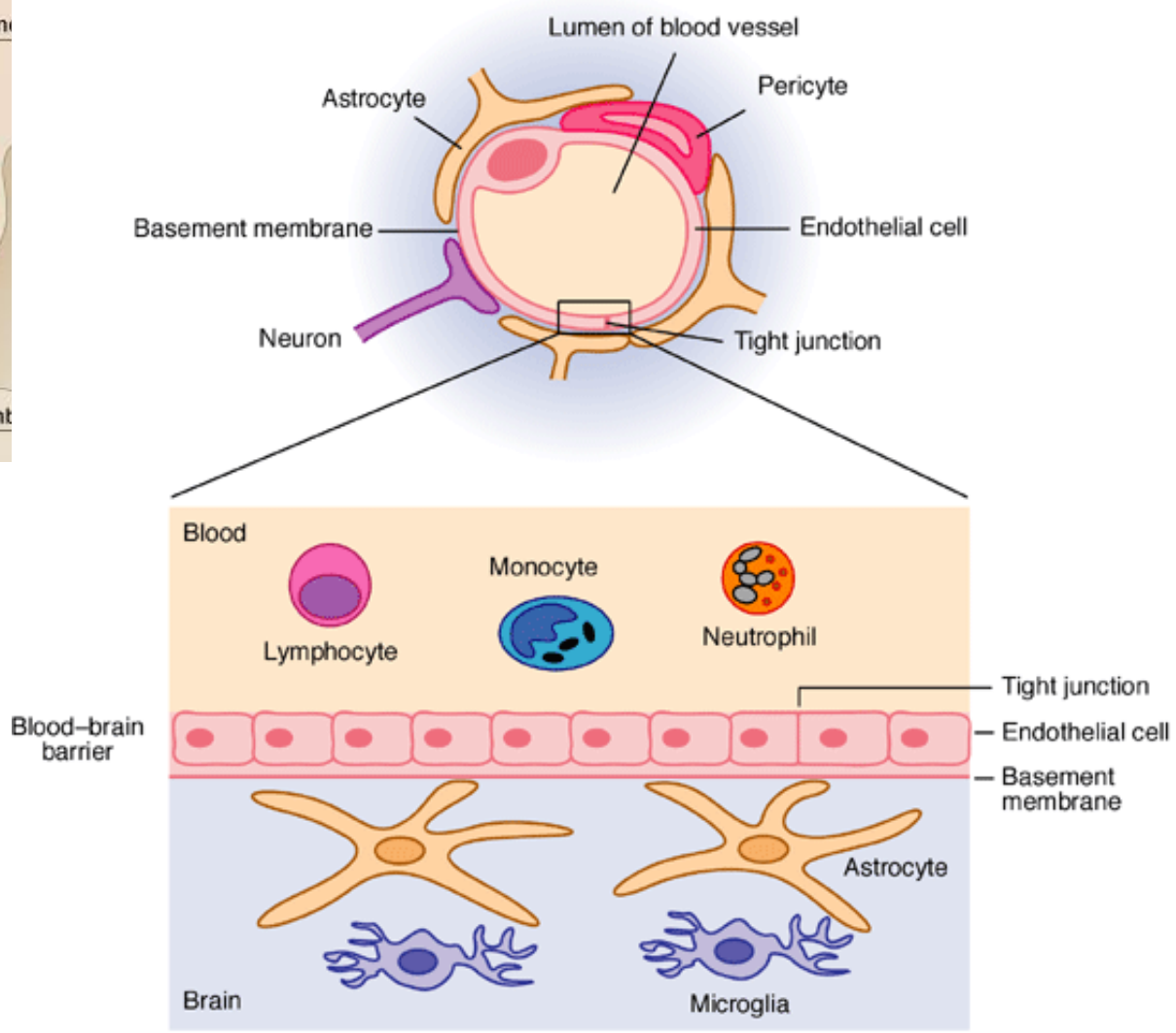
Blood-brain barrier (BBB)





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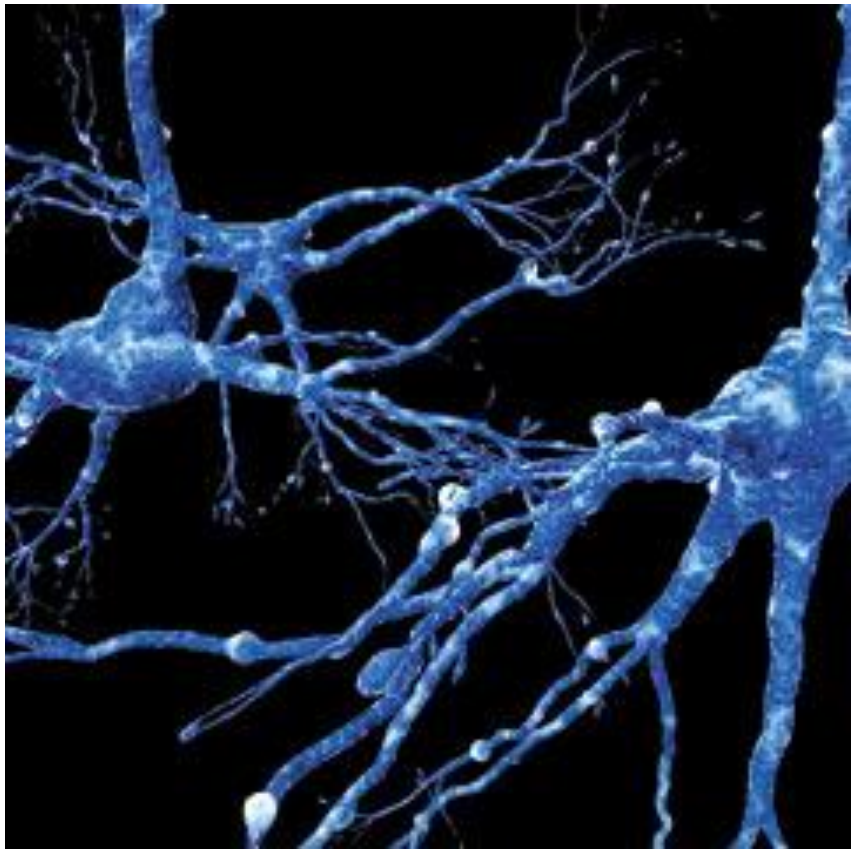
Neural plasticity



- 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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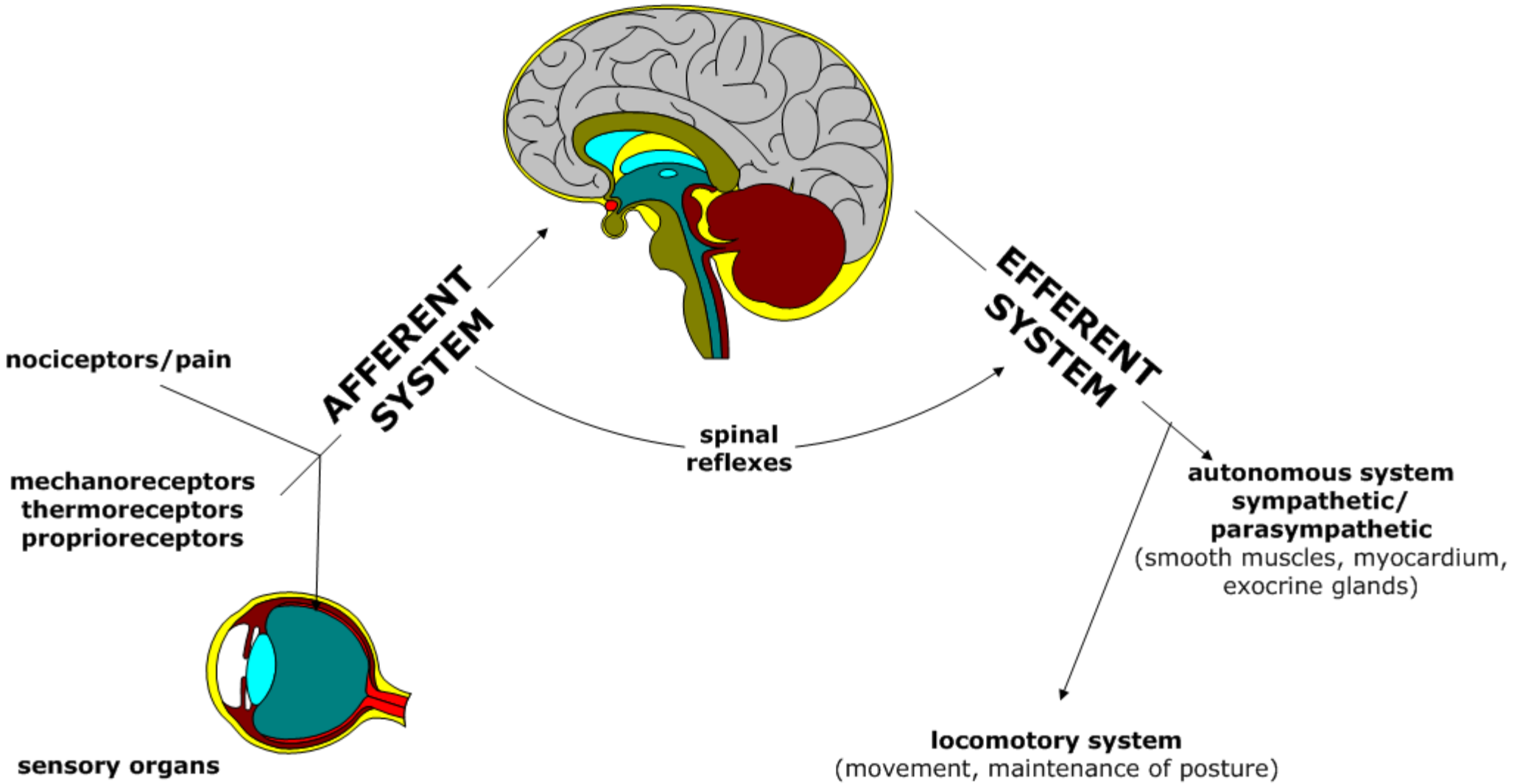
Organisation of NS



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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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Motoric system a its disorders

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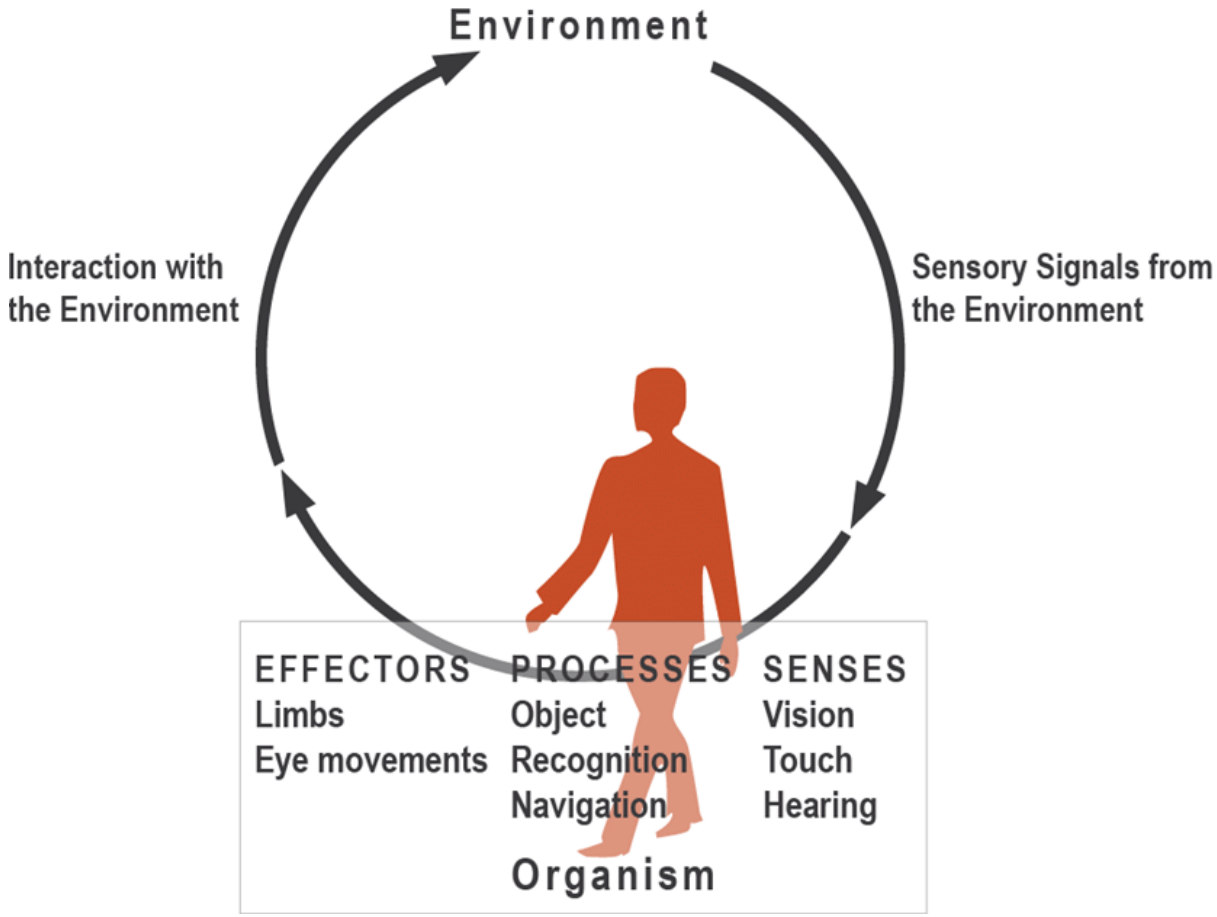
Motorika, její kontrola a komponenty

- 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.



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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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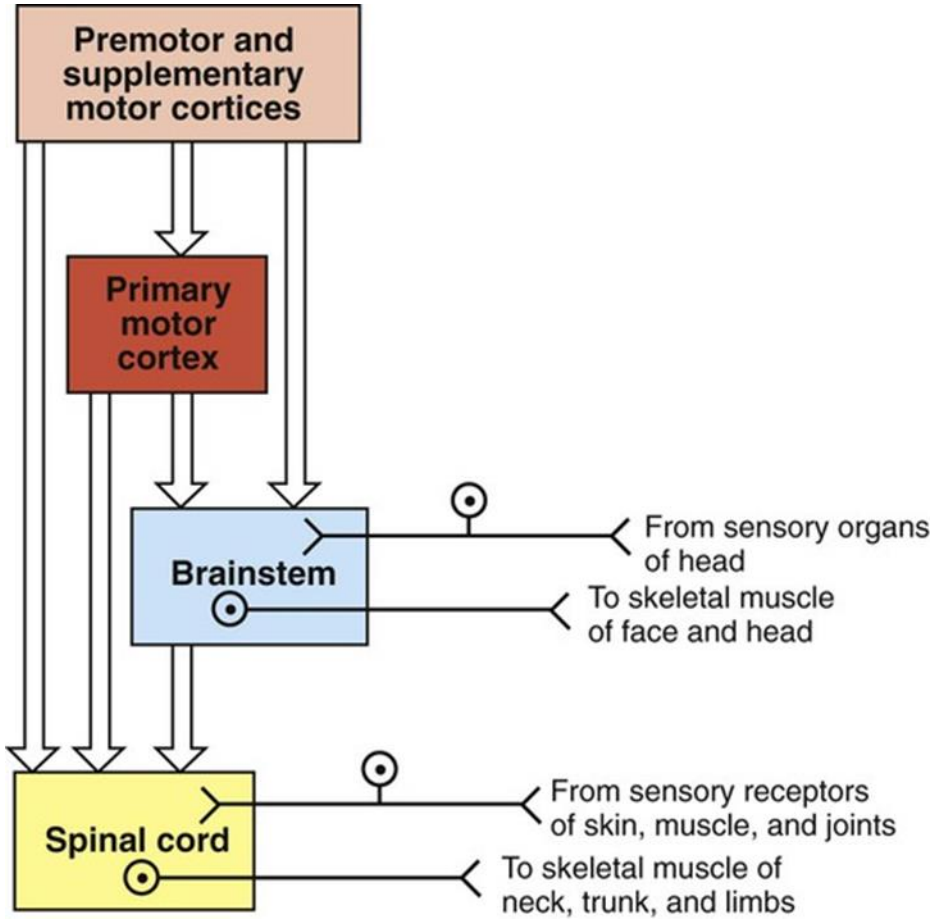
Hierarchical organisation of the motoric system

- 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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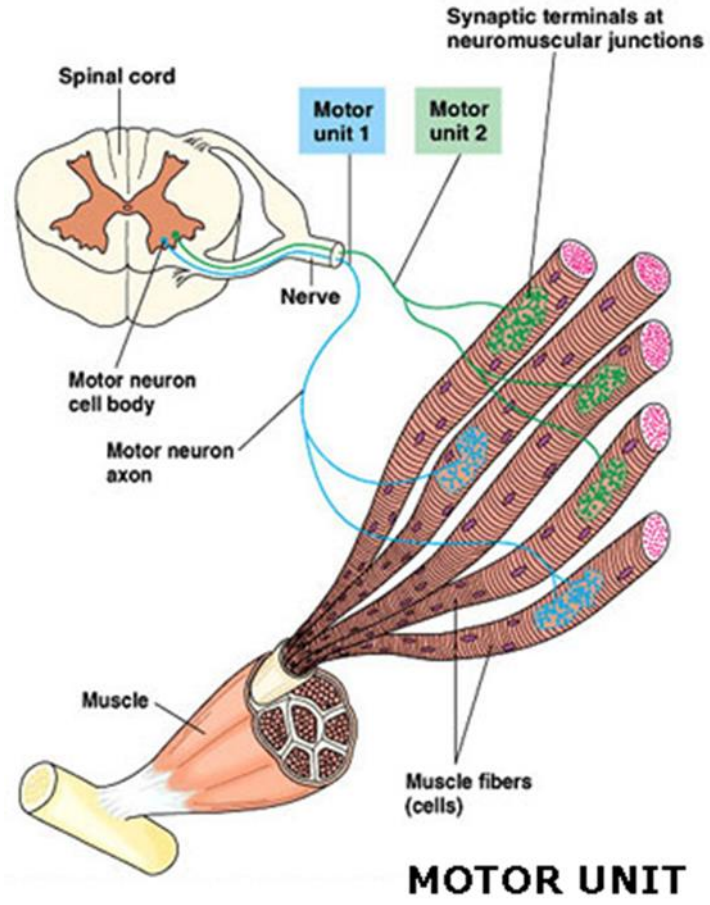
Level (1) spinal cord: α-motoneurons

- 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
- 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



Organisation 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)

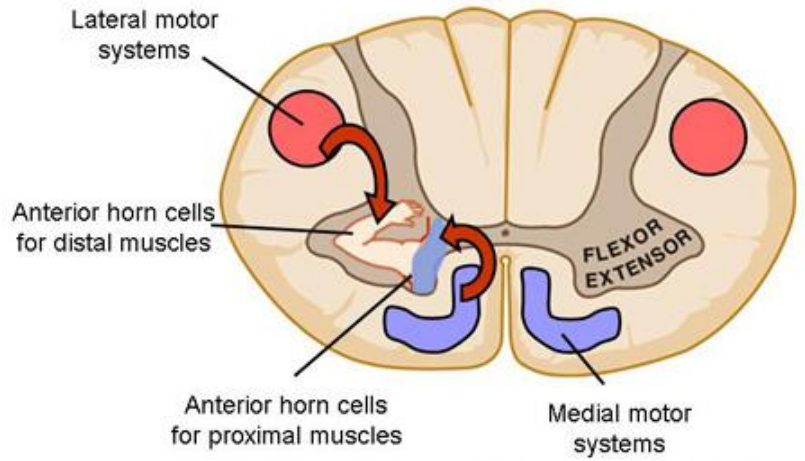
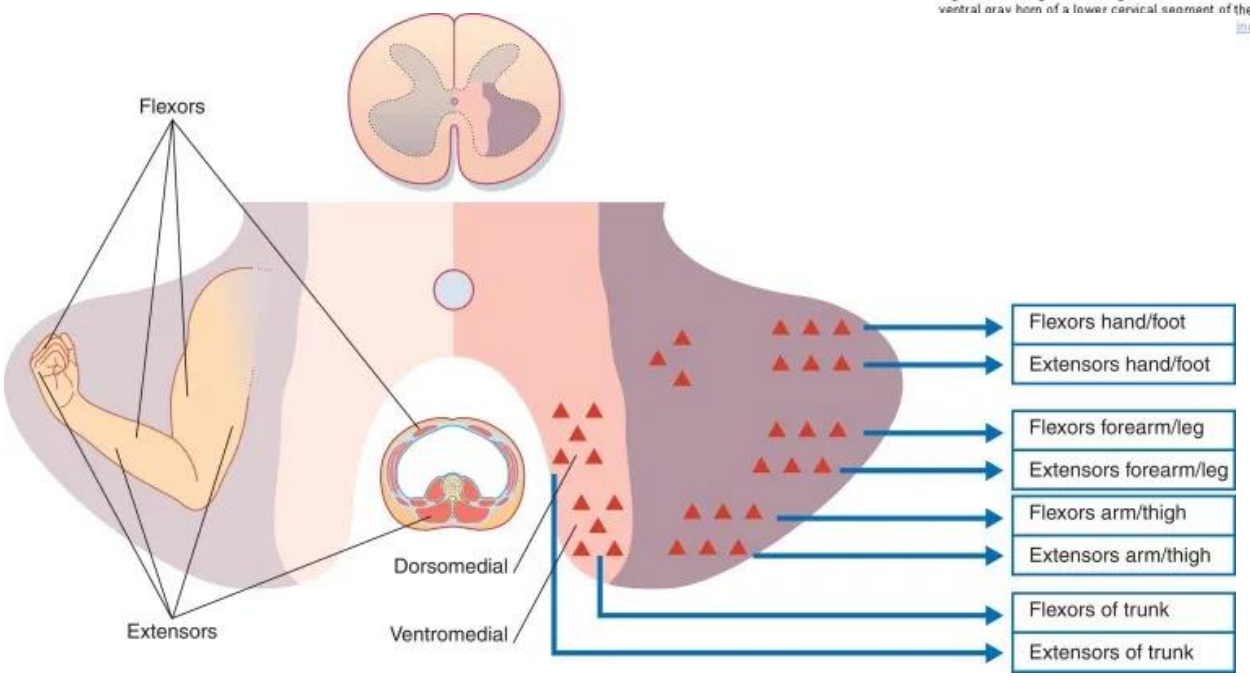


Figure 5-12. Diagram showing the functional localization of motor neuron groups in the ventral gray horn of a lower cervical segment of the spinal cord. In: Waxman SG. *Clinical* ine.com. Accessed January 3, 2010.



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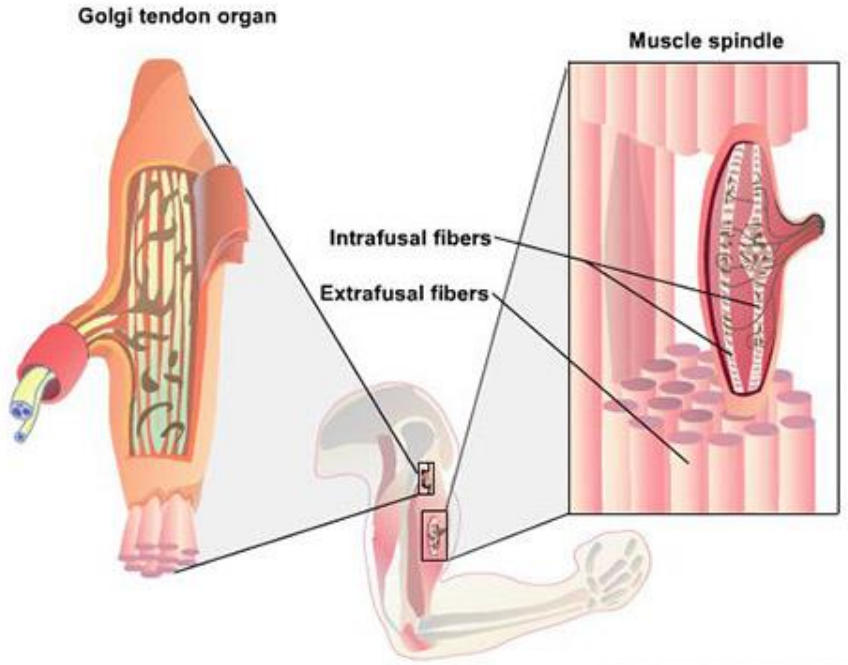
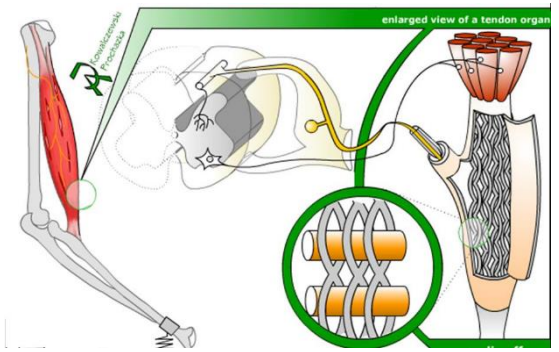
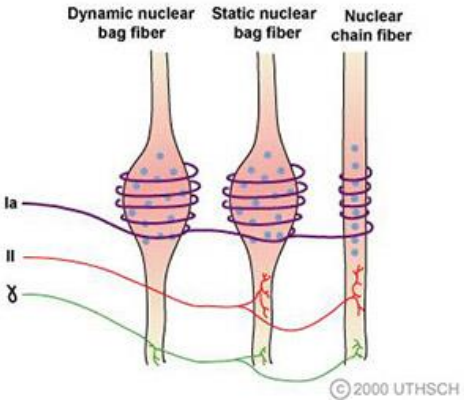
Level (1) spinal cord : Muscle Receptors and Proprioception

- **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
    - collagen capsule
    - afferents called group Ib fibers weave in between the collagen fibers being 'crushed' by movement and thus depolarized







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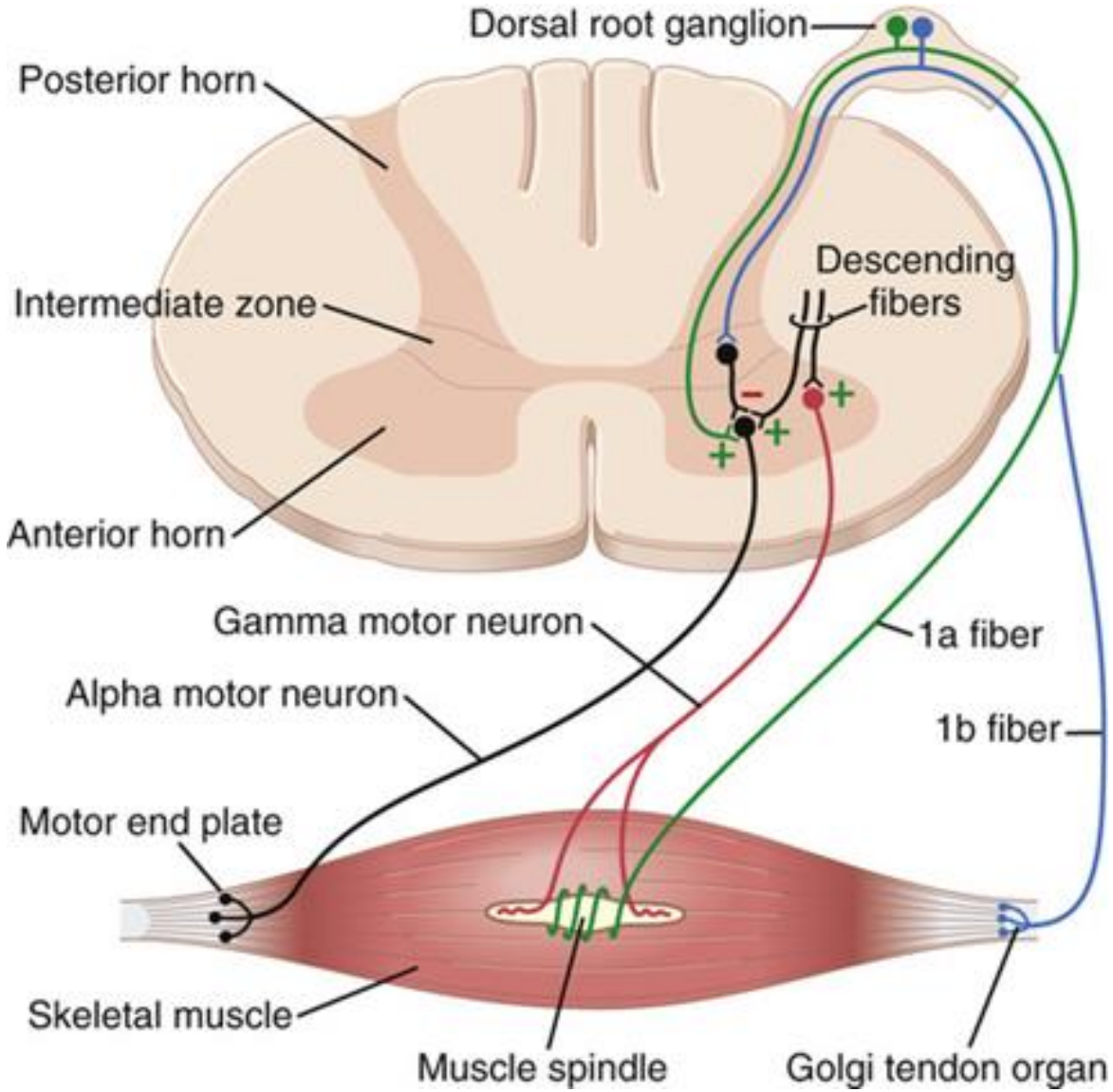
In summary



- **Muscle spindles** signal information about the length and velocity of a muscle
- **Golgi tendon organs** signal information about the load or force applied to a muscle

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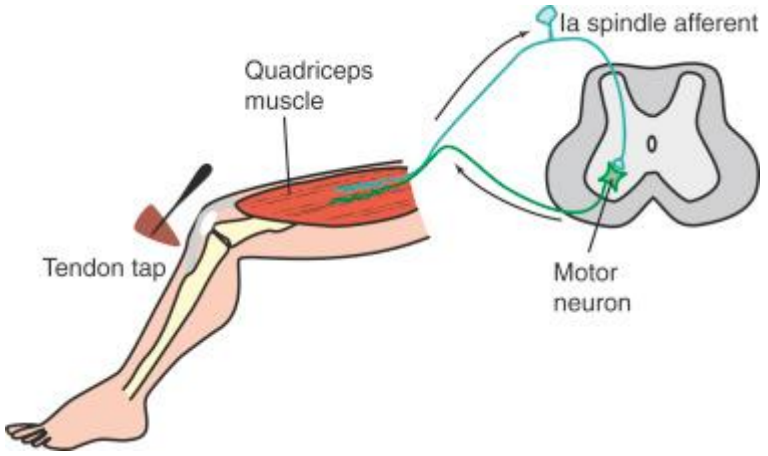
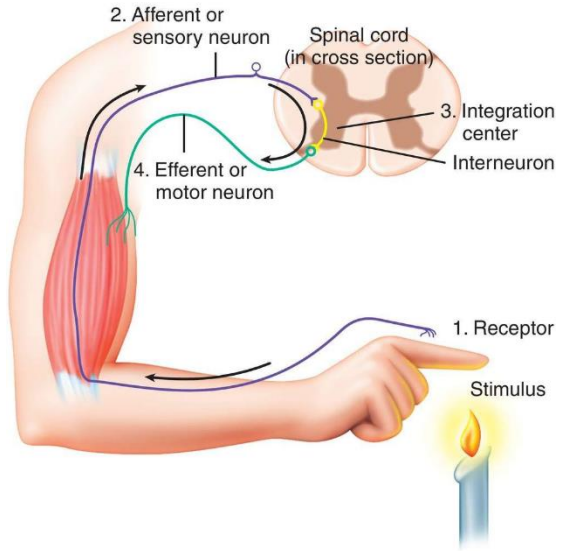
Level (1) mícha: míšní reflexy a role interneuronů

- reflex je základní funkční jednotkou motoriky
  - jejich morfologickým podkladem jsou specializované neuronální okruhy, které řídí funkci svalů tak, aby daly vznik účinným pohybům
  - bez těchto okruhů by nemohly být provedeny ani ty nejjednodušší pohyby
- reflexní oblouk
  - 1) senzor (např. sval. vřeténko či Golgi orgán)
  - 2) aferentní dráha (dostředivá)
    - neurony spinálních ganglia
      - táhnou se od příslušného receptoru a do CNS vstupují zadními rohy míšními
      - v míše se okamžitě dělí na dvě kolaterály:
        - k danému míšnímu segmentu
        - aferentace do vyšších hierarchických center
  - 3) centrum reflexu
  - 4) eferentní dráha (odstředivá) – ke svalu
  - 5) efektor – kosterní sval
- typy reflexů
  - monosynaptické
    - napínací (např. patelární) – senzorem je svalové vřeténko
  - polysynaptické – často obranné
    - flexorový reflex – senzorem je nociceptoir
      - aktivaci alfamotoneuronu příslušného flexoru
      - a inhibici alfamotoneuronu protilehlého extenzoru (antagonisty)
    - zkřížený extenzorový reflex – následuje po flexorovém
      - extenze kontralaterální končetiny
      - smyslem je lepší rozložení váhy a tím k udržení rovnováhy - evolučně se však pravděpodobně jedná o rudiment z předchozího kvadrupedického stadia





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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

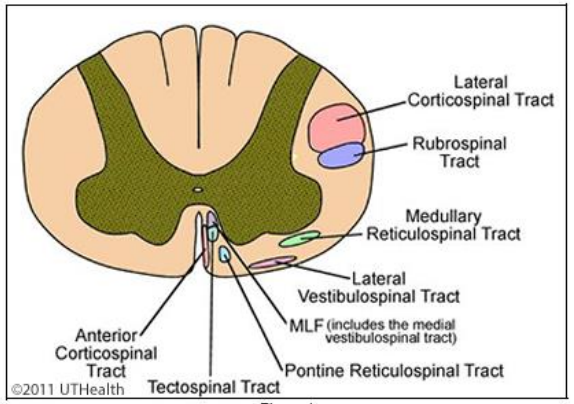
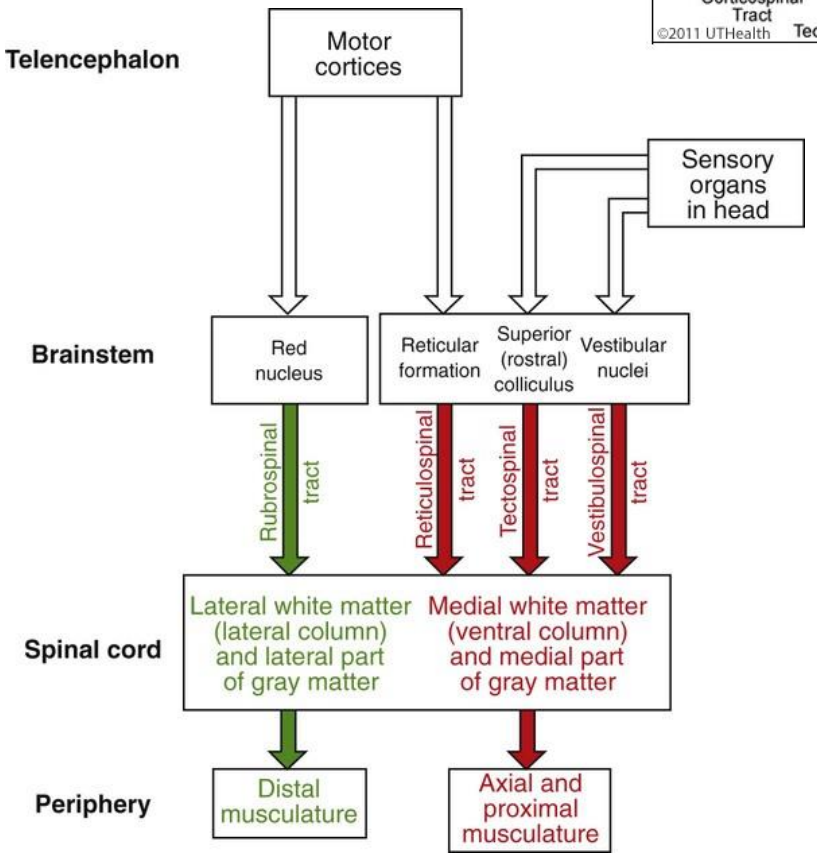
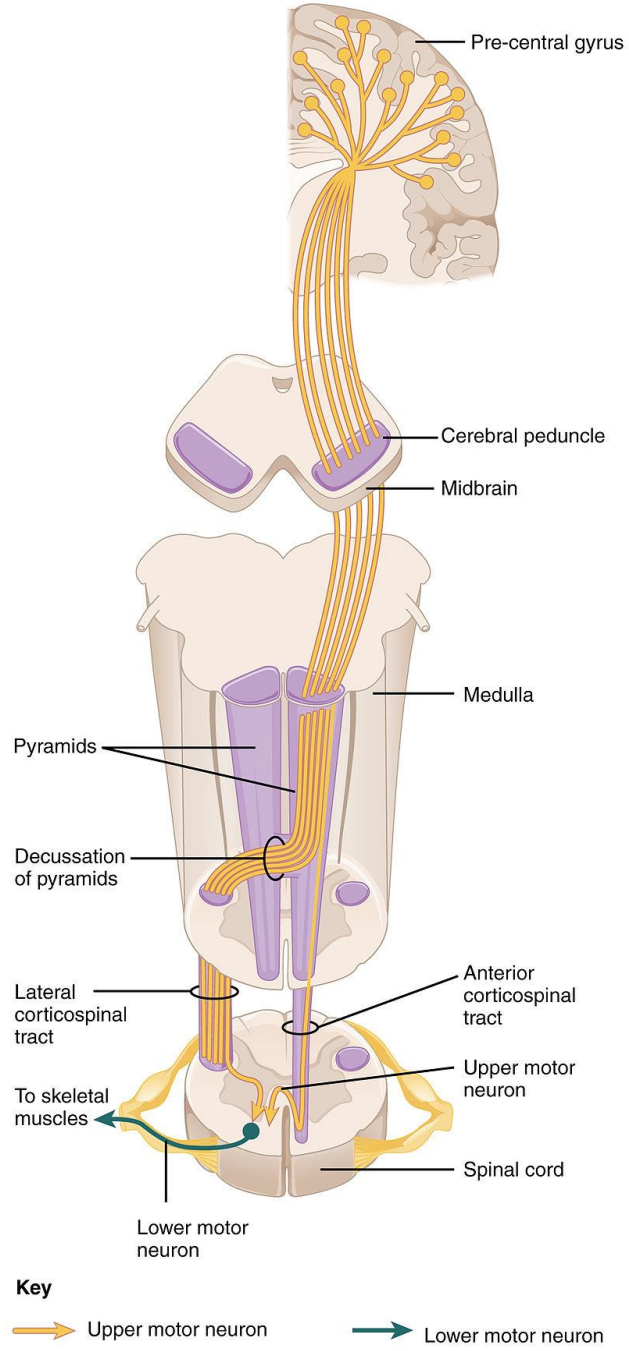


Figure 1

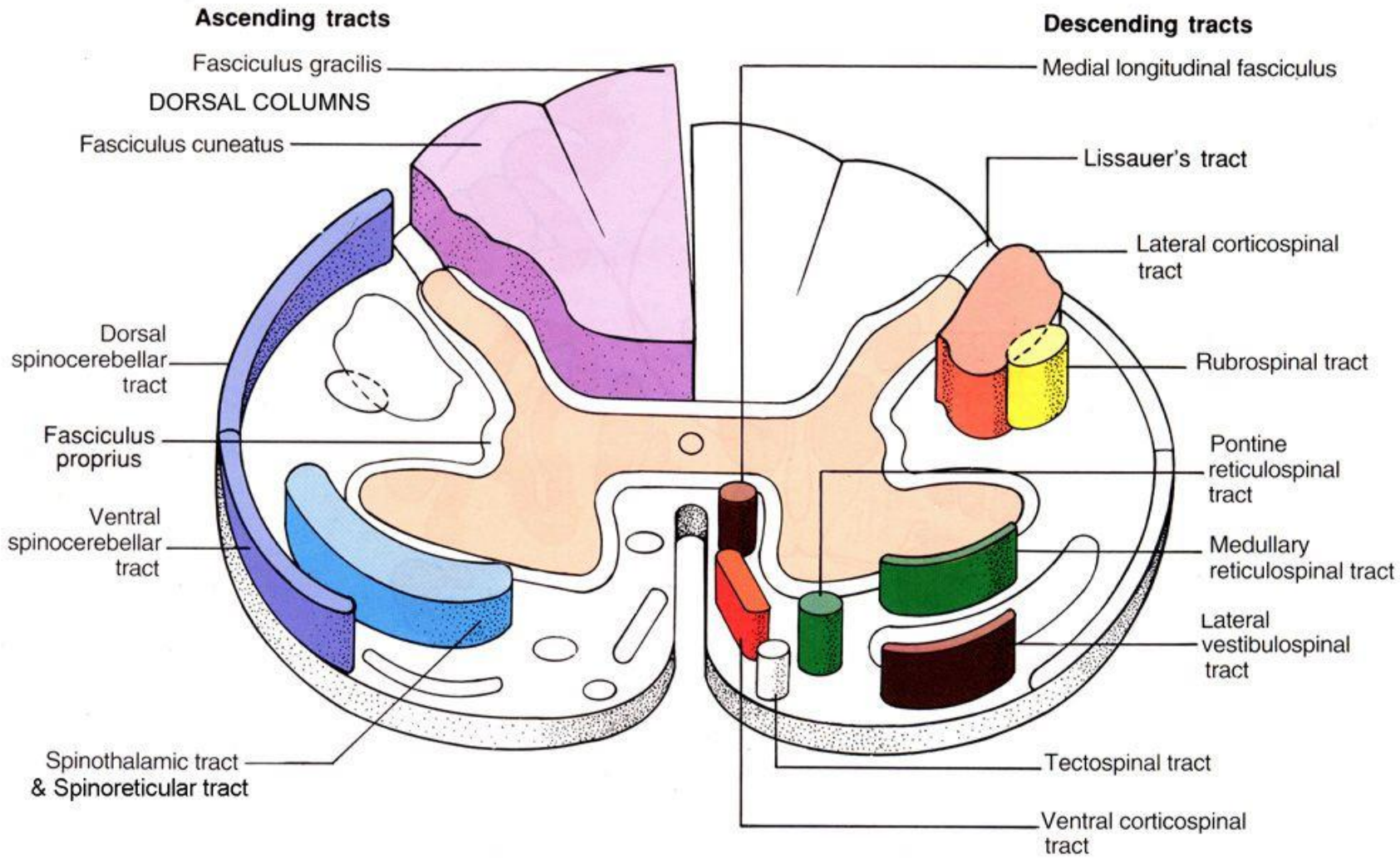


Corticospinal/corticobulbar tract

- The **corticospinal system** controls motor neurons and interneurons in the spinal cord
- The **corticobulbar system** controls brainstem nuclei that innervate cranial muscles
- originates in the motor cortex
  - capsula interna, crus cerebri (midbrain), pyramids of medulla oblongata – decussation (here it splits into two funiculi)
- **the primary pathway** that carries the motor commands that underlie voluntary movement
  - 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 corticospinal tract** (10% of axons) is responsible for the control of the proximal musculature
- both the lateral and anterior corticospinal tracts are crossed pathways; they cross the midline at different locations, however
- The percentage of axons in the corticospinal tract that innervate alpha motor neurons directly is greater in humans and nonhuman primates than in other mammals
  - presumably reflecting the increased manual dexterity of primates
- Damage to the corticospinal tract results in a permanent loss of the fine control of the extremities

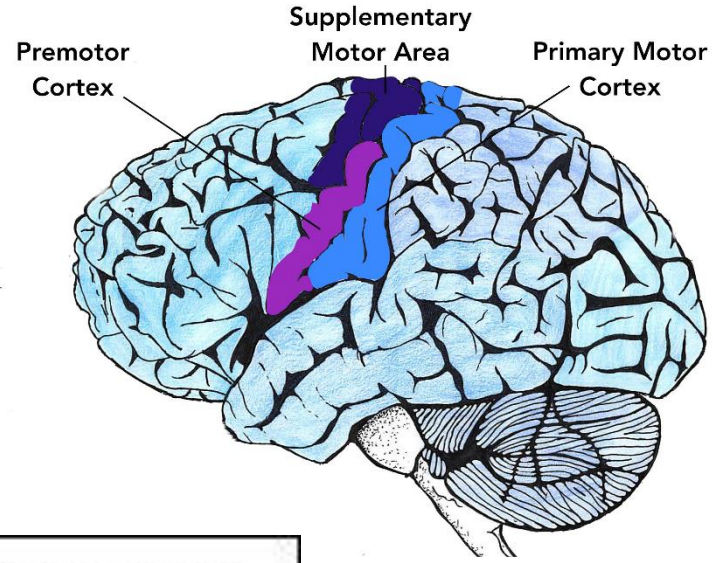


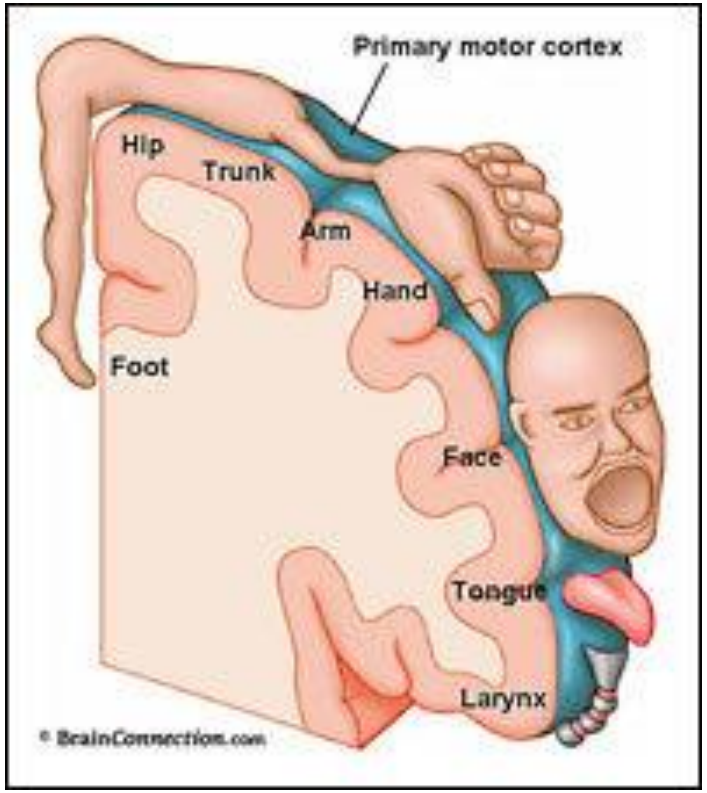
Overview of tracts in a spinal cord



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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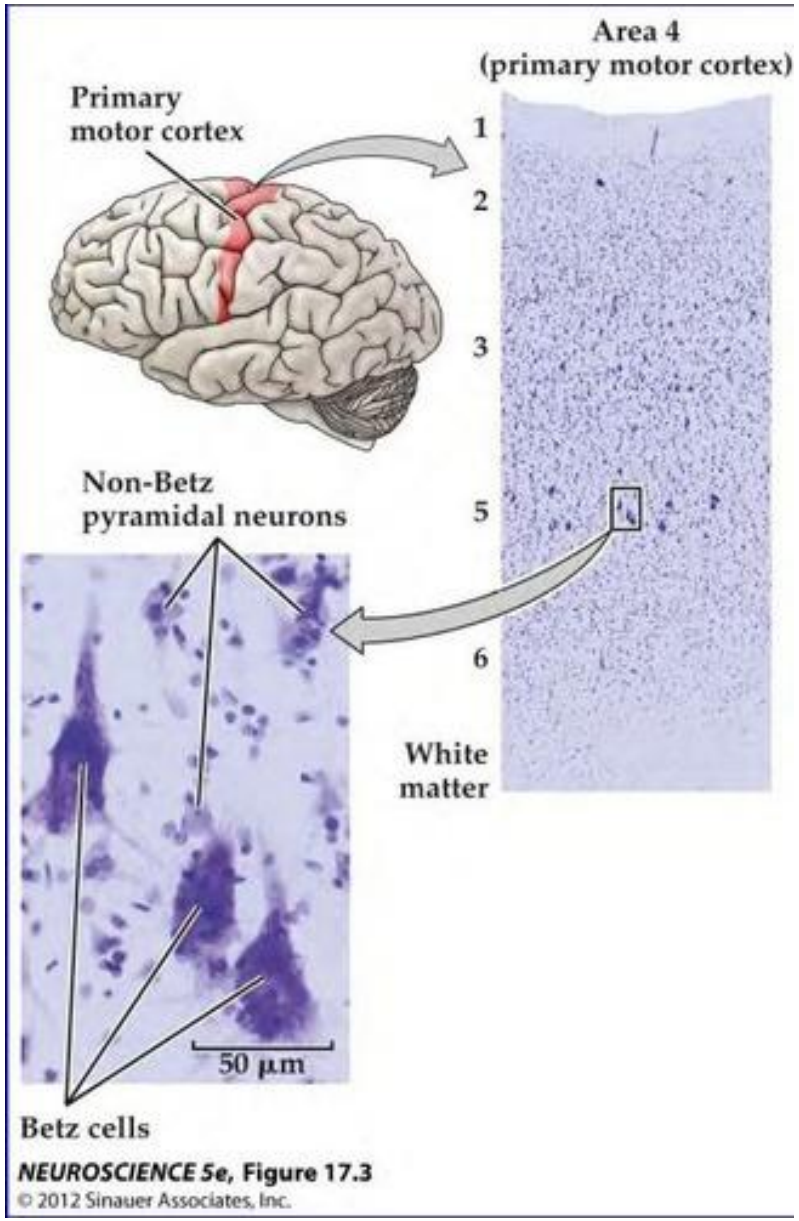
Cyto-architecture of the motor cortex

- brain cortex is very sensitive to hypoxia
- motor cortex even more
- pre-/peri-/ and early post-natal development is a vulnerable period
  - cerebral palsy
    - pre-term deliveries
    - perinatal asphyxia
    - postnatal (up to 3yrs of age) hypoxia
- adulthood
  - cardiac arrest
  - haemorrhage
  - stroke



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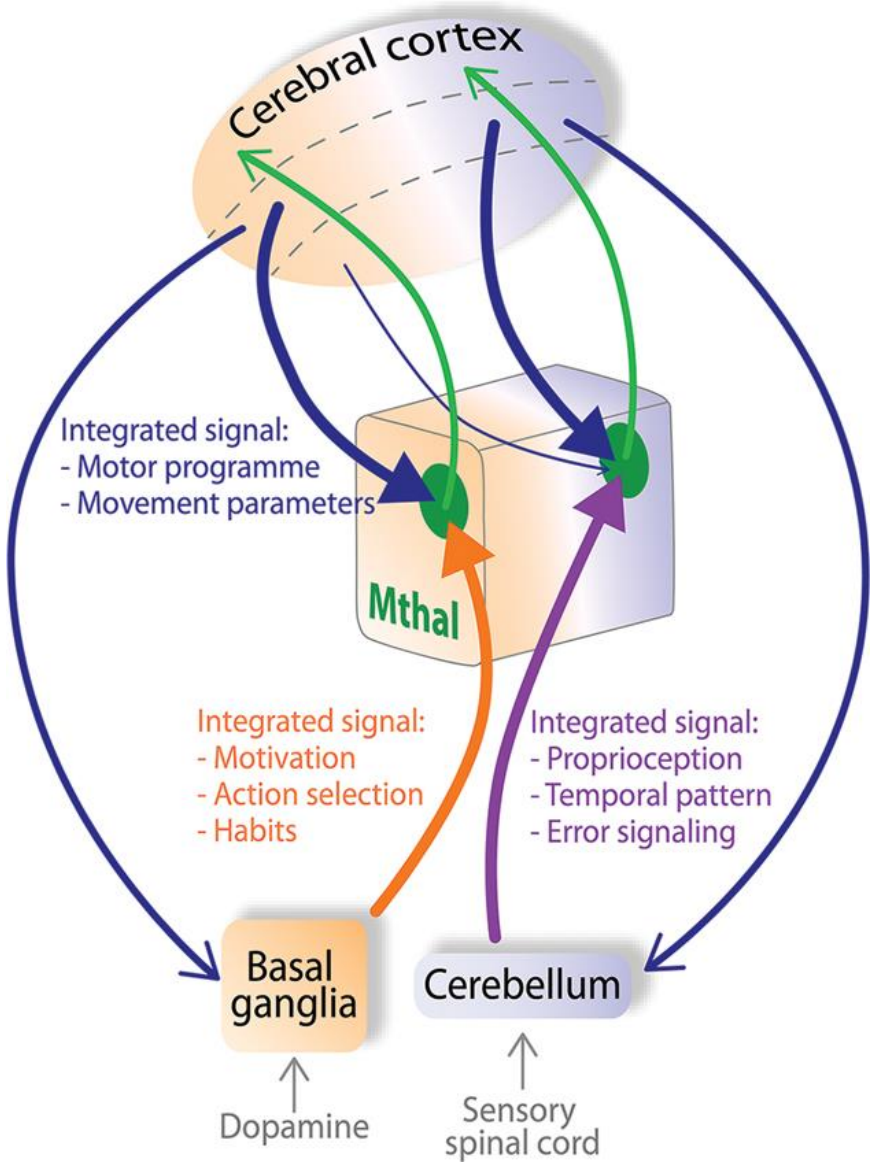
Cortical Afferents and Efferents and cytoarchitecture

- 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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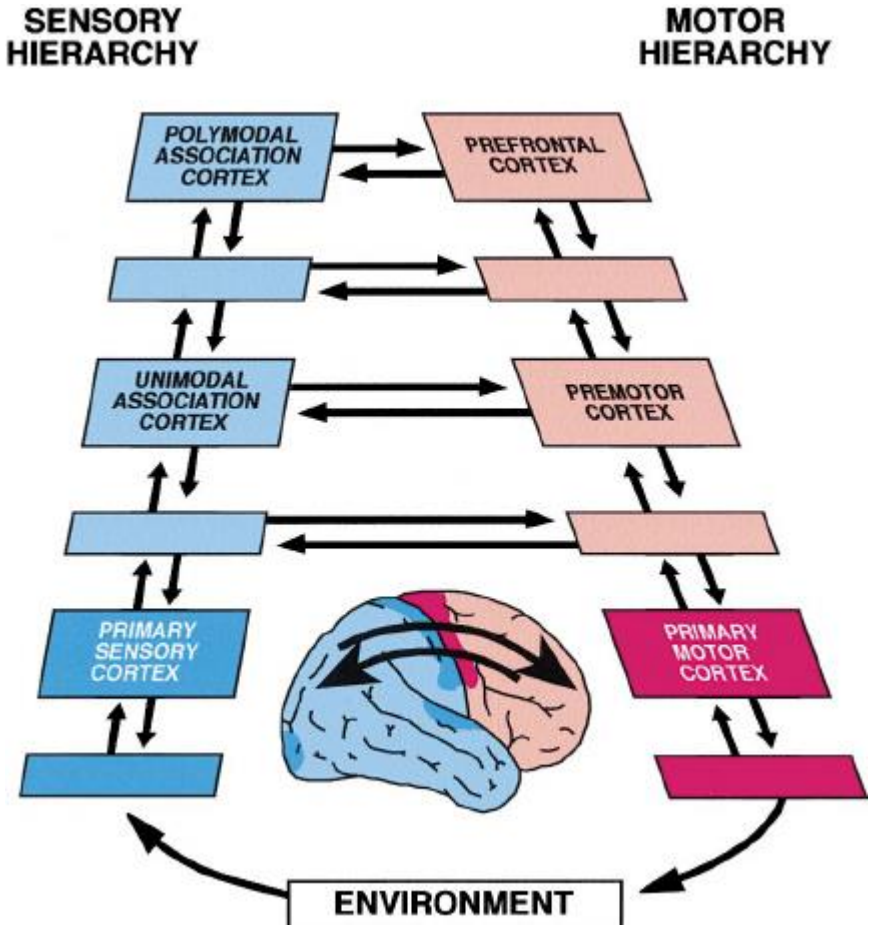
Level (4): Association cortex

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



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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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Paralysis

Upper and Lower moto neuron disease

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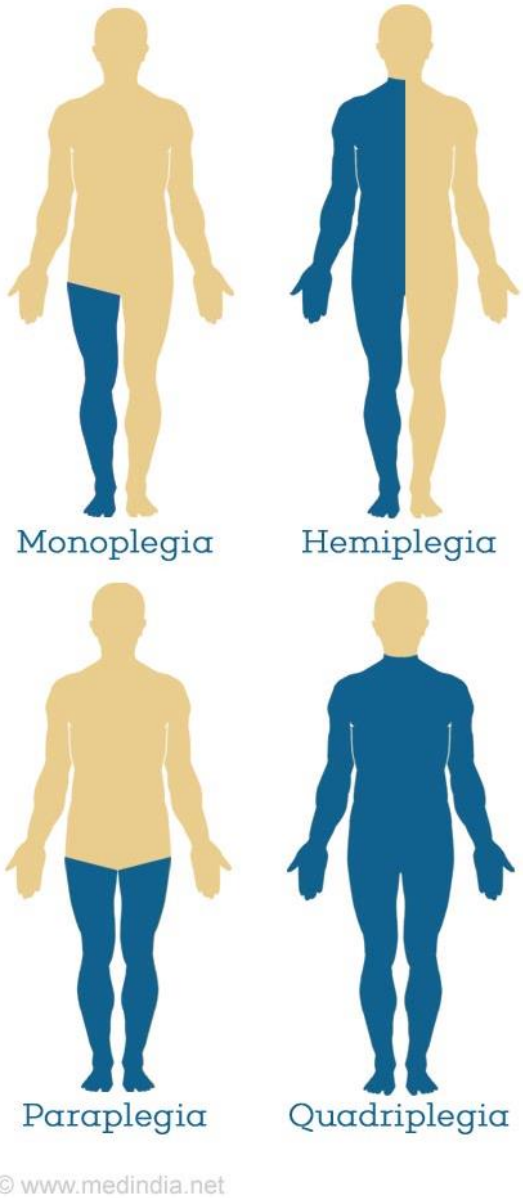
Paralysis (↓ voluntary muscle activity)

- loss of muscle function 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 **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
    - ↑ 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
    - ↓ muscle mass (atrophy), fasciculations and fibrillations
    - ↓ or no spinal reflexes



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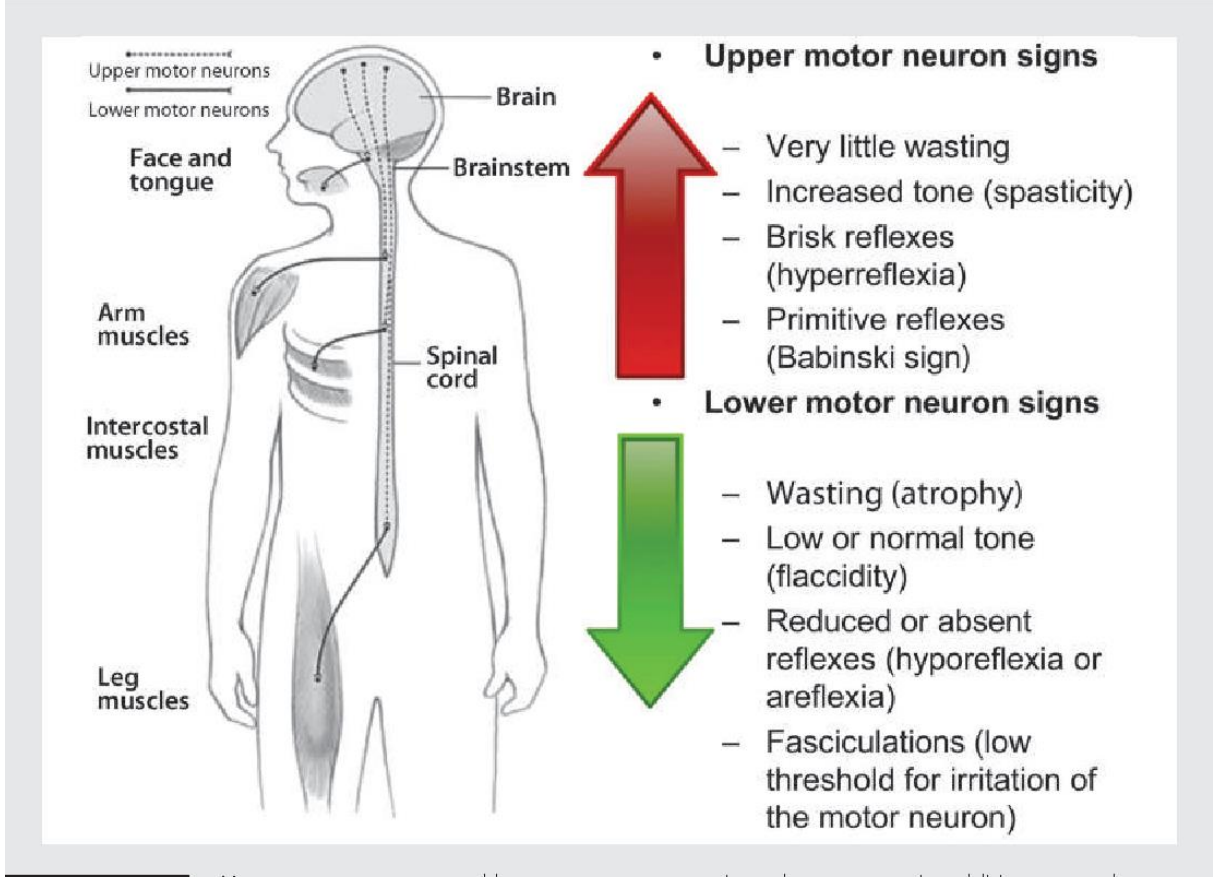
Etiology of paralysis

- 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)



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Selected examples of paralyses due to UMND or LMND

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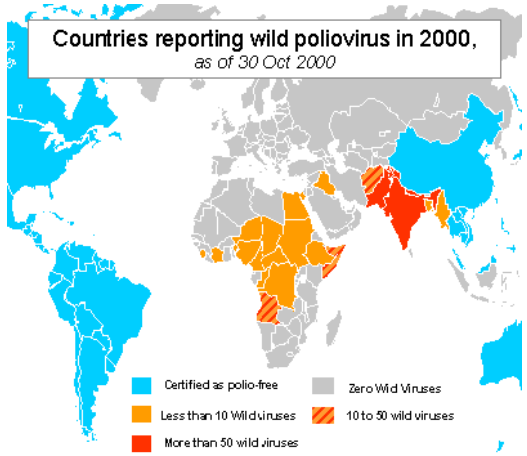
(1) Polio and the beauty of vaccination



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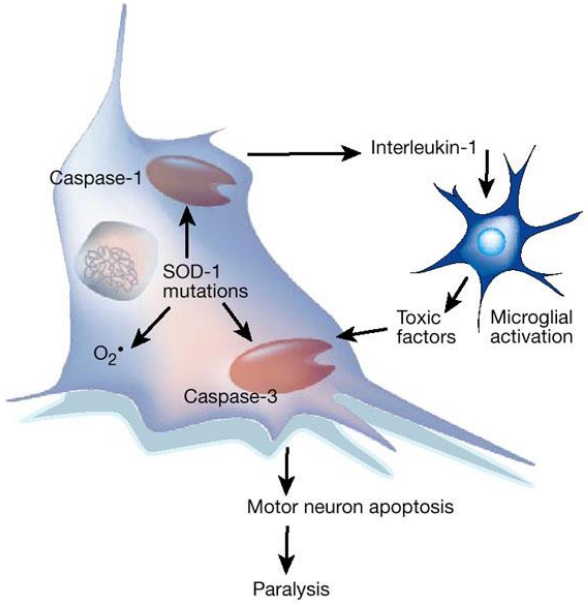
(2) Amyotrophic Lateral Sclerosis (ALS, Lou Gehring disease)

- 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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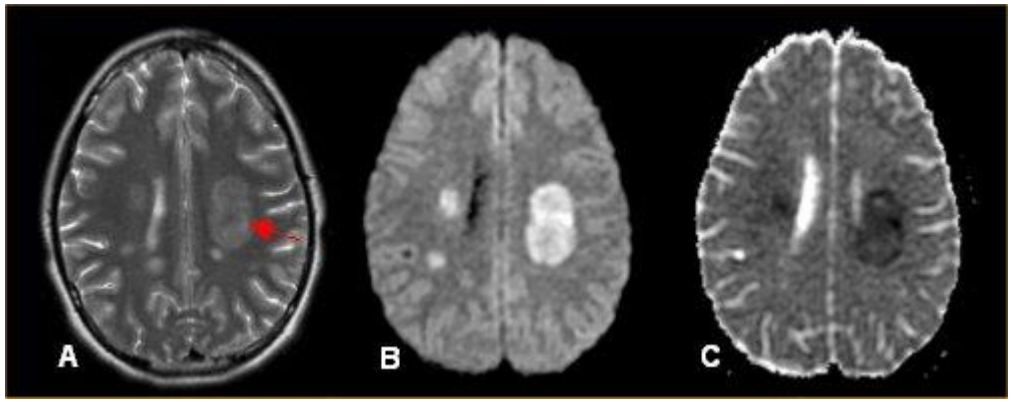
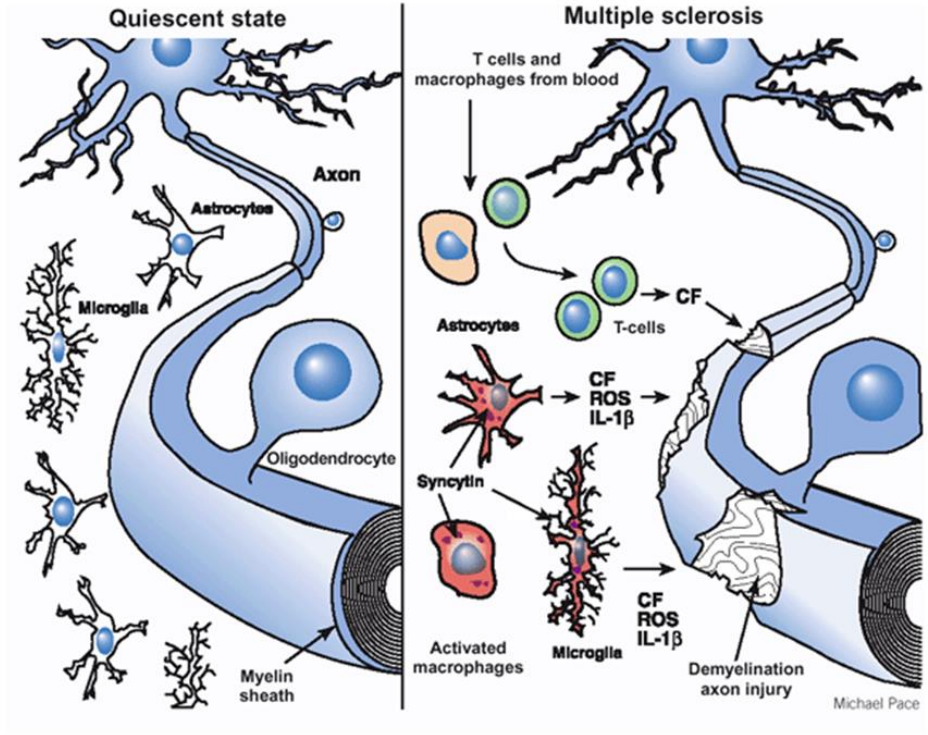
(3) Demyelinisation diseases - multiple sclerosis

- young adults (20 – 45), 2x more women, moderate regions of the Northern hemisphere
- etiology
  - genetic predisposition (MHC genes)
  - environmental triggers
- pathogenesis
  - myelin produced by oligodendrocytes permits rapid conductance
  - loss of myelin results in conduction abnormalities (decreased velocity to block)
  - autoimmune injury (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)
- 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
  - secondary progressive
  - primary progressive
- **Guillain-Barre syndrome**
  - post-inflammation peripheral polyneuropathy due to demyelinisation (Schwan cells)





(4) Spinal cord injury

- affects motor functions, spinal reflexes, afferent sensation and vegetative functions below the lesion
- **(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 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