Pathophysiology of nervous system II:
Control of motor function and its disorders – part 2

Role of basal ganglia and cerebellum (extrapyramidal system) in the control of movement

Disorders of BG (incl. Parkinson's and Huntington's diseases as examples)

Disorders of cerebellum

Neuromuscular junction and its disorders (myasthenia syndromes)

Muscle diseases (muscular dystrophy)

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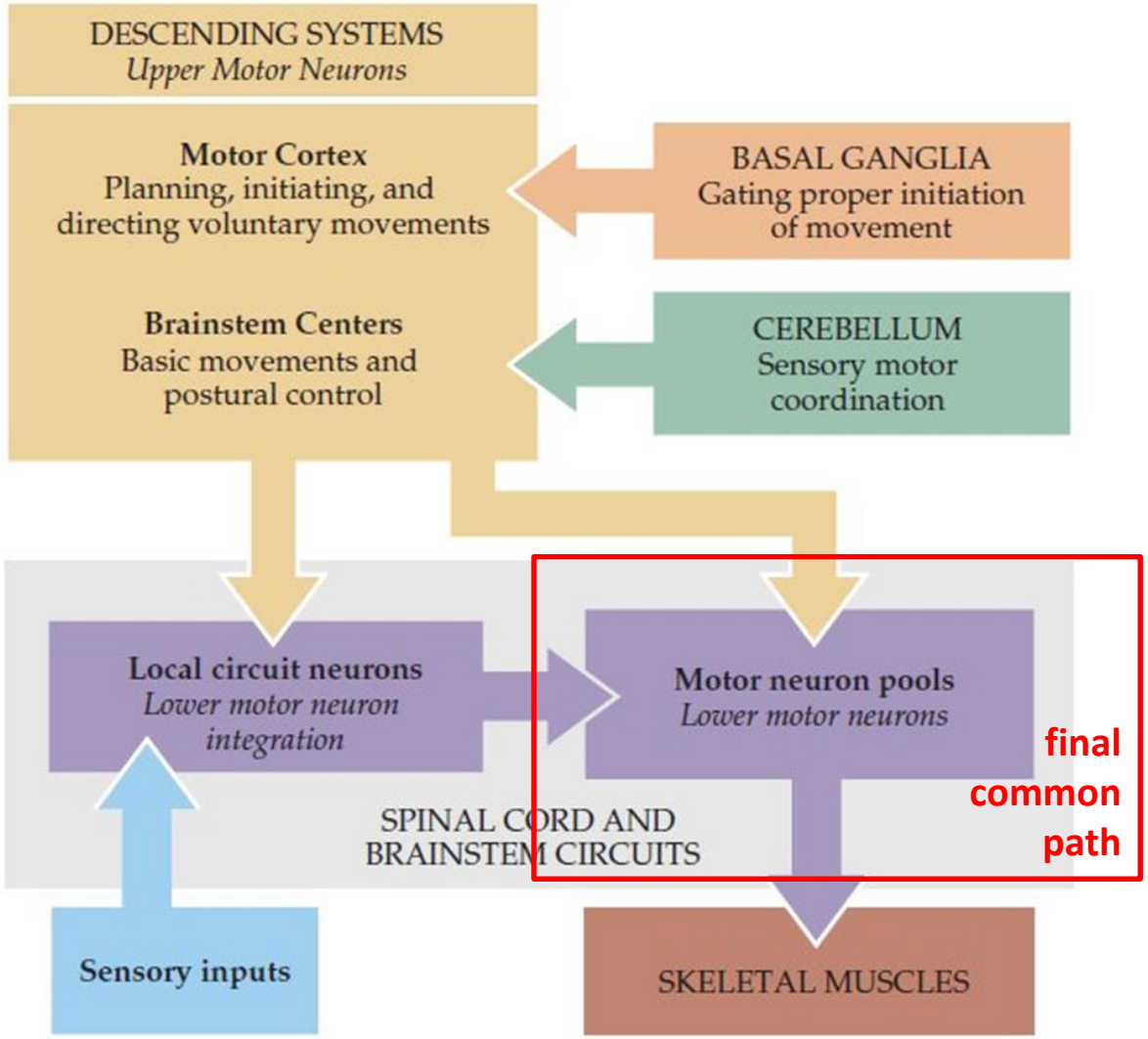
Functional Segregation and Hierarchical Organization

- (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**)
    - understanding of 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
    - i.e. **„go" signal**
  - 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
    - i.e. **micro-management of 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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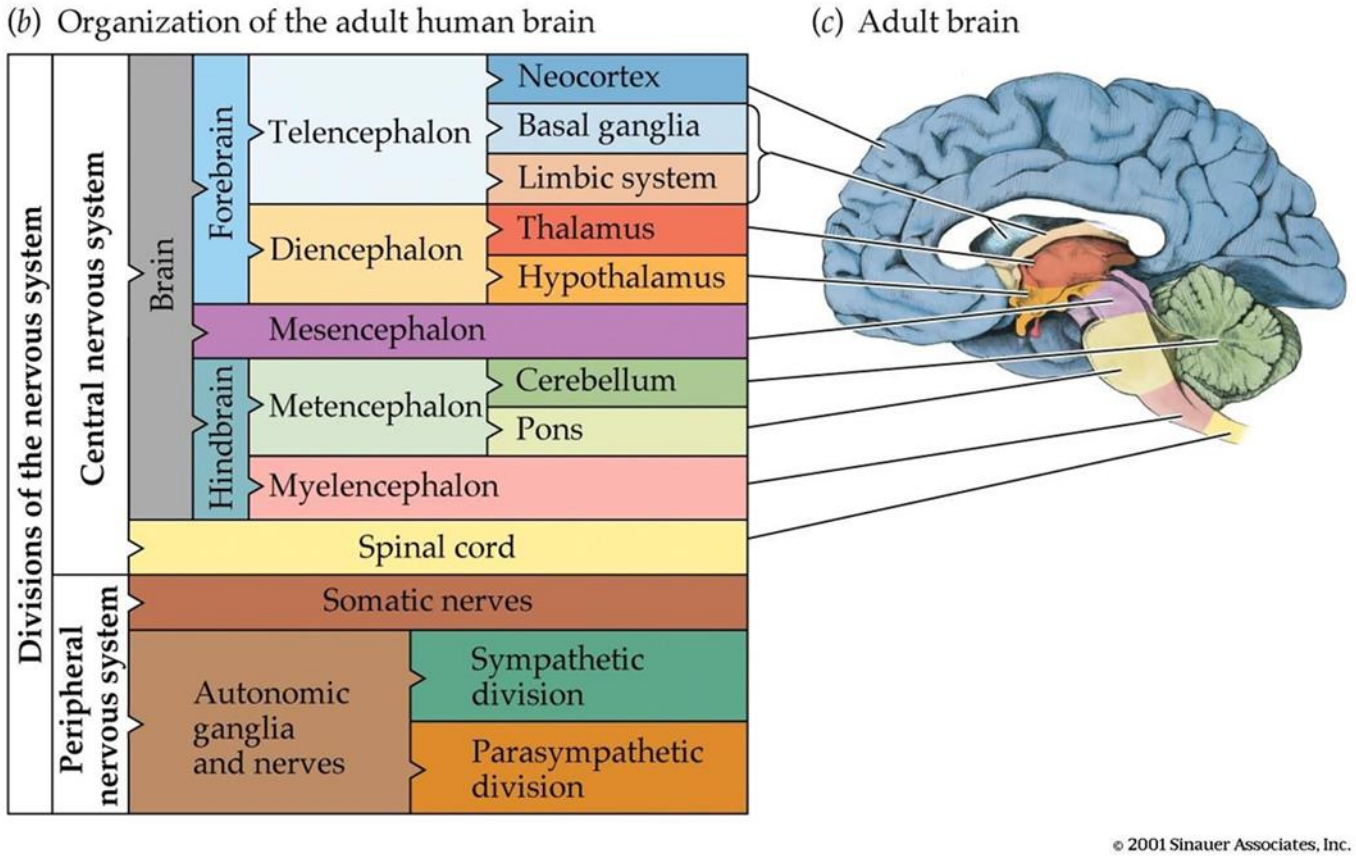
Anatomy and physiology of the NS in the BG context



- **peripheral nervous system**
  - spinal and cranial nerves
- **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**) incl. **BG**

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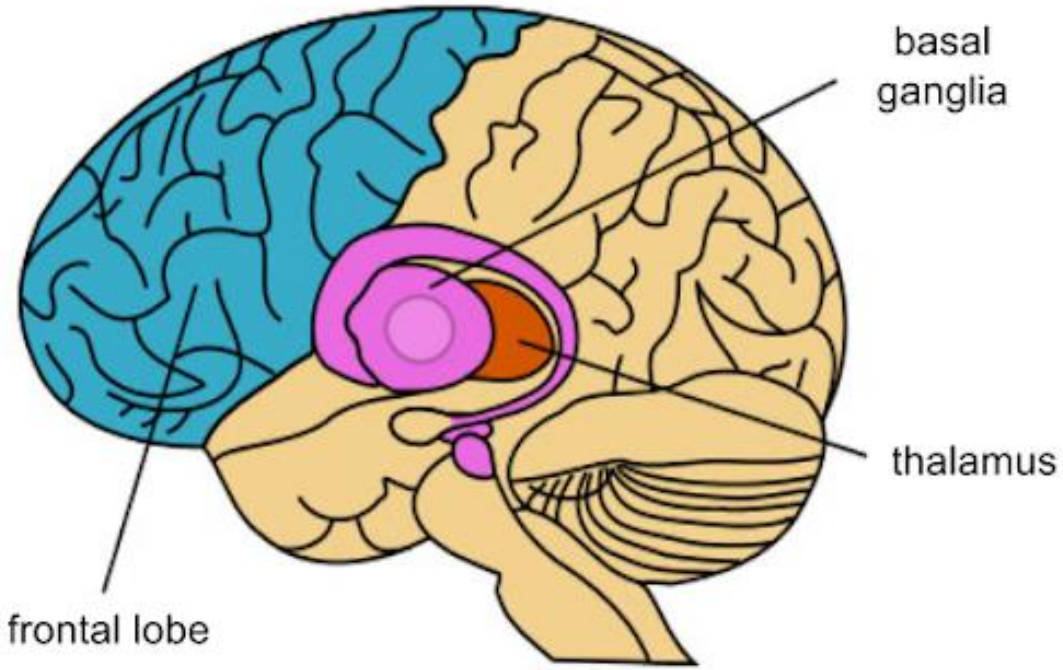
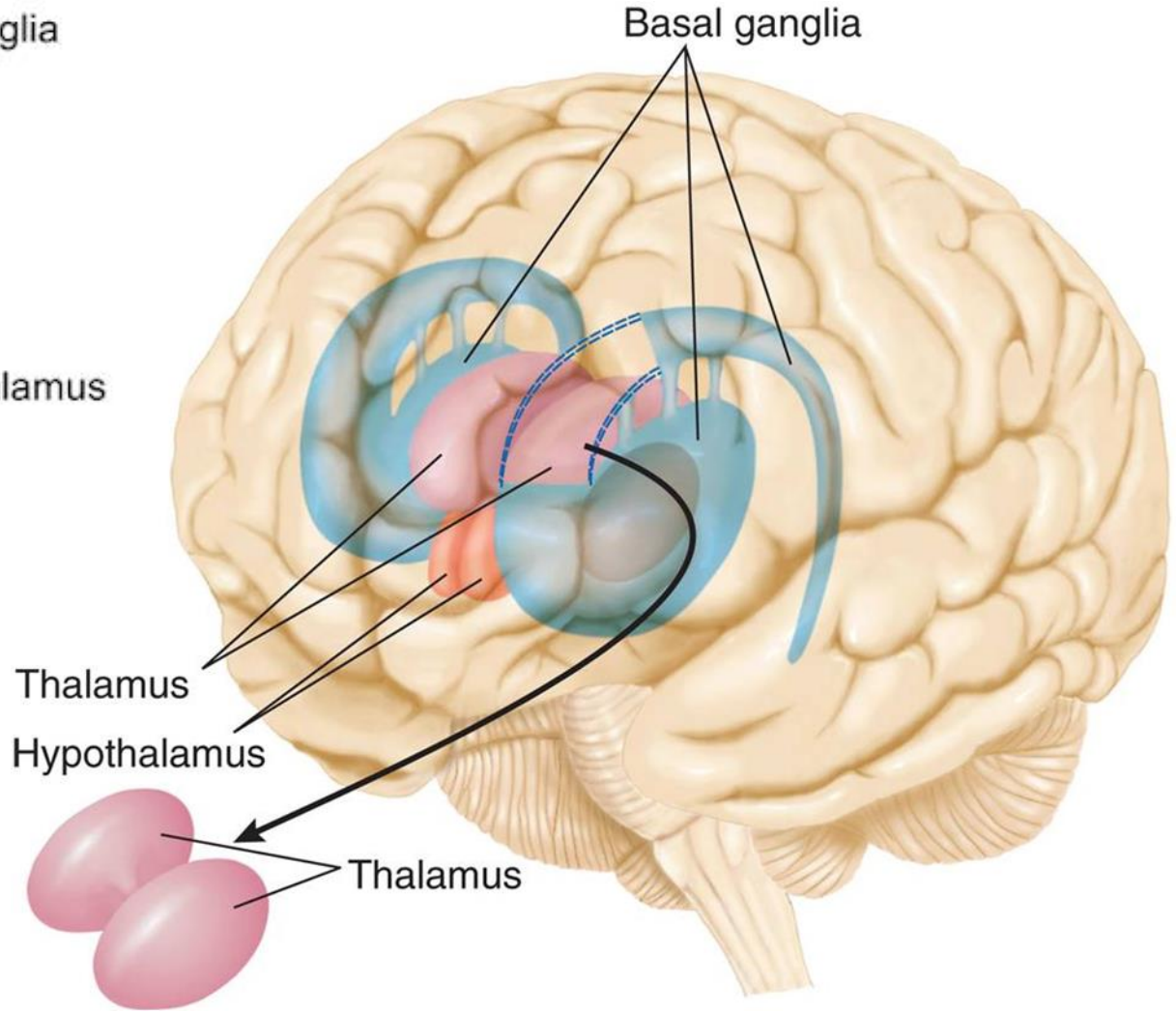
Anatomy of BG (should be basal nuclei in fact) and thalamus





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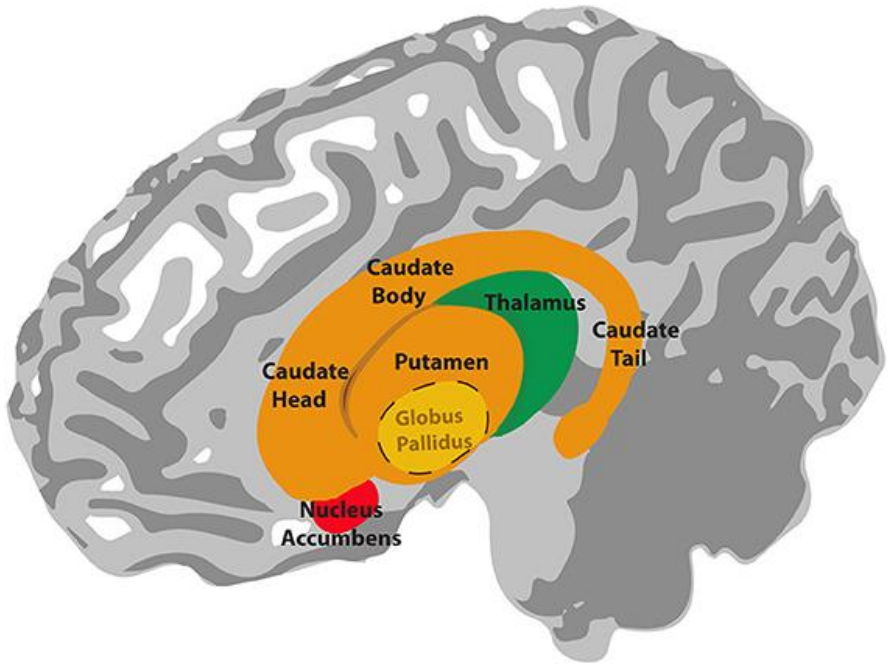
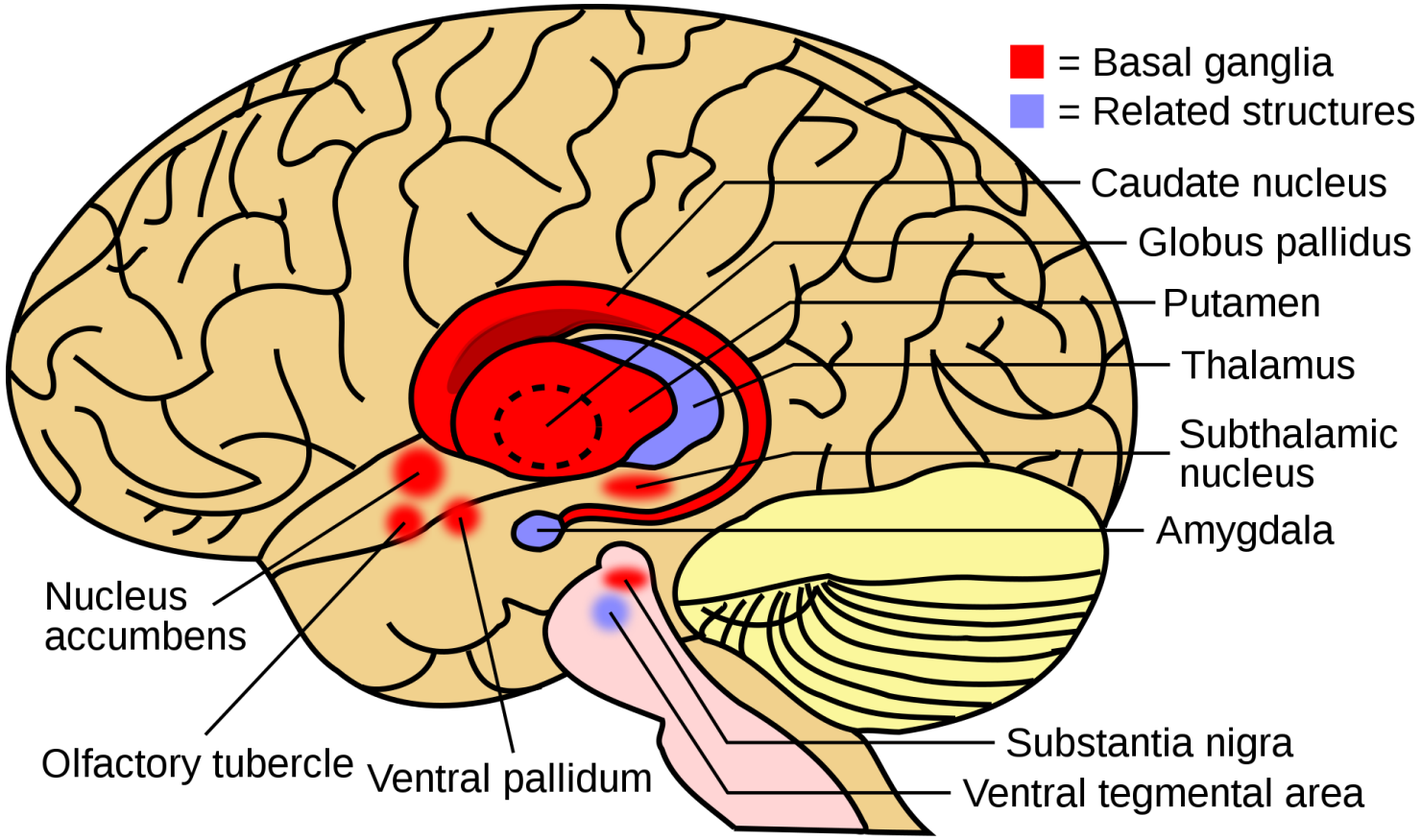
Divisions of BG (should be basal nuclei in fact)





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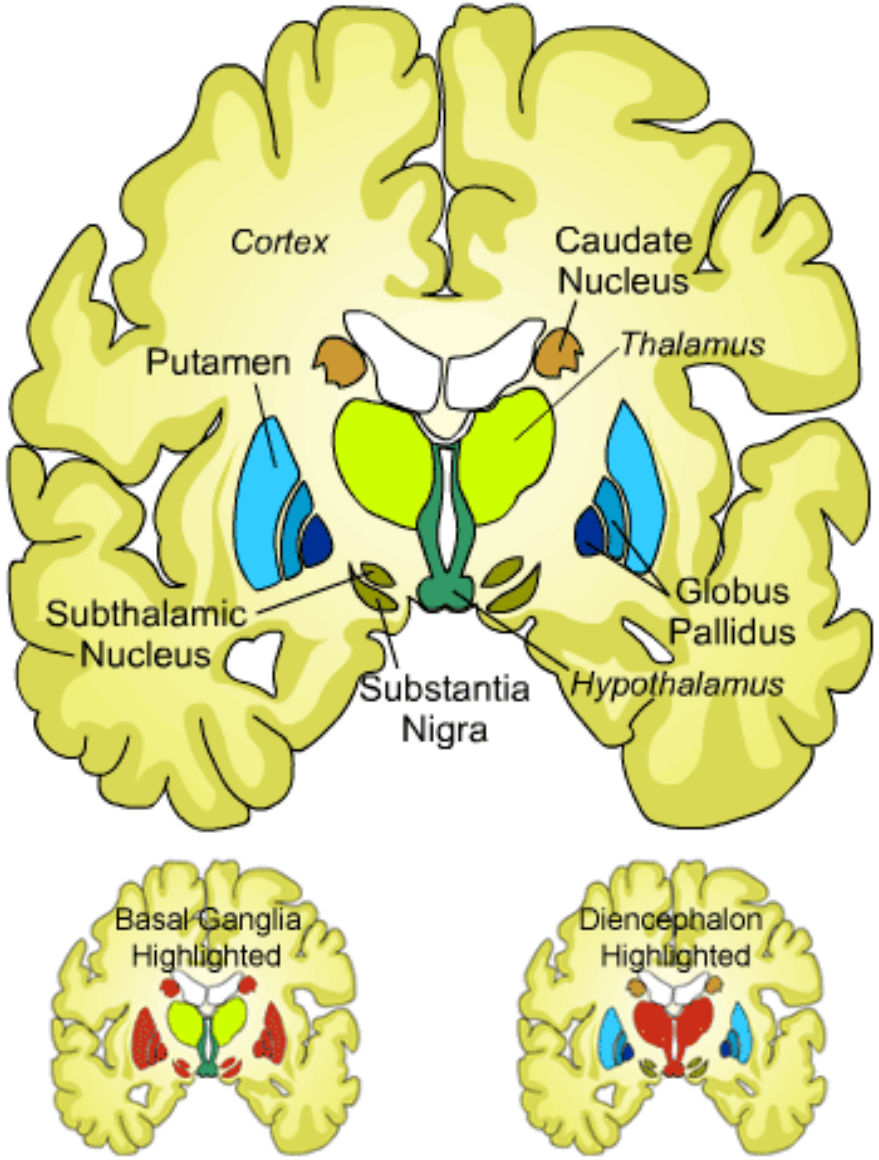
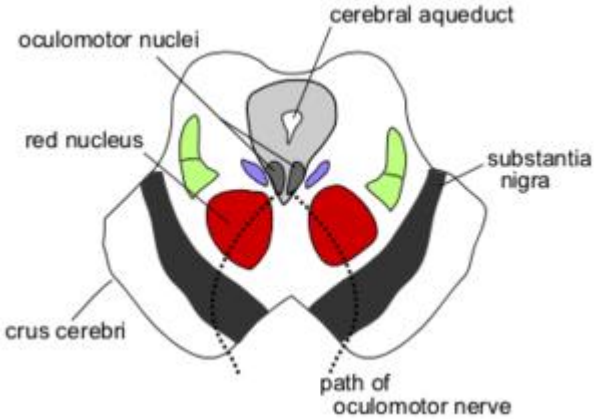
Divisions of BG (should be basal nuclei in fact)



- forebrain
  - telencephalon
    - **striatum**
      - caudate nucleus
      - putamen
    - n. accumbens = ventral striatum
    - **pallidum**
      - globus pallidus - internal segment (GPi)
      - globus pallidus - external segment (Gpe)
  - diencephalon
    - subthalamic nucleus
- midbrain = mesencephalon
  - substantia nigra
    - pars compacta
    - pars reticularis



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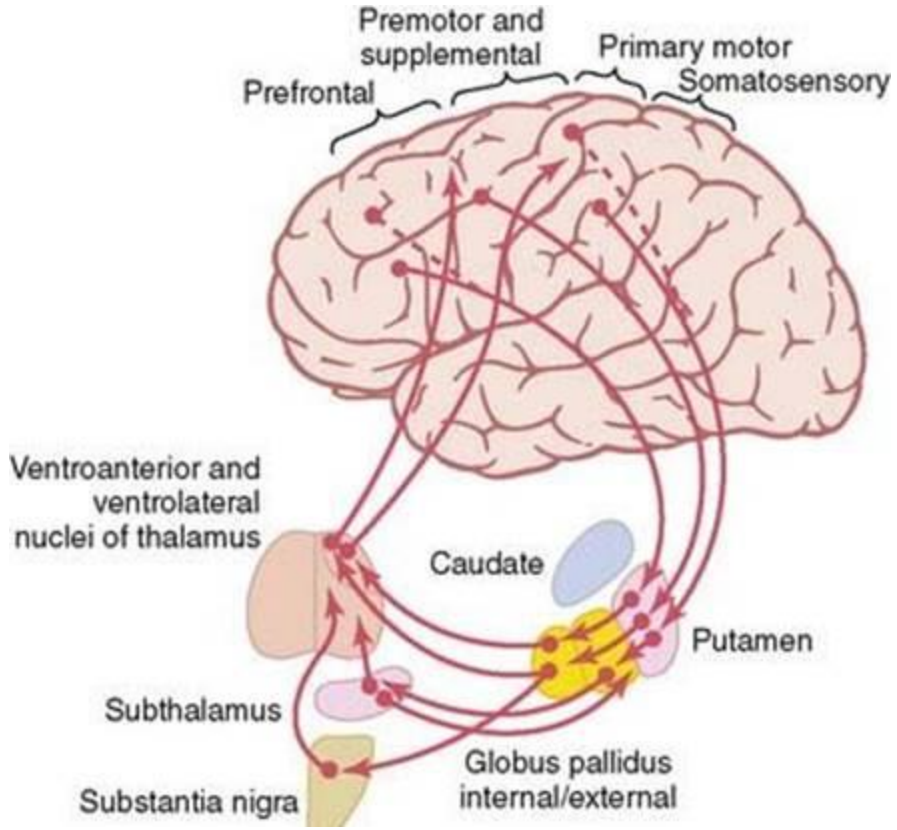
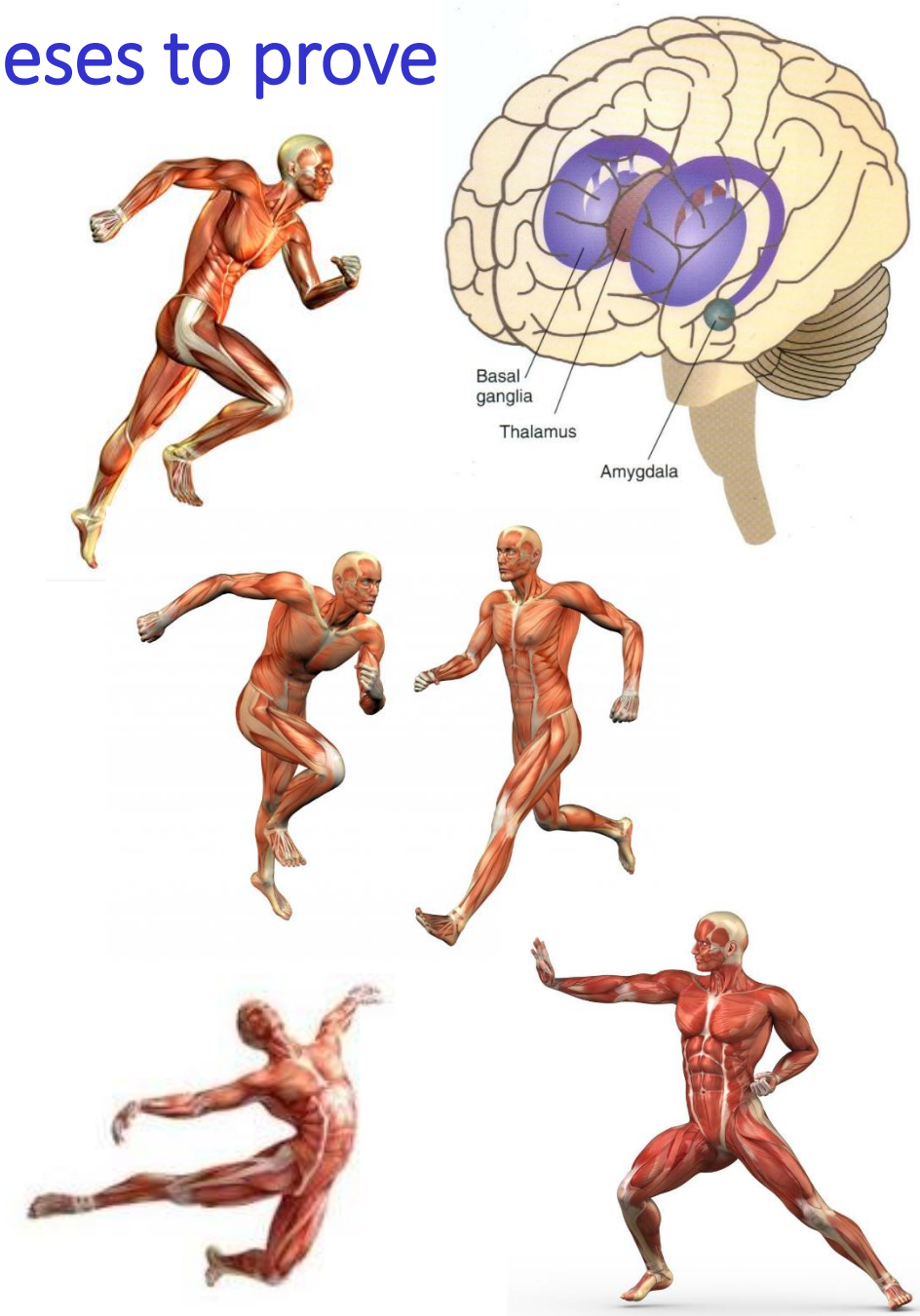
How are BG integrated into the control of movement - why we need them?

- We can perform many various movements with our limbs and facial musculature and certain motoric plan can be executed by multiple ways
  - but for given situation (plus experience, context, …) only one might be appropriate
  - we are choosing best one with the help of BG
- How does the BG receive information above the desired/planned movement?
  - be **widespread connections with cerebral cortex**
- How does the BG output influence the movement?
  - via **motoric thalamus**
    - BG execute an **inhibitory control over the motoric thalamus**
    - this keeps our movement under the check
      - temporary removal of the inhibition (= **disinhibition**) allows to perform optimal movement and not all sorts of unwanted and competing movements
- Therefore, **BG operate in the circuit of cerebral cortex → BG (multiple processing) → thalamus → cerebral cortex**
  - there are also outputs to brainstem

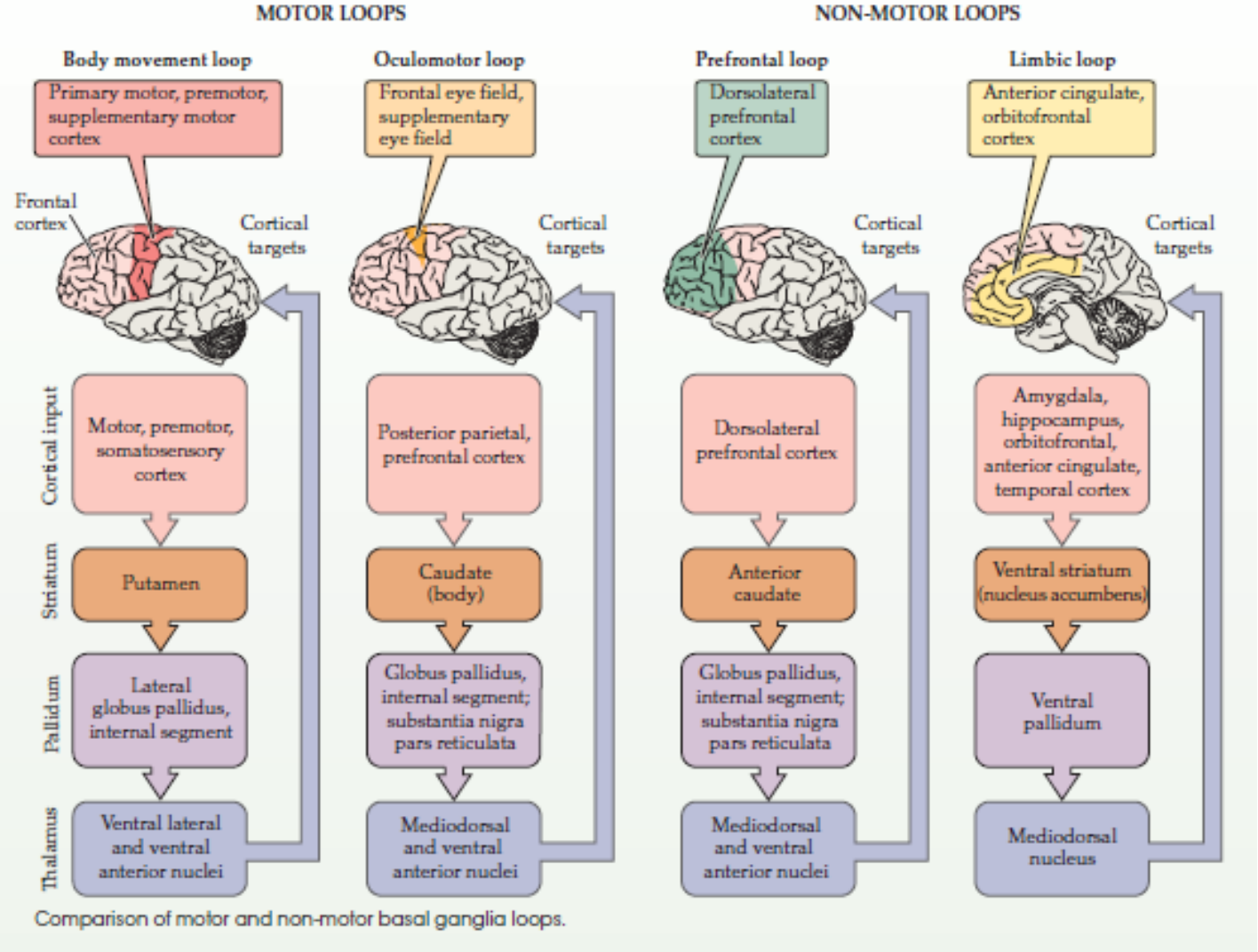


BG functions – still quite a lot of hypotheses to prove

- (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, appropriateness and smoothness
  - influence on and the modulation of 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 velocity of movement
  - **BG are heavily inter-connected with cortical structures and brainstem**
    - see further



BG process several parallel cortico-basal ganglia-thalamo-cortical loops (CBGTC loops)



- clinical relevance to
  - **motor disorders**
    - hyperkinetic – hypo-dystonic movement disorders
      - such as Huntington's disease
    - hypo-/akinetic – hypertonic movement disorders
      - such as Parkinson's disease
  - **mental disorders**
    - of control
      - such as attention deficit hyperactivity disorder (ADHD)
    - obsessive–compulsive disorder (OCD)
    - Tourette syndrome
    - addictions

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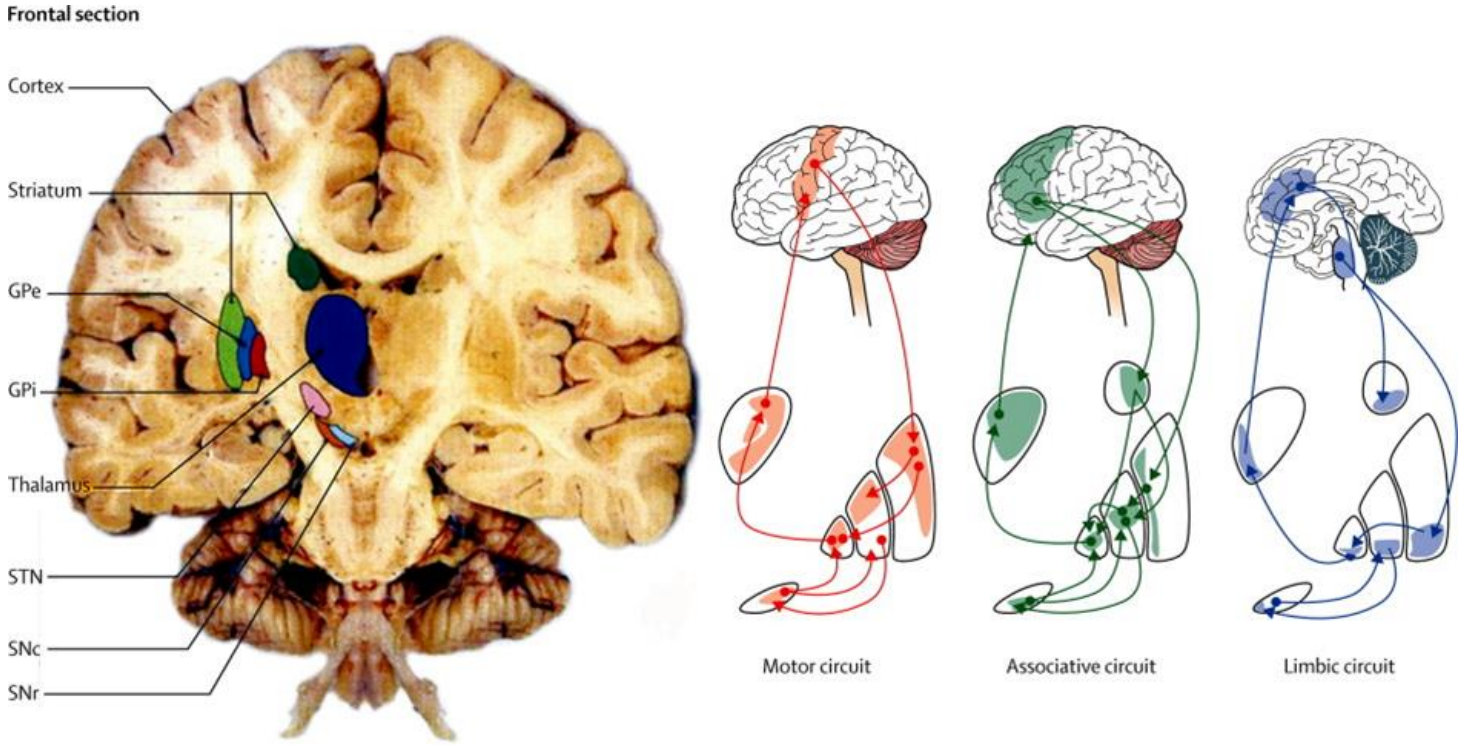
BG functions – still quite a lot of hypotheses to prove



- BGs are involved in cognitive functions
  - there are a number of cortical loops through the BG that involve prefrontal association cortex and limbic cortex
  - the loops comprise the motor, associative, and limbic domains, which respectively transit through the posterior, anterior, and ventral striatum, thus segregated functionally and anatomically
  - 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
- 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

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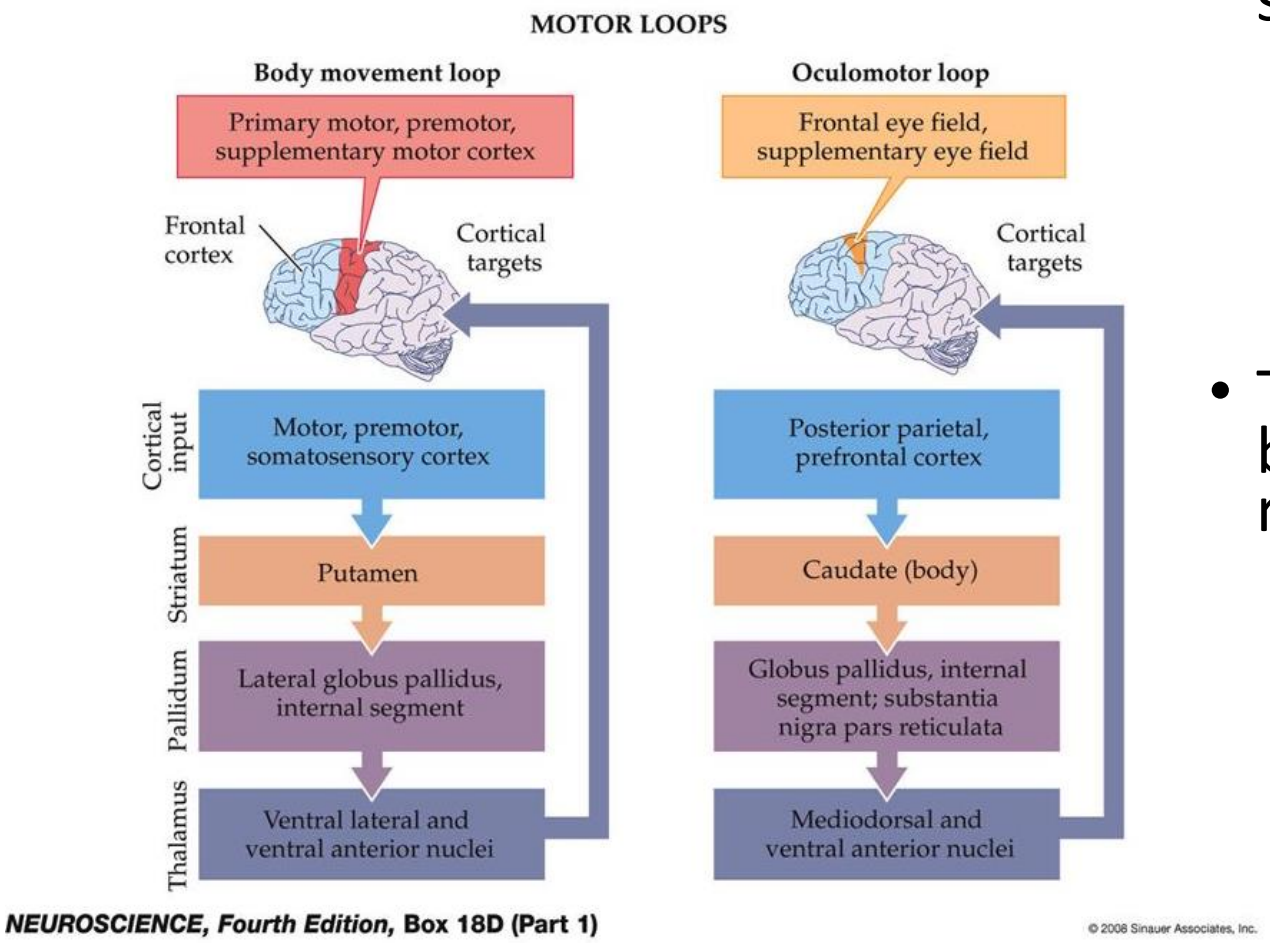
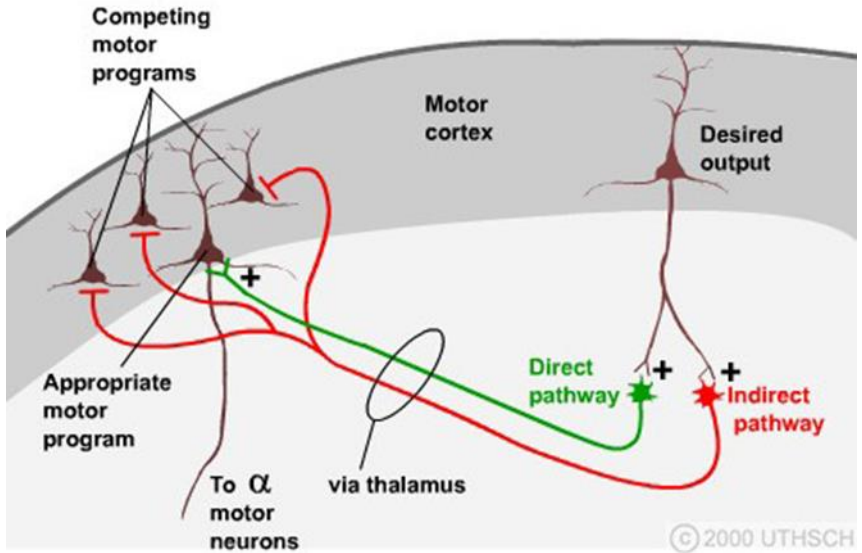
BG loops controlling body movements

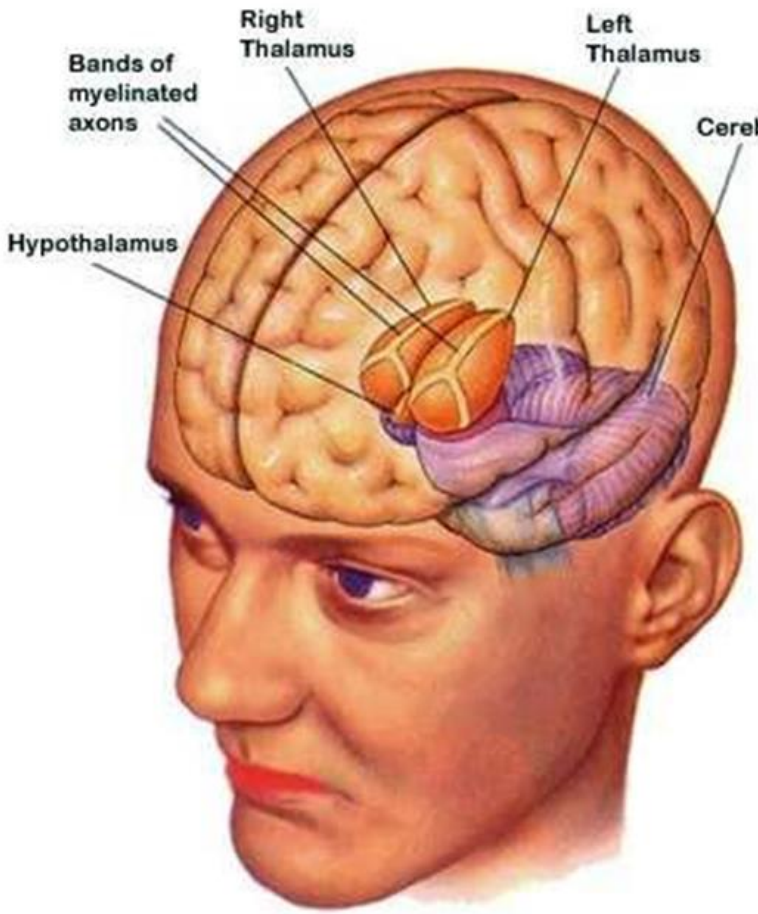


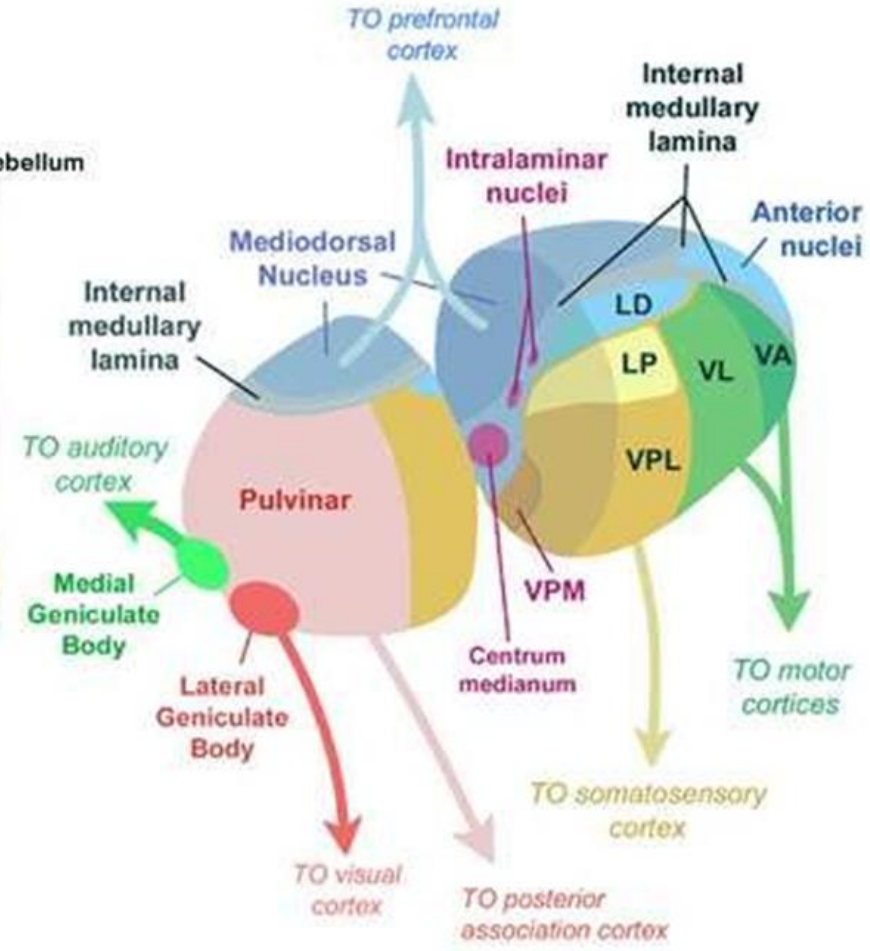
- BG select/modulate motor programs stored in the motor cortex
  - BG and motor cortex form a processing loop whereby the basal ganglia enables **initiation of the proper motor program** stored in motor cortex circuits via the **direct pathway** and inhibits competing motor programs via the **indirect pathway**
- The proper motor programs are selected based on the desired motor output relayed from cortex



Thalamus

- an ovoid, paired grey matter structure found in the centre of the brain, just superior to the brainstem
- each side of the thalamus contains six groups of nuclei
  - anterior nuclei
  - lateral nuclei
  - medial nuclei
  - intralaminar nuclei
  - paraventricular (midline) nuclei
  - reticular nucleus
- The thalamic nuclei relay and modulate information incoming from the periphery to the cerebral cortex.
  - almost all ascending neural pathways synapse within a thalamic nucleus, where the information is sorted, integrated, and analysed before sent further to the cerebral cortex
- This fact makes the thalamus a so-called "**gateway**" to the cerebral cortex for limbic, motor, and all sensory modalities besides olfaction, including vision, hearing, taste, and somatic sensation





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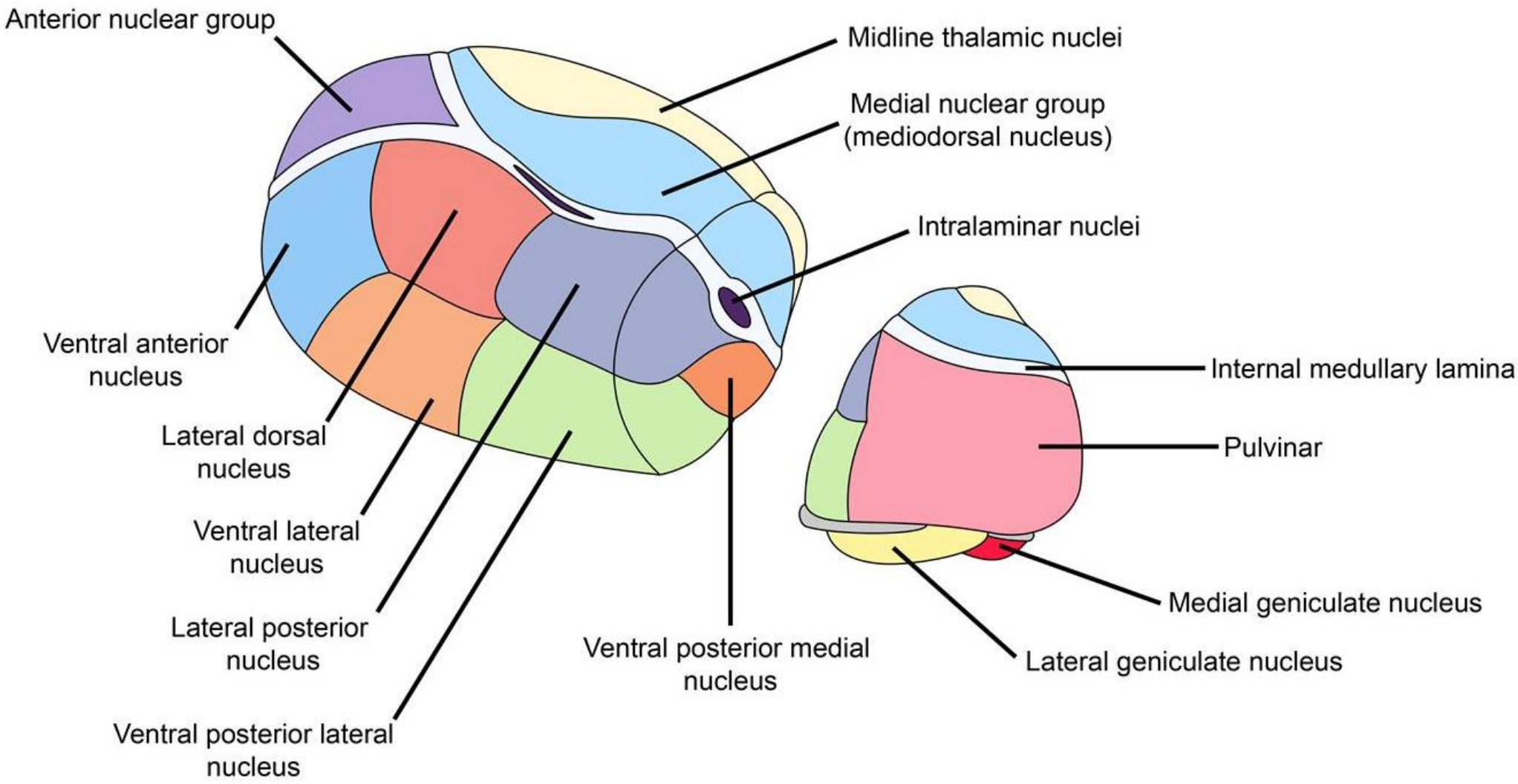
Thalamus – „motoric “ nuclei related to movement



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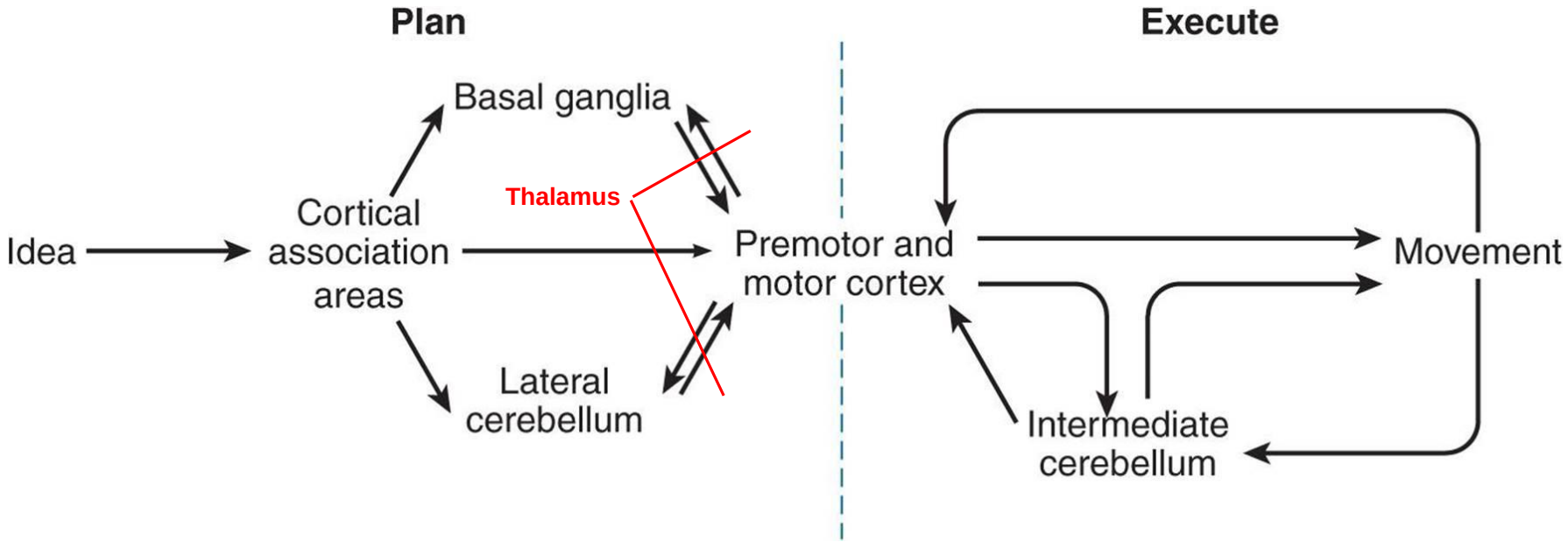
Summary of levels (5-6): Control of voluntary movement



- Commands for voluntary movement originate in cortical association areas
- The cortex, basal ganglia, and cerebellum work cooperatively to plan and optimise 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 smoothen the movement

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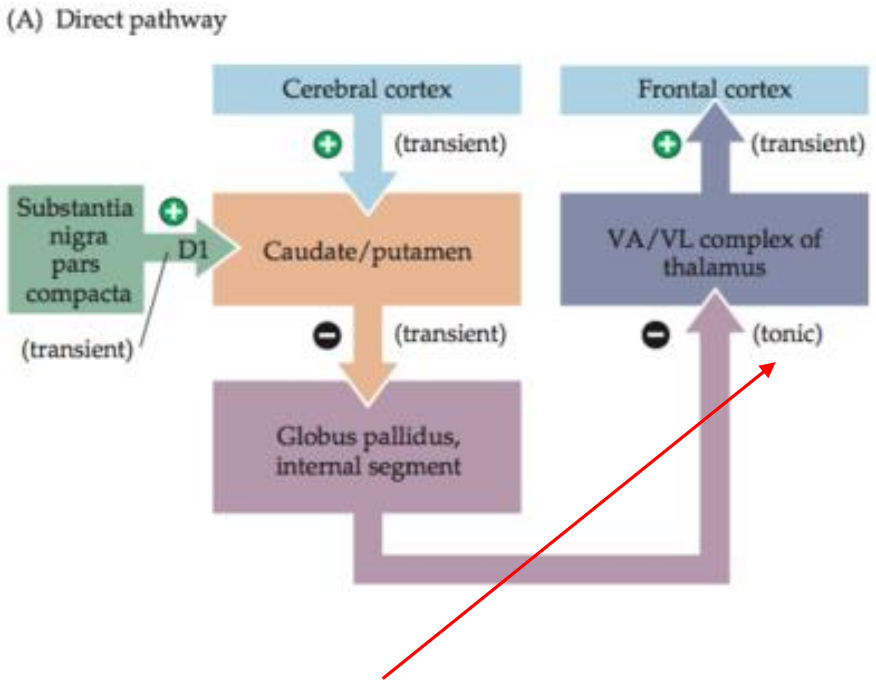
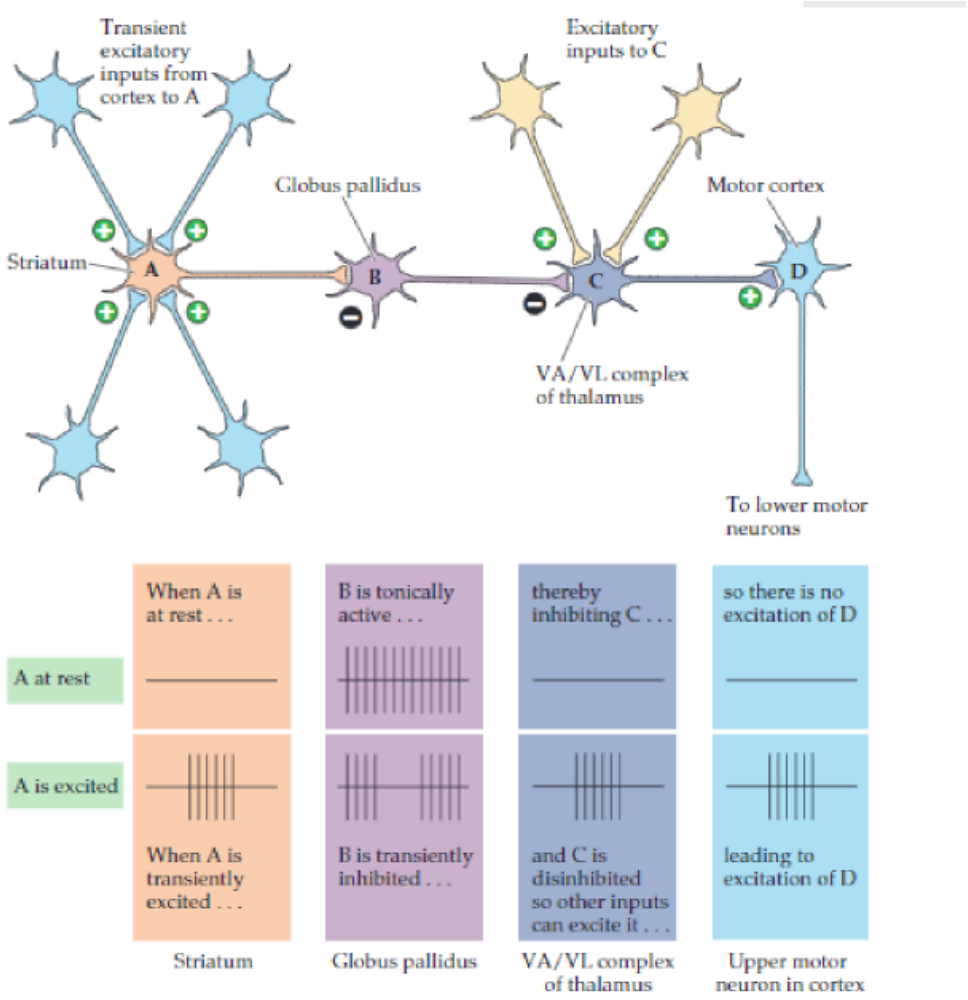
Direct pathway through BG and disinhibition of thalamus





- **GPi has a tonic** (= permanent) **inhibitory effect** on thalamus and therefore cerebral cortex
  - should we move, this inhibitory effect has to transiently removed (inhibited)
- positive feed-back
  - 2nd and 3rd neurons/ connections are inhibitory, therefore inhibition of inhibition (= **disinhibition**) causes excitation

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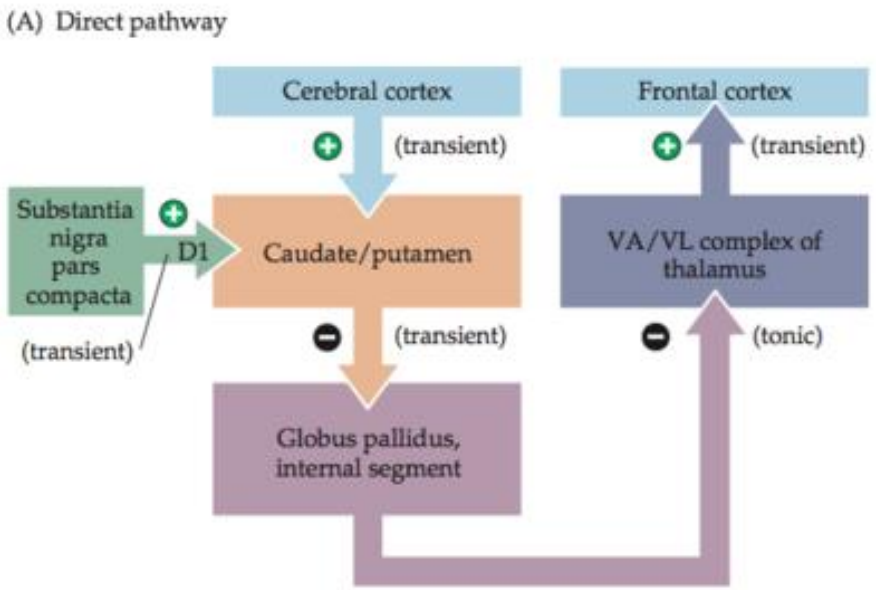
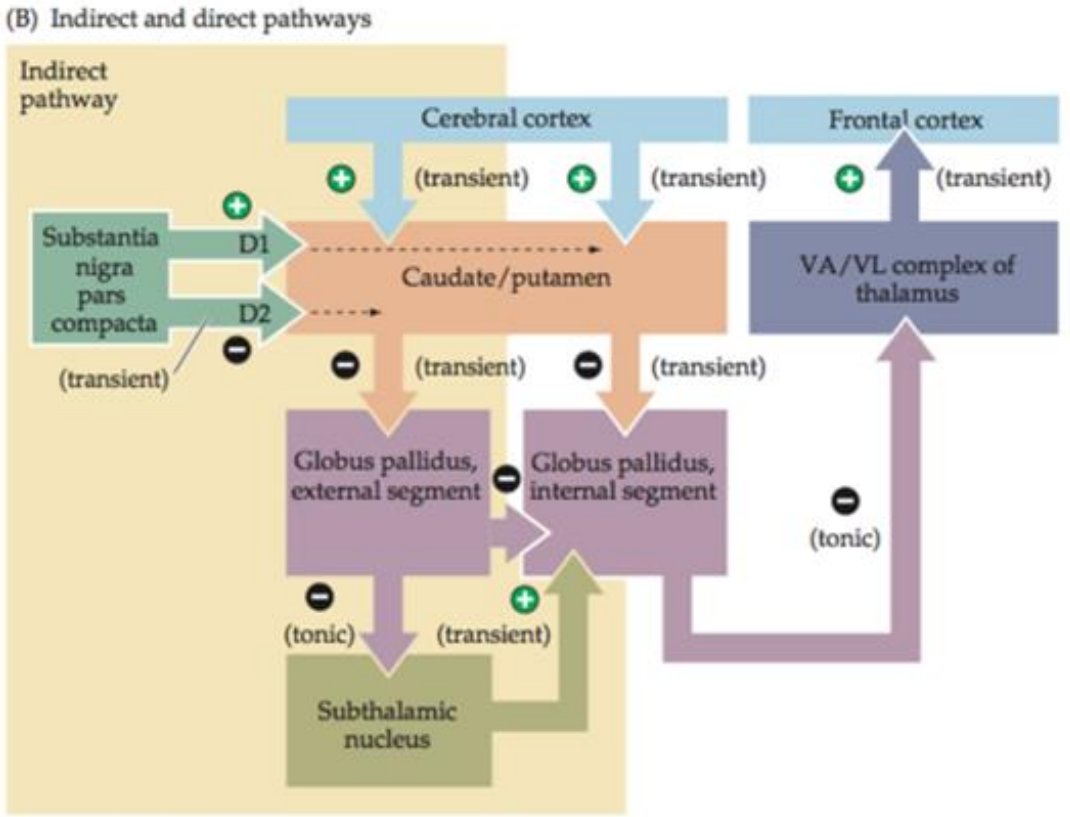
Direct (+) vs. indirect (–) pathways through BG





- **GPi has a tonic** (permanent) **inhibitory effect** on thalamus and therefore cerebral cortex
  - should we move, this inhibitory effect has to transiently removed
- positive feed-back
  - 2nd and 3rd neurons/ connections are inhibitory, therefore inhibition of inhibition (= **disinhibition**) causes excitation

- **reinforcement of tonic inhibitory effect of GPi** on thalamus and therefore cerebral cortex
  - negative feed-back
    - 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

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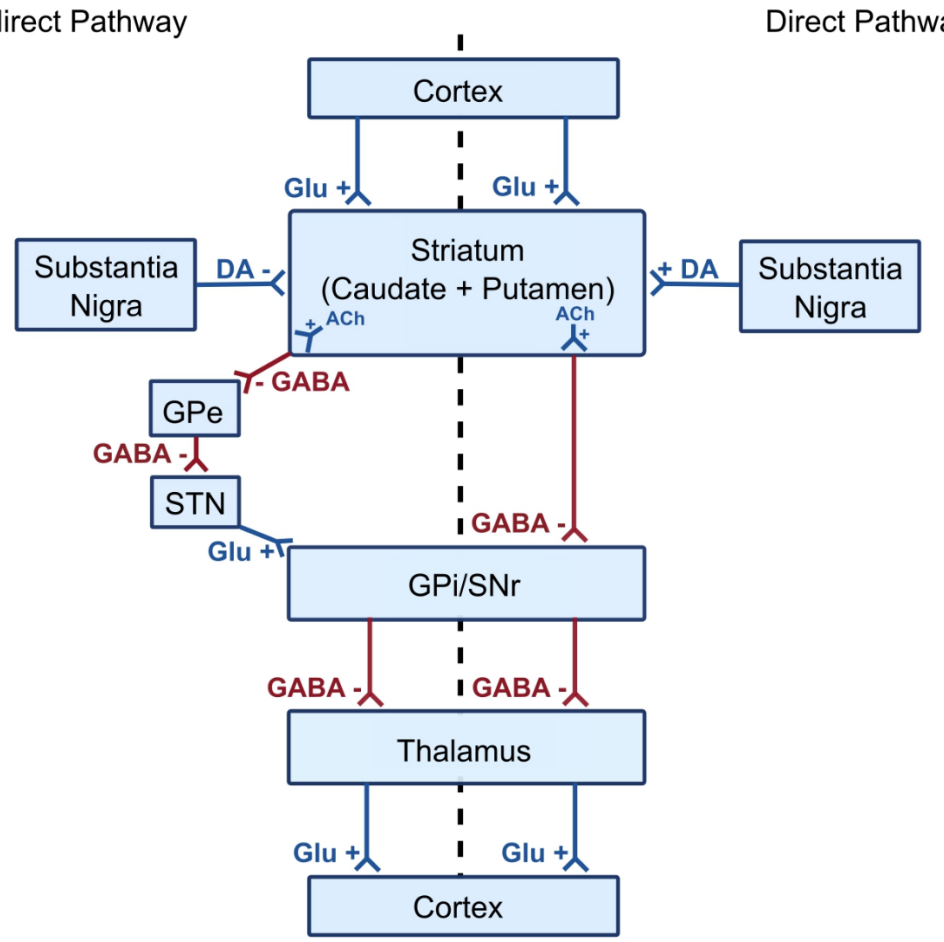
The critical role of dopamine in the activity of BG



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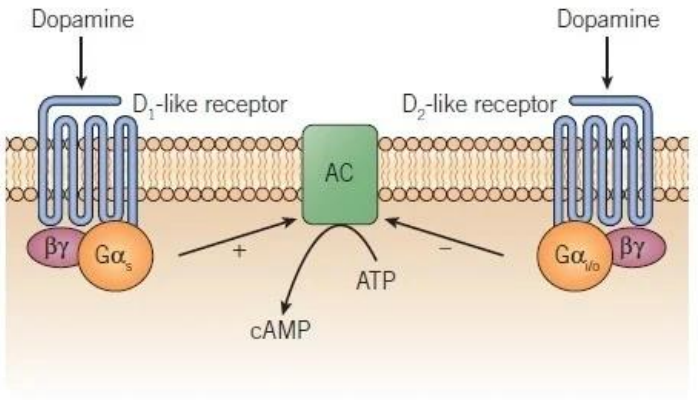
- These two pathways have **opposite net effects** on thalamic target structures
  - how come we ever move?
  - the normal functioning of the basal ganglia apparently involves a proper balance between the activity of these two pathways
- the direct pathway
  - the net effect is the cortex exciting (positive 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



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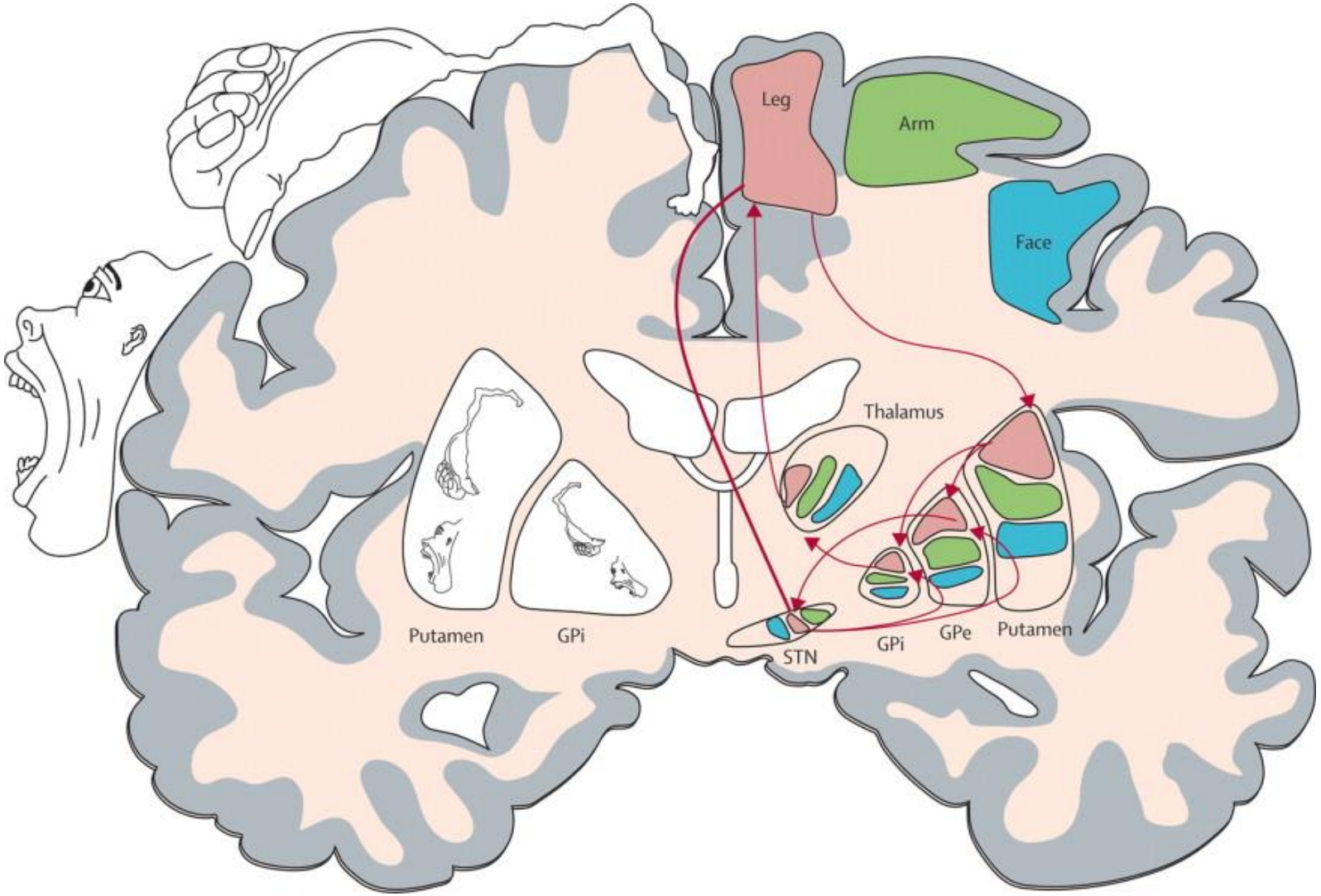
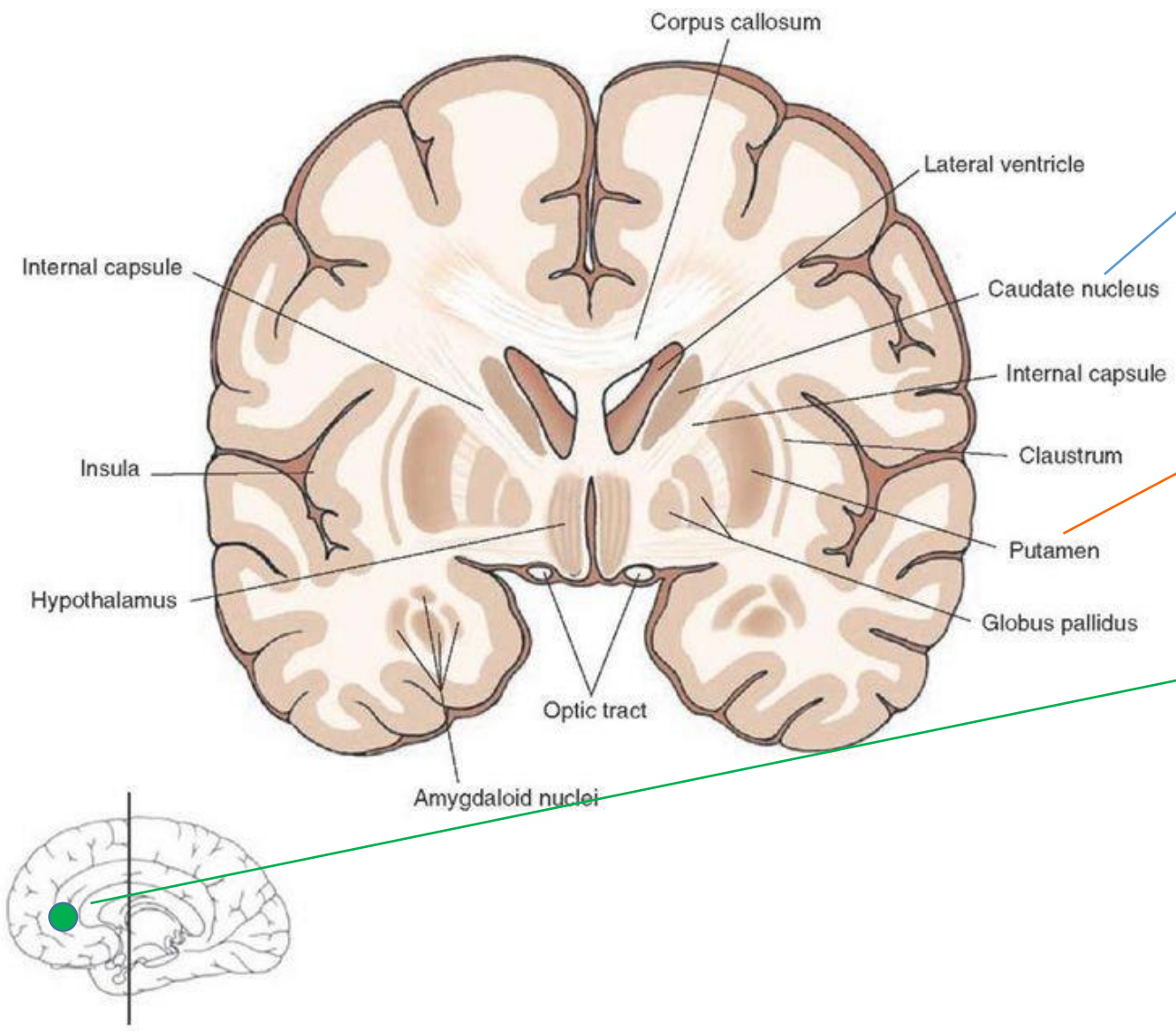
BG have a somatotopic organisation similar to motor cortex



Functional contribution of different parts of BG to movement



- **input - striatum**
  - CN receives projections from pre-frontal cortex and visual areas = movement of eyes (oculomotor loop) and cognitive faculty
  - PU receives projections from motor and sensory cortex = movement of the body (body movement loop)
  - n. accumbens (*not shown in the cross-section*) receives projections from ventro-medial parts of forebrain processing emotions = modulation of affect
- **output - pallidum**

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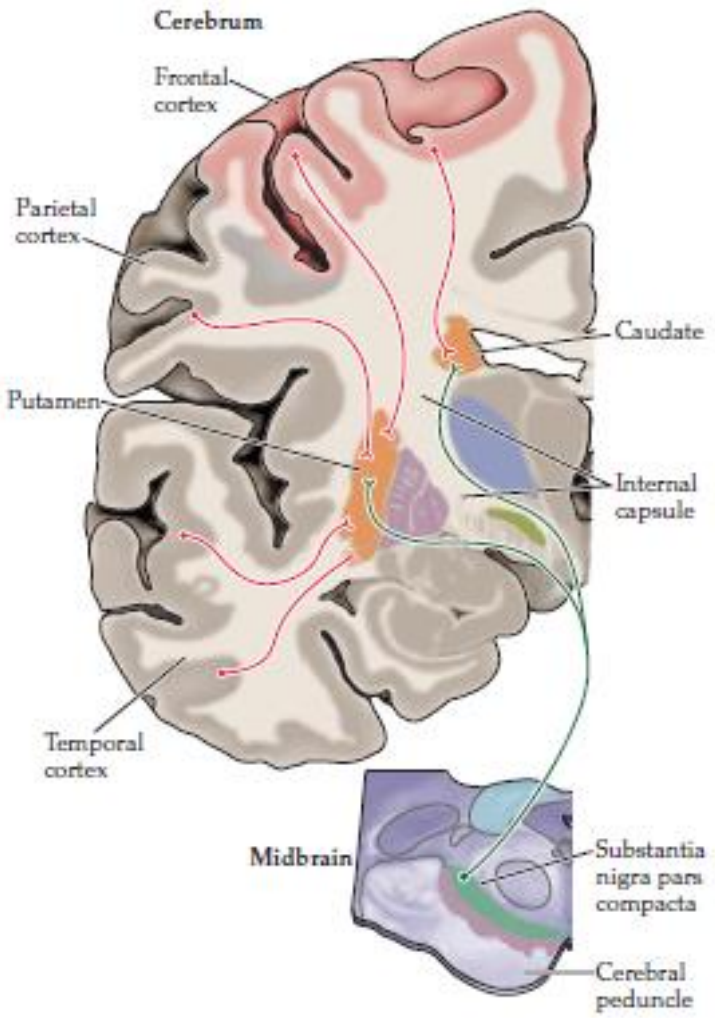
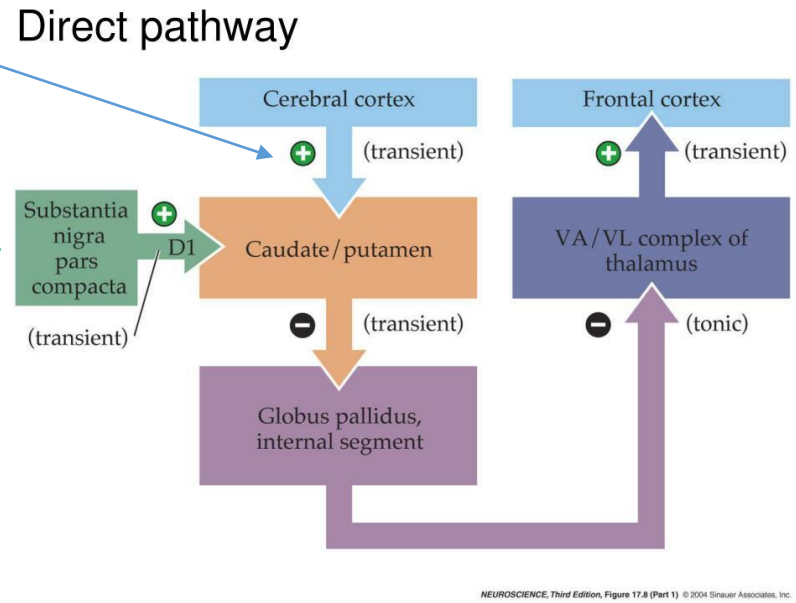
Inputs to the BG and intrinsic pathways



- There are two main inputs to the BG terminating in the striatum
  - (1) from multiple regions of the cerebral cortex (**corticostriatal pathways**)
    - excitatory – glutamate
      - from intralaminar nuclei of the thalamus (**thalamostriatal pathway**)
  - (2) from the substantia nigra pars compacta (**nigrostriatal pathway**)
    - excitatory – dopaminergic
      - NOTE dopaminergic connection from ventral tegmental area to n. accumbens in limbic loop



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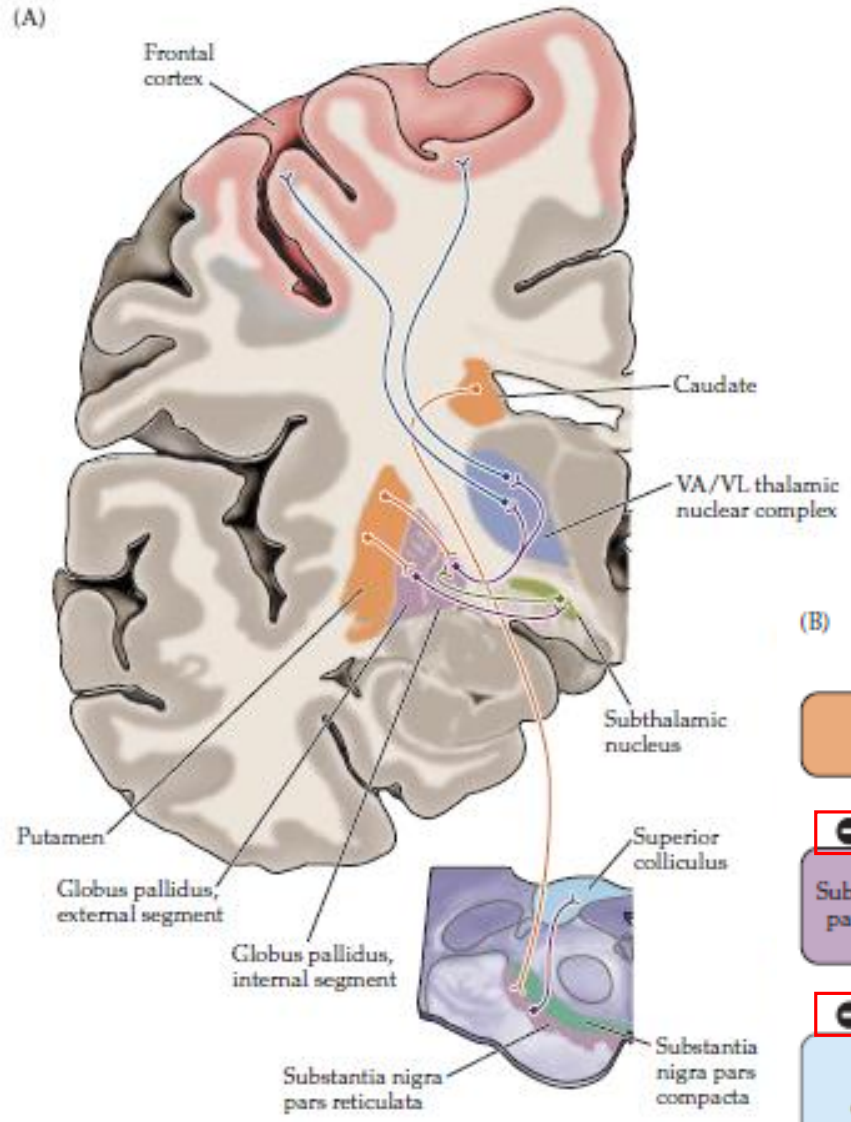
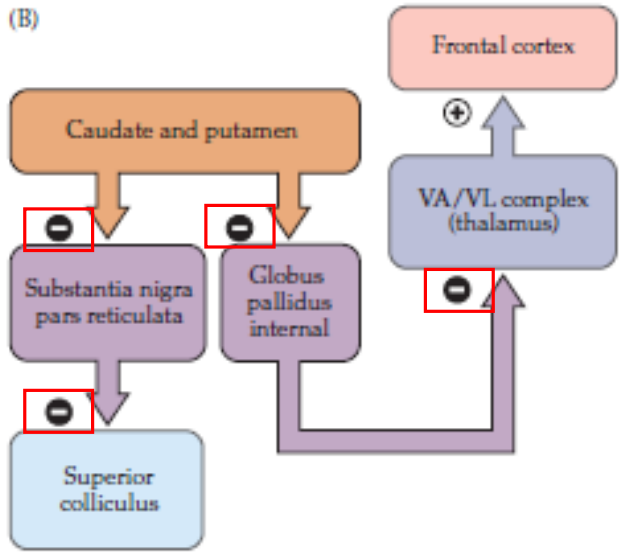
Outputs from the BG and intrinsic pathways



- Striatum communicates via inhibitory GABAergic projections with
  - substantia nigra pars reticulata
  - with GPi
    - and with GPe also – see further
- The two major outputs of the BG (both are inhibitory GABAergic) projecting from
  - GPi to the thalamus
    - to a number of thalamic structures by way of two fibre tracts:
      - the ansa lenticularis and the lenticular fasciculus
  - substantia nigra pars reticulata to the superior colliculus, which is involved in eye movements, as well as to the VA/VL thalamic nuclei



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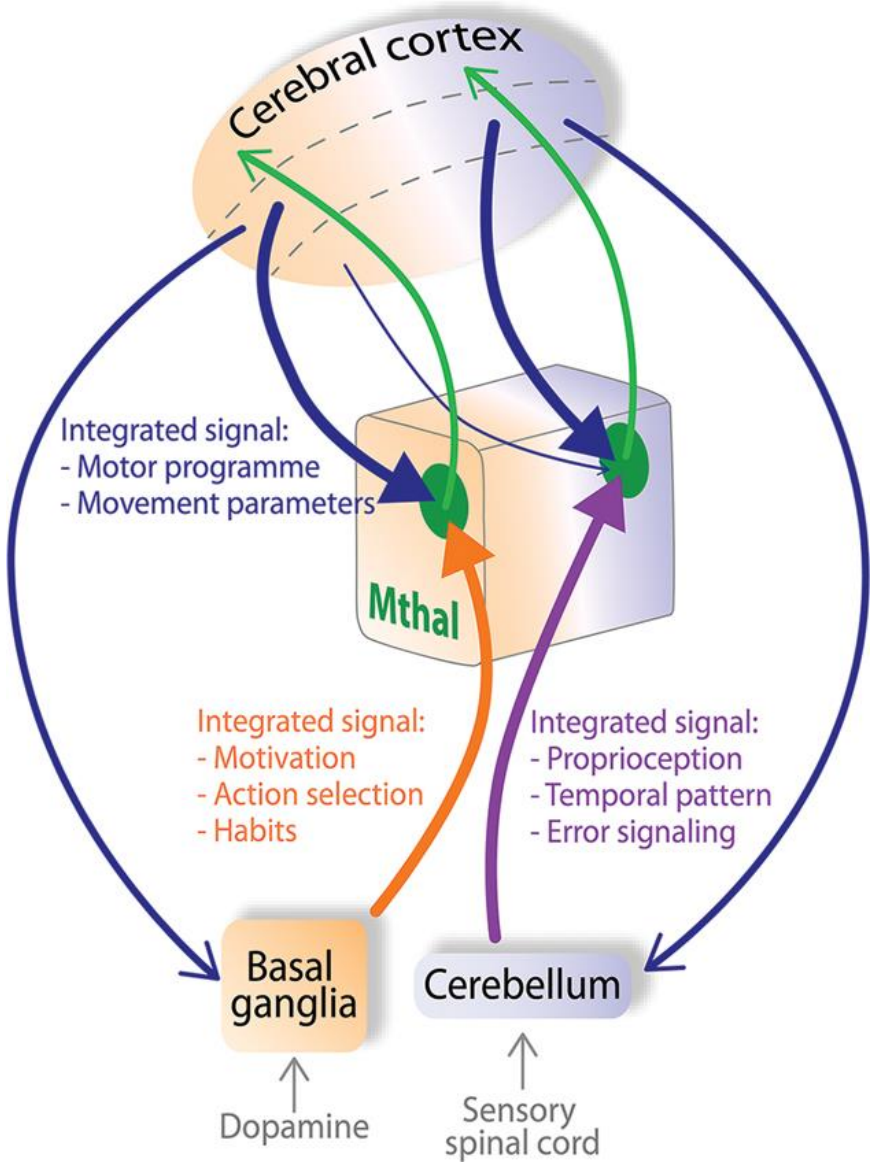
Cortical Afferents and Efferents and cytoarchitecture

- 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 corticostriatal 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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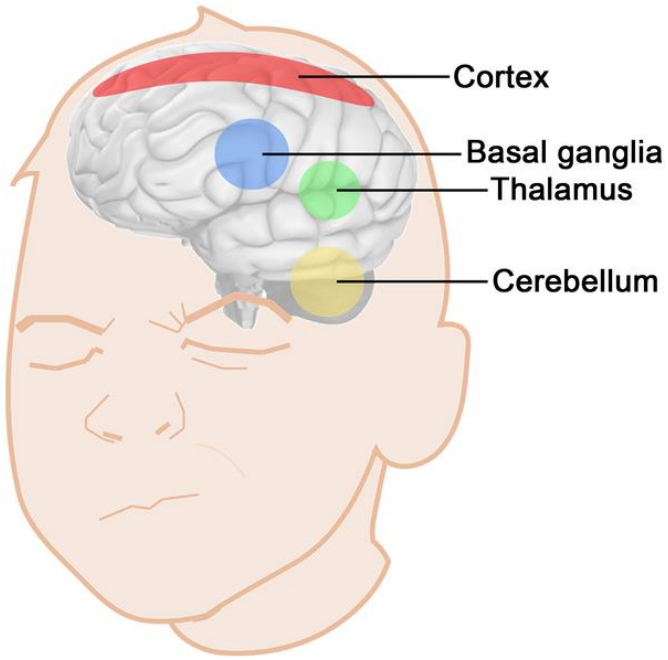

Disorders of extrapyramidal motor system

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

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

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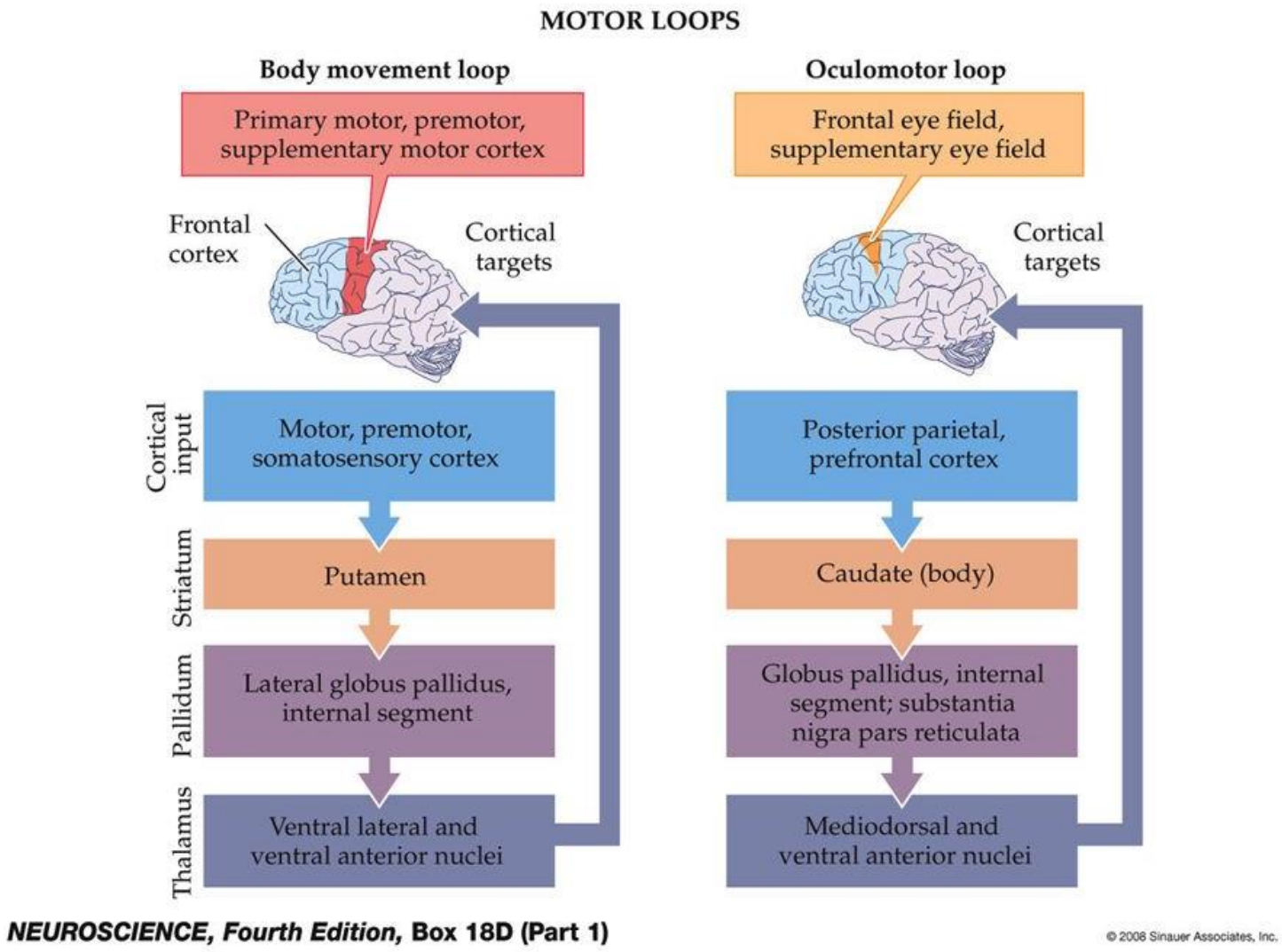
BG loops in controling body movements



***NEUROSCIENCE, Fourth Edition*, Box 18D (Part 1)**

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Extrapyramidal syndromes related to BG

- (1) hypo-/akinetic syndromes
  - 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 – competing programmes
  - Parkinson disease
- (2) dys-/hyperkinetic syndromes
  - excessive, involuntary motor activity due to the reduced BG inhibitory loop
    - chorea
    - athetosis
    - ballism
    - dystonia
    - tardive dyskinesia (drug induced)
  - Huntington disease/chorea
  - Sydenham chorea (usually reversible)
    - neurological disorder of childhood resulting from infection via Group A beta-hemolytic streptococcus (GABHS), the bacterium that causes rheumatic fever
  - 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
- instructive videos to watch on https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)62418-6/fulltext#sec1 and many other internet resources

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

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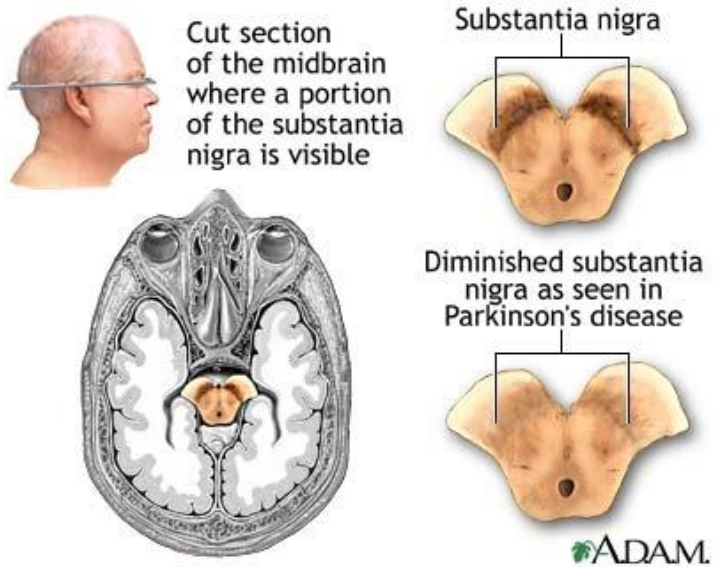
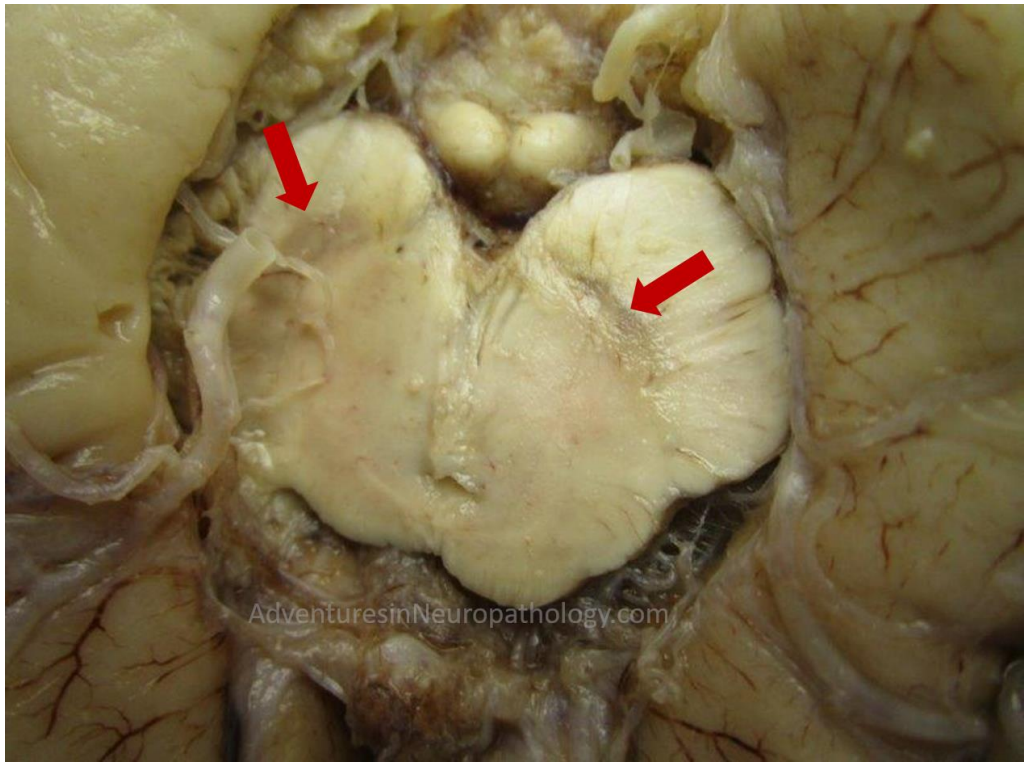
Parkinson´s disease – etiology

- degenerative condition due to the loss of cells producing dopamine (SNpc)
  - progressive destruction of the nigrostriatal pathway with subsequent reduction of the dopamine in the striatum
    - manifest at loss of 70 to 85 percent of dopaminergic neurons
  - 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**
    - GPi 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
- etiology
  - idiopathic – degeneration of the substantia nigra
    - autooxidation of catecholamines during melanin synthesis?
    - another hallmark is the presence of Lewy bodies—oligomeric deposits of a protein called alpha-synuclein inside the neurons
  - cerebral vascular disease
  - toxic (e.g. CO poisoning)
  - early-onset – genetic
    - mutations in the α-synuclein and parkin gene

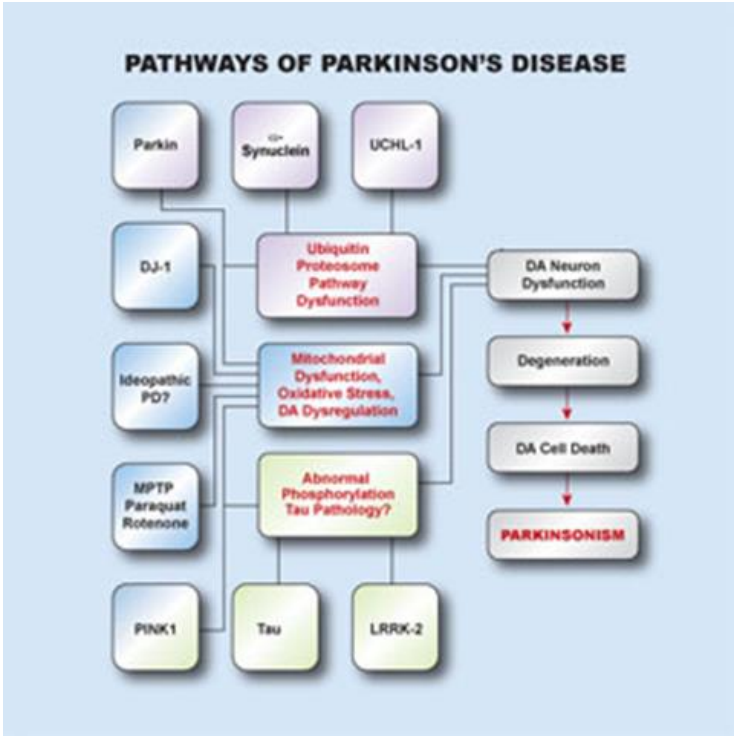




Etiopathogenesis of PD

- 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 dopamine metabolites
    - 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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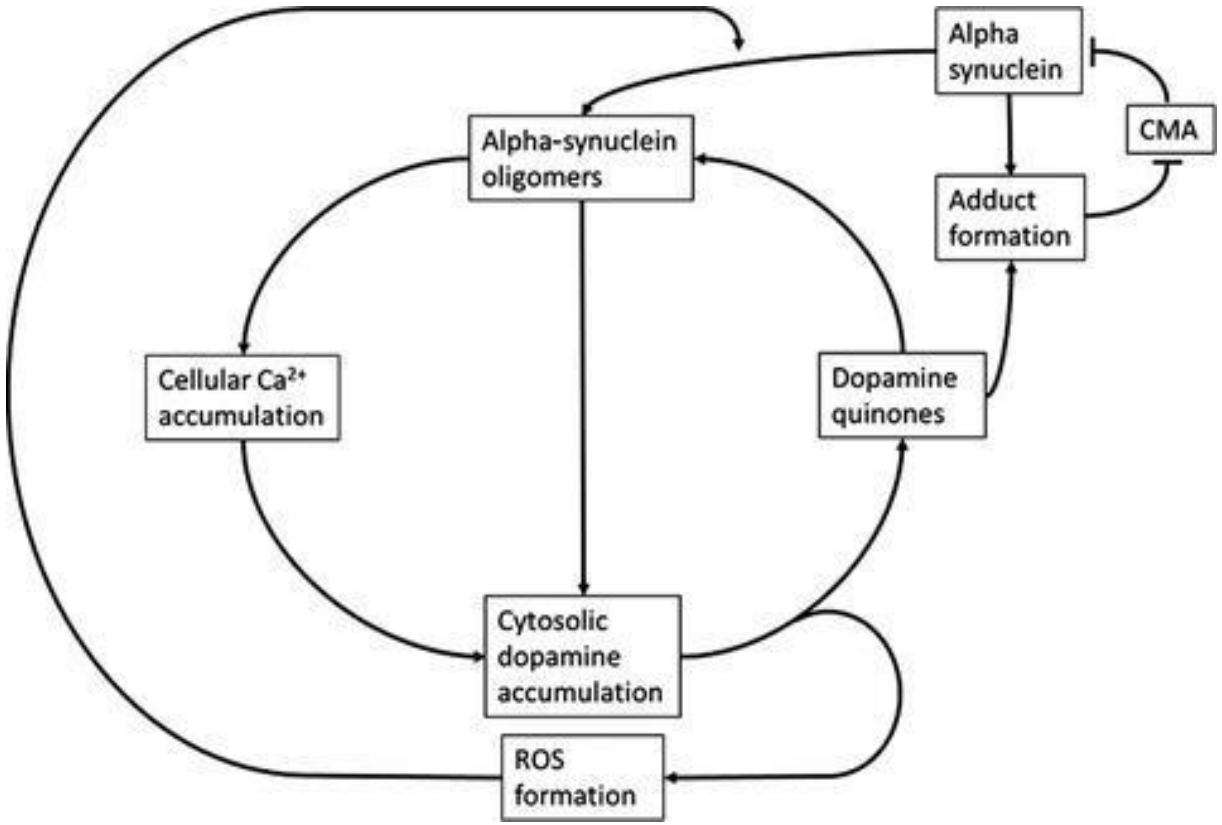
Parkinson´s disease - etiology



- Parkinson's disease (PD) is characterised by selective and severe degeneration of the substantia nigra pars compacta and the locus coeruleus (LC), which underlies the most prominent symptoms
- An *α*-synuclein deposition at synaptic sites can impair synaptic dopamine release and induces the death of nigrostriatal neurons
- Although α-synuclein accumulation has long been established to play a causal role in the disease, it alone cannot explain the selective degenerative pattern
- Recent evidence shows that the selective vulnerability could arise due to the large presence of cytosolic catecholamines and Ca2+ ions in the substantia nigra pars compacta and LC specifically that can be aberrantly affected by α-synuclein accumulation
- Moreover, each has its own toxic potential, and disturbance of one can exacerbate the toxic effects of the others
- This presents a mechanism unique to these areas that can lead to a vicious degenerative cycle
- Interestingly, in familial variants of PD, the exact same brain areas are affected, implying the underlying process is likely the same
    - however, the exact disease mechanisms of many of these genetic variants remain unclear. Here, we review the effects of the PD-related genes Parkin, PINK1 and DJ-1.

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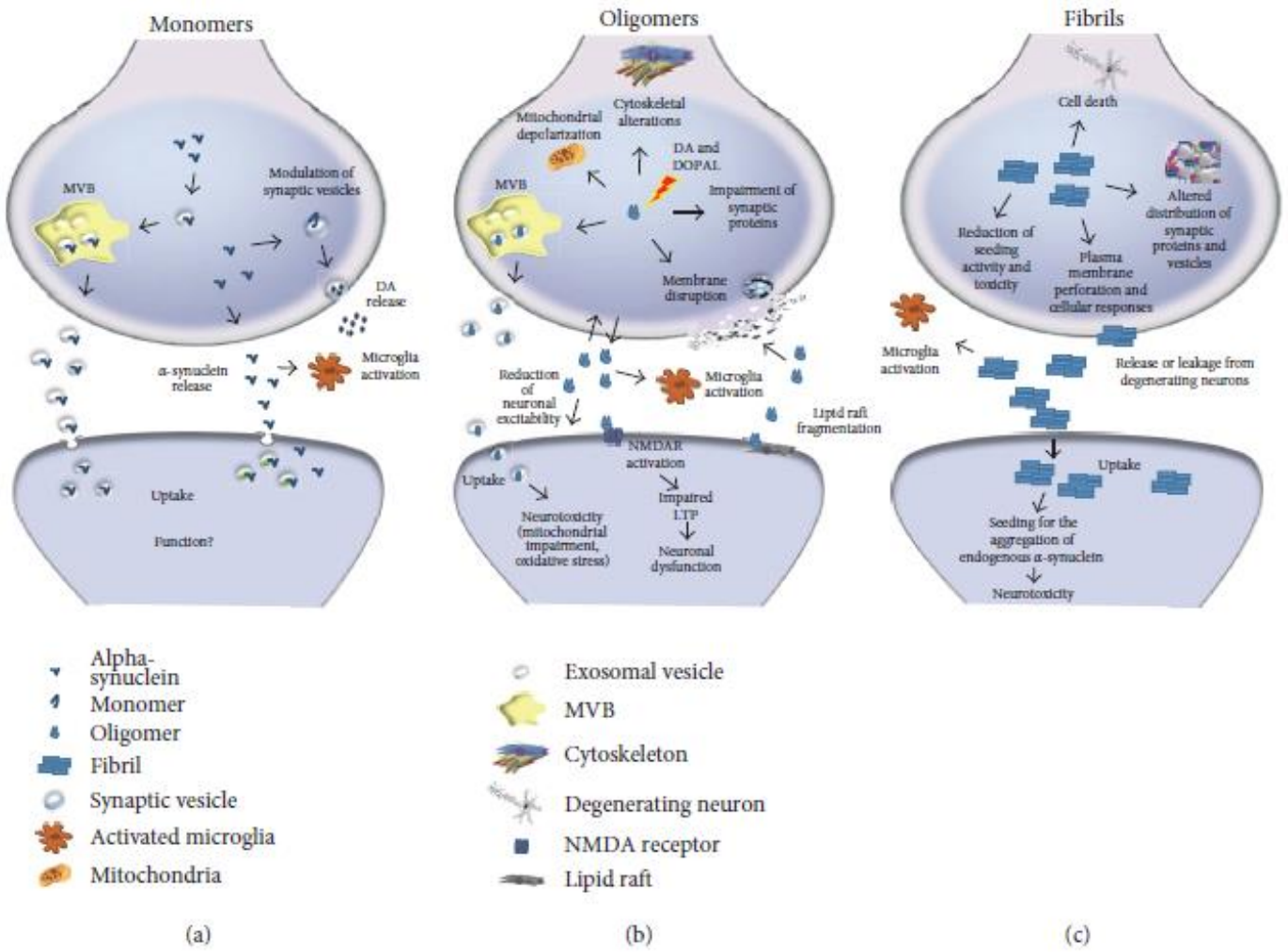
Monomeric, oligomeric, and fibrillary α-synuclein at the synaptic terminal



- (a) Monomeric α-synuclein modulates synaptic function by controlling synaptic vesicle release. This form of the protein can be released in association with exosomes, activates microglial cells, and can be internalized at postsynaptic sites.
- (b) Oligomeric α-synuclein formation is enhanced by interaction of monomeric protein with DA. Alpha-synuclein oligomers can form a stable adduct with the toxic dopamine metabolite DOPAL. Oligomers can be released in association with extracellular vesicles and then activate microglia. Alpha-synuclein oligomers can disrupt synaptic vesicles membranes as well as presynaptic and postsynaptic membranes. Exogenous α-synuclein oligomers can damage lipid rafts and affect LTP by activating NMDA receptors. Intracellular α-synuclein oligomers with endogenous or exogenous origin impair mitochondrial functions and cytoskeletal architecture.
- (c) Fibrillary-aggregated α-synuclein alters synaptic vesicle release by clustering synaptic vesicles and by perforating plasma membrane. Extracellular fibrils deriving from degenerating neurons in the PD brain can activate microglial cells and actively contribute to alpha-synuclein pathology spreading. The formation of endogenous α-synuclein fibrils can reduce seeding activity and toxicity although exogenous α-synuclein fibrils function as a seed for the aggregation of endogenous α-synuclein in recipient cells.

Francesca Longhena, Gaia Faustini, Cristina Missale, Marina Pizzi, PierFranco Spano, Arianna Bellucci, "The Contribution of α-Synuclein Spreading to Parkinson's Disease Synaptopathy", *Neural Plasticity*, vol. 2017, Article ID 5012129, 15 pages, 2017. https://doi.org/10.1155/2017/5012129

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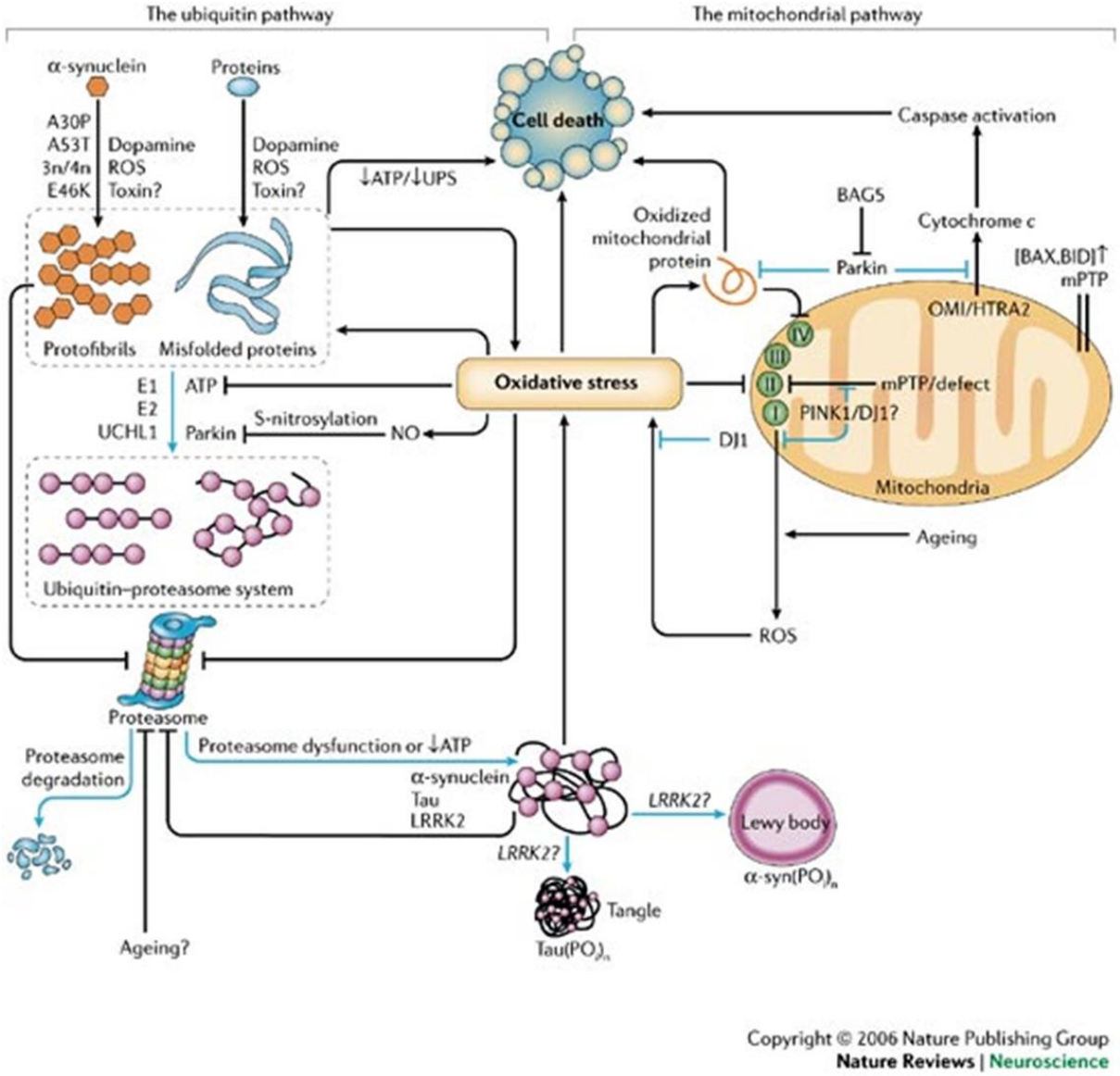
Neurodegeneration pathways in Parkinson's disease



- 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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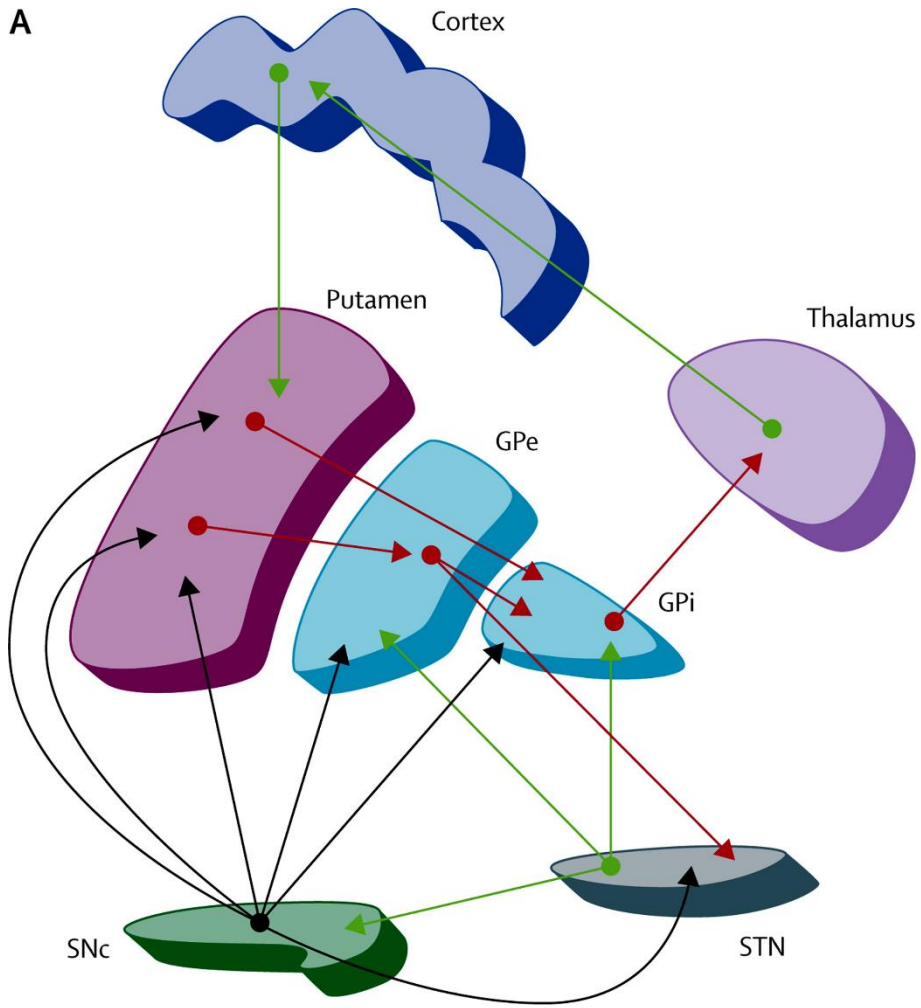
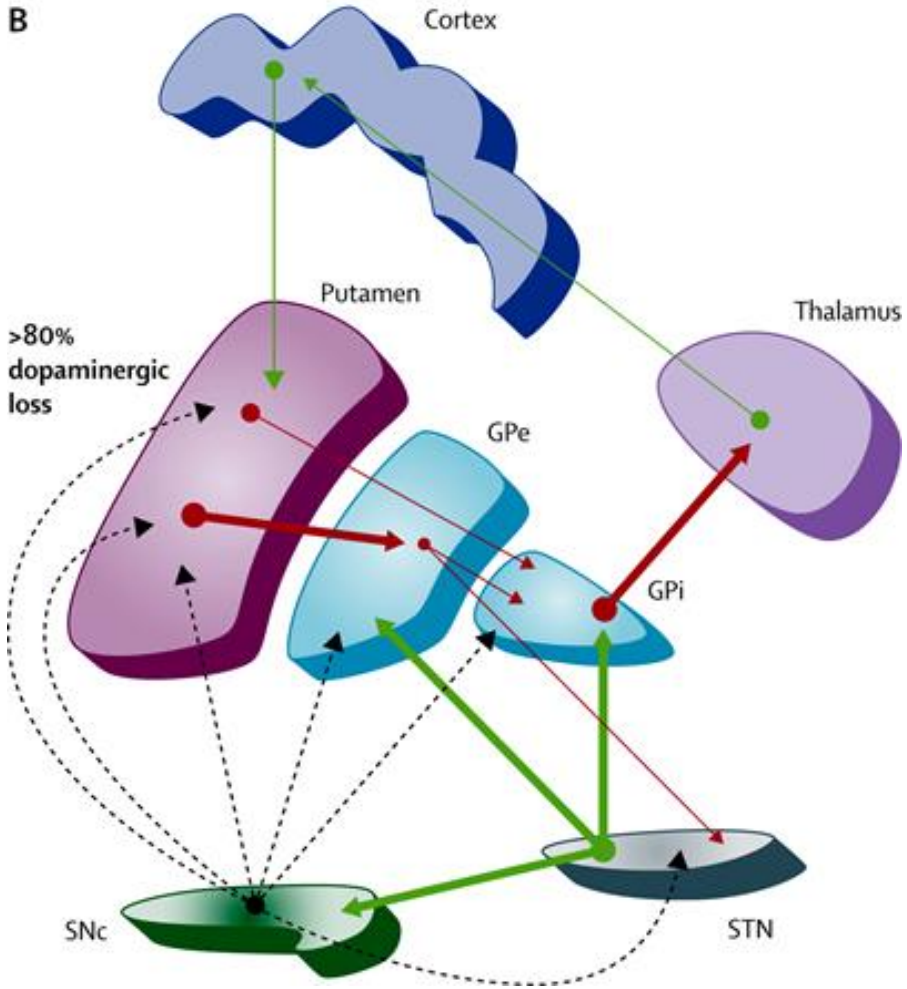
Parkinson´s disease – pathophysiology





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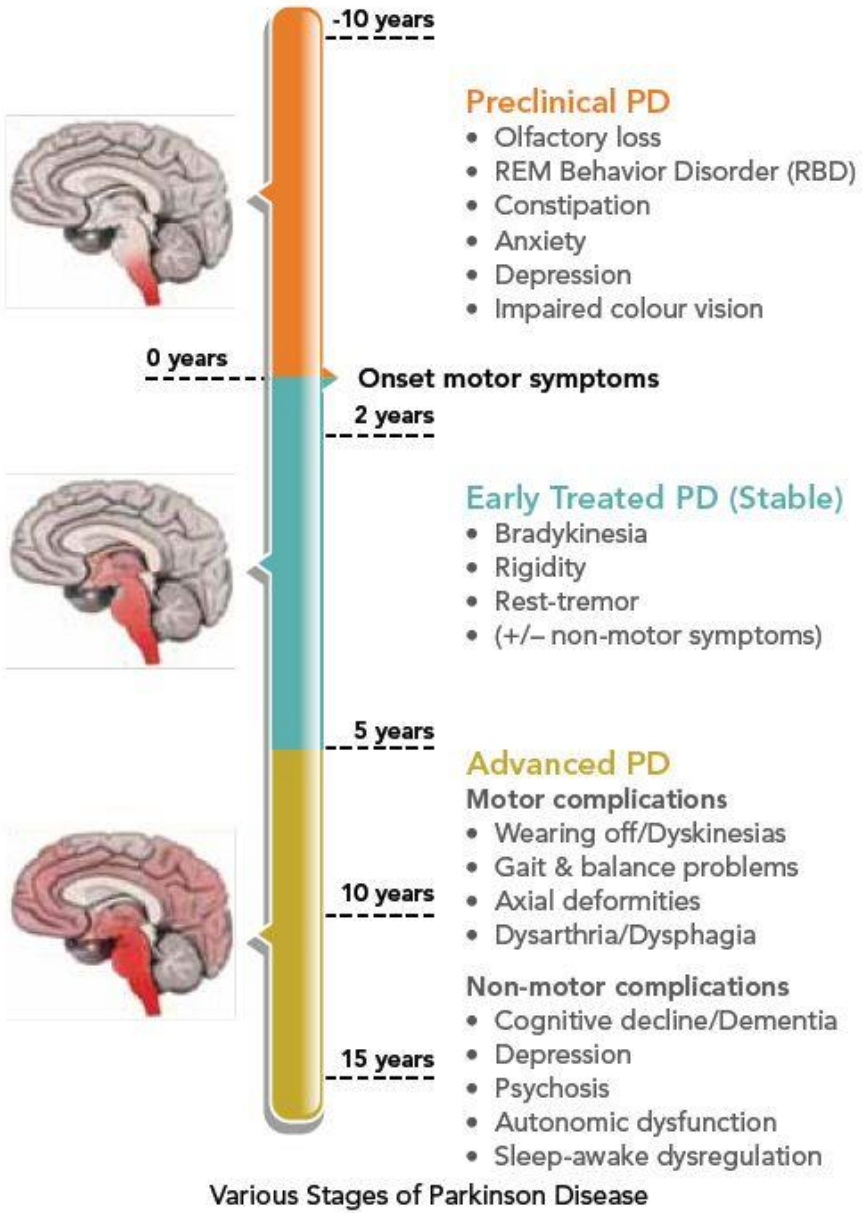
Parkinson´s disease - symptoms



Various Stages of Parkinson Disease

- resting tremor
  - characteristically disappears with purposeful movement but is evident when the extremities are motionless
  - often unilateral
  - slow turning motion (pronation– supination) of the forearm and the hand and a motion of the thumb against the fingers as if rolling a pill
- rigidity
  - passive movement of an extremity may cause the limb to move in jerky increments referred to as cogwheeling
  - increases when another extremity is engaged in voluntary active movement
- bradykinesia (slow movements)
  - take longer to complete most activities and have difficulty initiating movement, such as rising from a sitting position or turning in bed
  - freezing phenomenon
  - shuffling gait with decreased arm swings
- loss of postural reflexes
  - standing with the head bent forward due to forward flexion of the neck, hips, knees, and elbows
  - difficulty in pivoting and loss of balance places the patient at risk for falls
- speech and swallowing problems
  - dysphonia (soft, slurred, low-pitched, and less audible speech)
  - dysphagia, drooling and risk for choking and aspiration
- loss of facial mimics
  - masklike and expressionless and the frequency of blinking decreases
- psychiatric symptomatology
  - depression
  - sleep disturbances
  - hallucinations
  - dementia (late onset, in 20% patients)
- vegetative dysbalances
  - excessive and un-controlled sweating, paroxysmal flushing, orthostatic hypotension, gastric and urinary retention, constipation, and sexual disturbances

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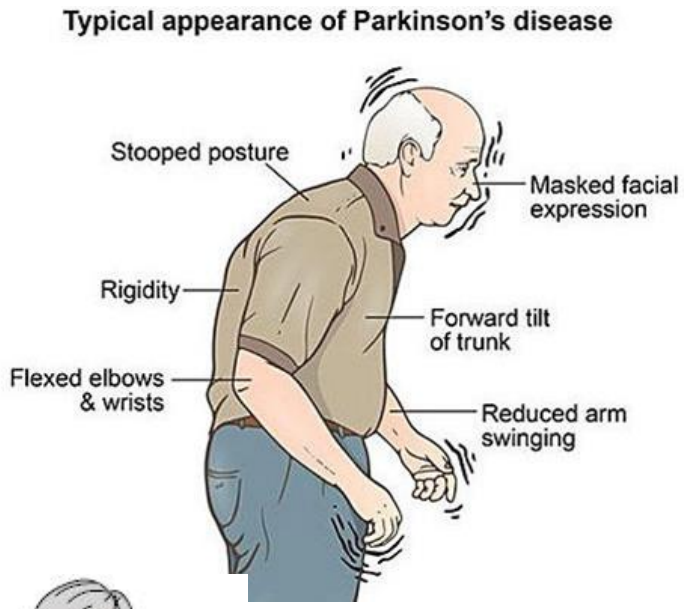
Parkinson´s disease - symptoms

- 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)



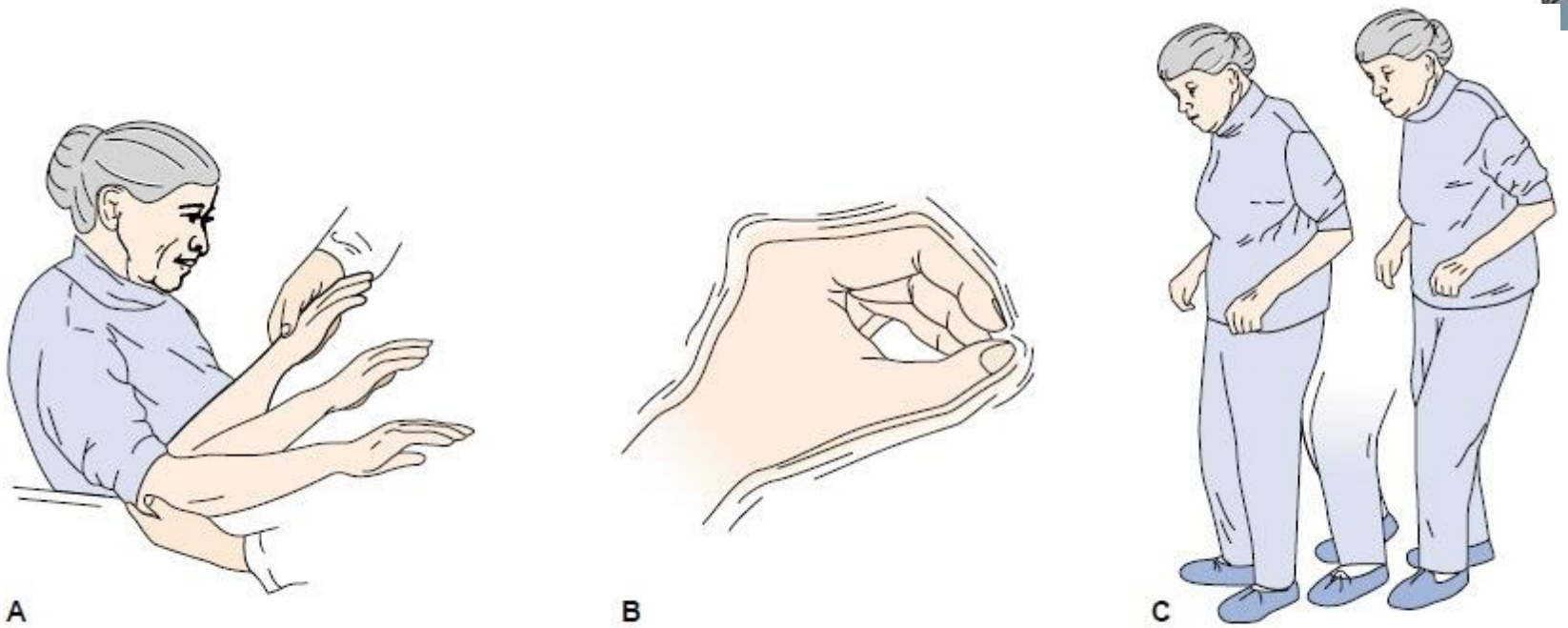


FIGURE 65-5 Manifestations of Parkinson's disease: (**A**) "cogwheeling" accompanies passive movement of the hand and arm; (**B**) "pill-rolling" tremor; (**C**) postural instability, forward stoop, shuffling gait.

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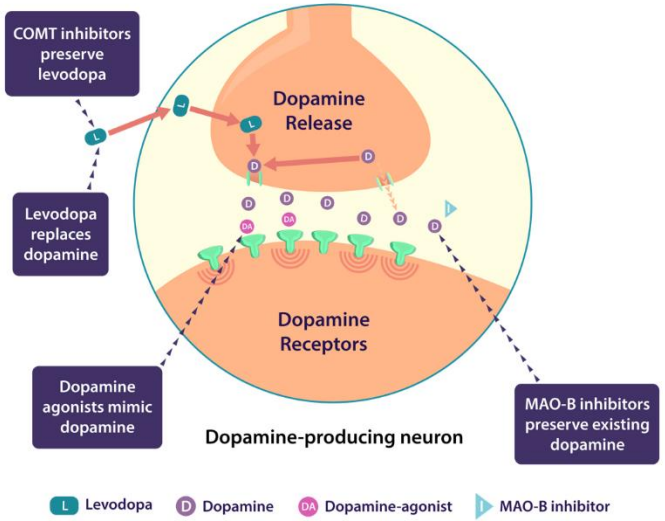
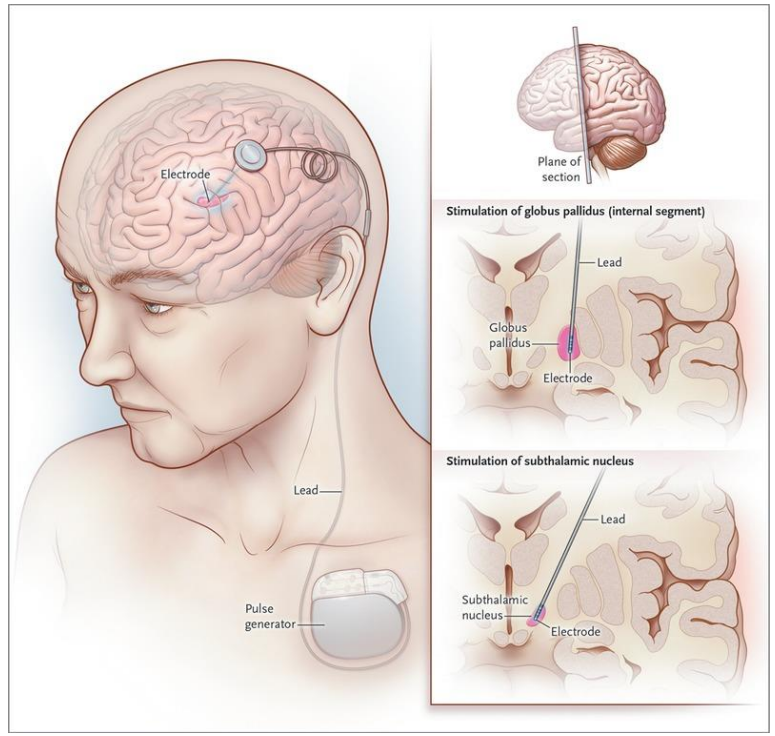
Parkinson´s disease - treatment

- pharmacotherapy – restoration of the dopaminergic system
  - L-DOPA or dopamine agonists
  - other drugs prolonging the dopamine half live
    - cathechol-O-methyltransferase (COMT) inhibitors
    - monoamine oxidase B (MAO-B) inhibitors



- deep brain stimulation



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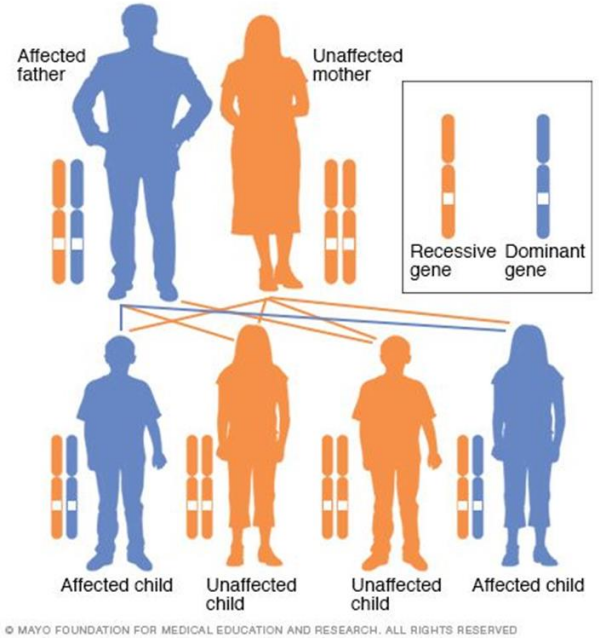
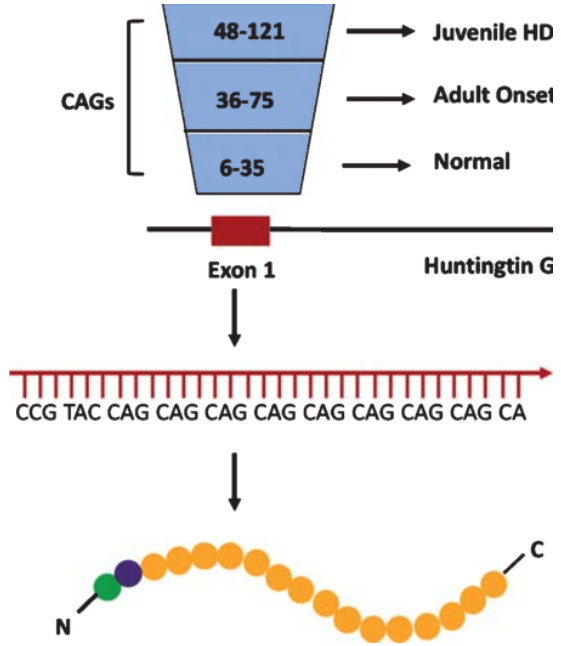
Huntington's disease (chorea)

- 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 D2-positive (GABA-ergic) neurons of striatum** (destruction of indirect pathway) and then in **cortex**
  - GPi constitutively disinhibited and leads to dyskinesia symptoms/movements - chorea
- etiopathogenesis
  - genetics - expansion of CAG (= glutamine) trinucleotide repetition in exon 1 (in total 67 exons) of the gene encoding huntingtin (ch. 4p16.3) leading to expansion of the polyglutamine tract in the N-terminus of this protein
    - htt is 350kDa protein encoded by gene with normal number (6 - 35) of CAG repetitions
    - in HD there are 36 – 121 repetitions
      - late manifestation when CAG <60
      - early manifestation CAG >60
      - in subjects with 36-40 repetitions < 100% penetrance !!
    - the number of repetitions increases with generations in paternal transmission **– phenomenon of anticipation**
  - the mutation is most prominent in the striatal part of the basal ganglia, and progressive differential dysfunction and loss of striatal projection neurons and interneurons account for the progression of motor deficits seen in this disease
    - misfolded htt is contained in inclusion bodies, mutant htt negatively affects critical gene expression and thus function of striatum and cortex
- symptoms
  - early – clumsiness, loss of balance, involuntary movements, lack of concentration, depression, irritability
  - late – chorea, dyskinesia, dysarthria, cognitive impairment to dementia
- MORPHOLOGICALLY a generalised brain atrophy (25-30%)





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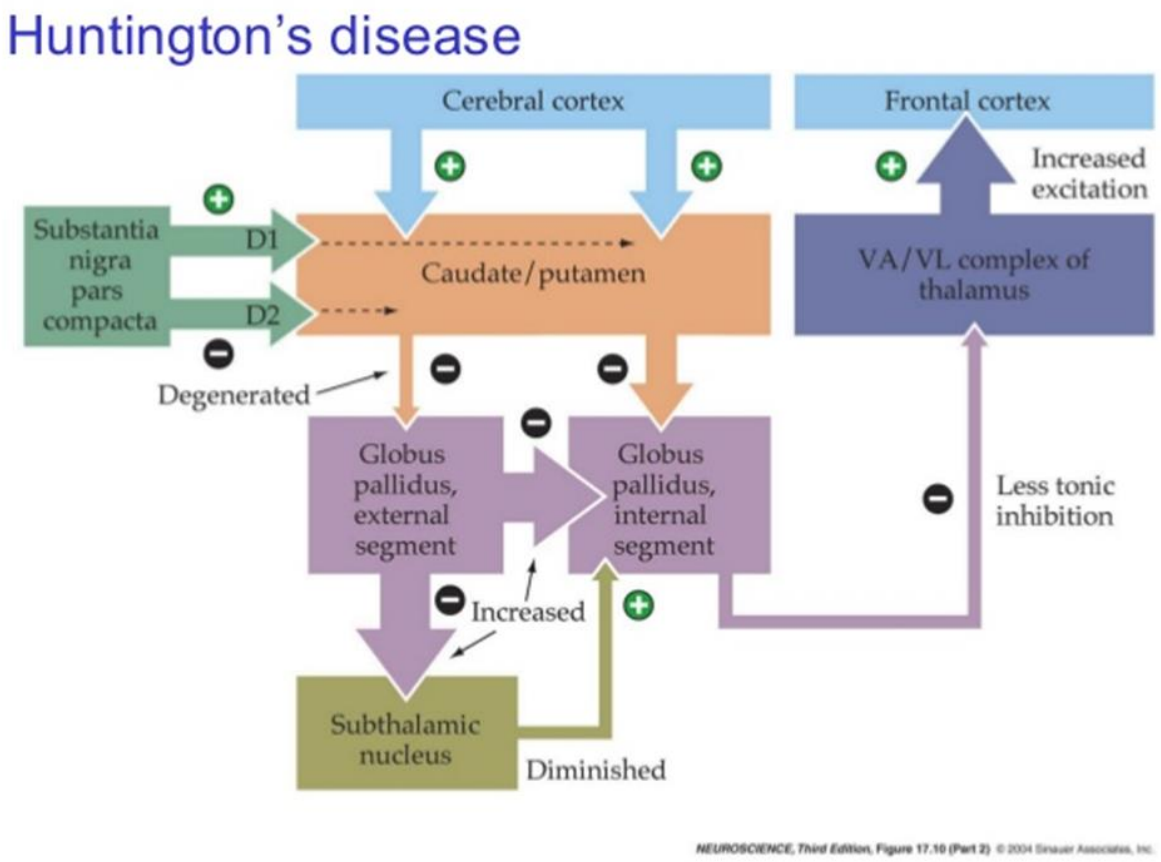
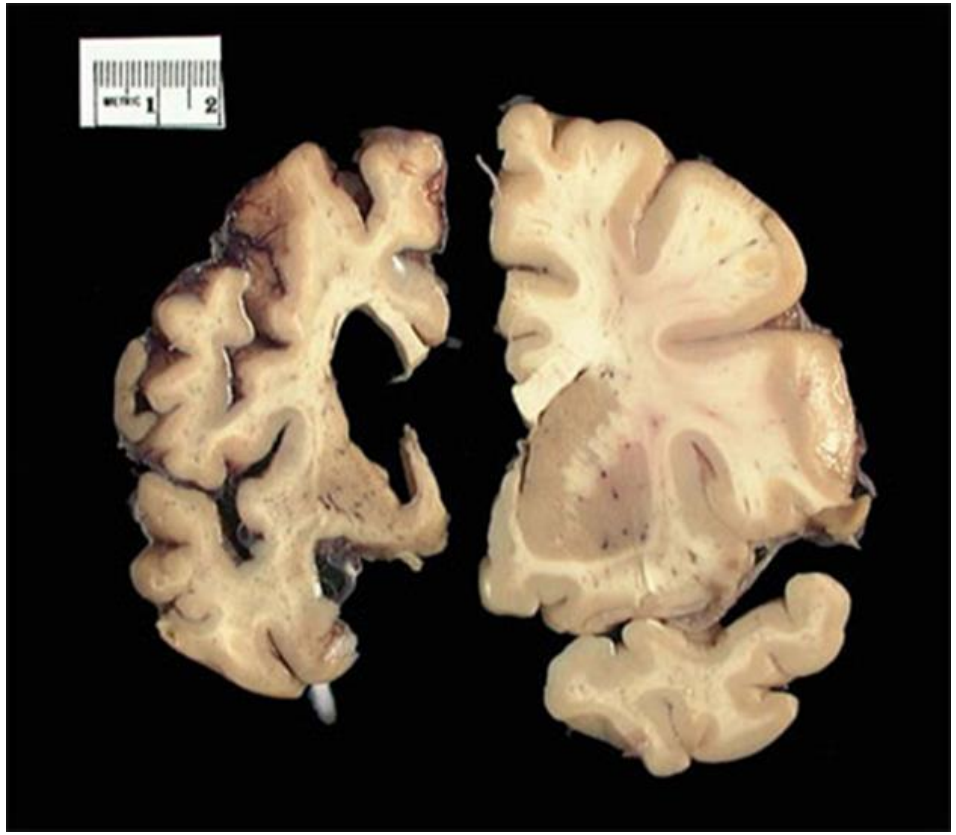
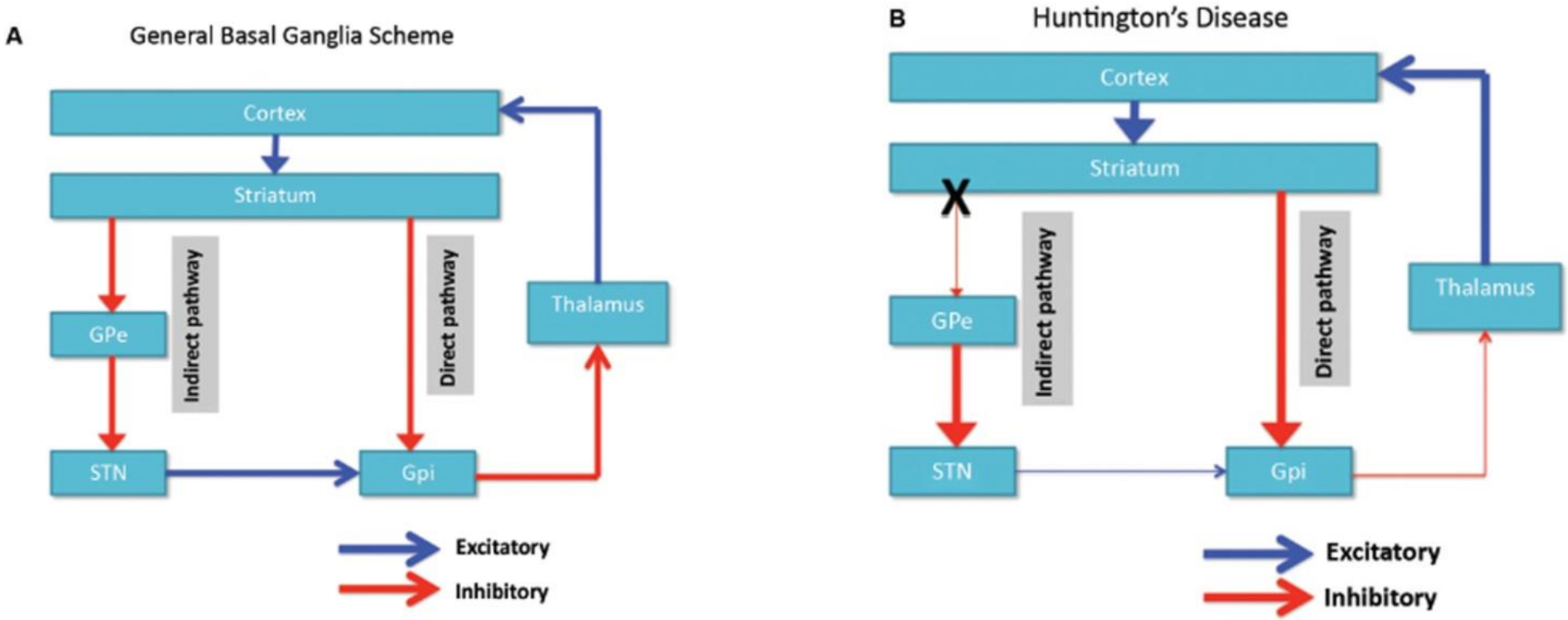
Simplified scheme of the HD pathophysiology





Pathology in the indirect pathway is a key to HD



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Cerebellum = error correction

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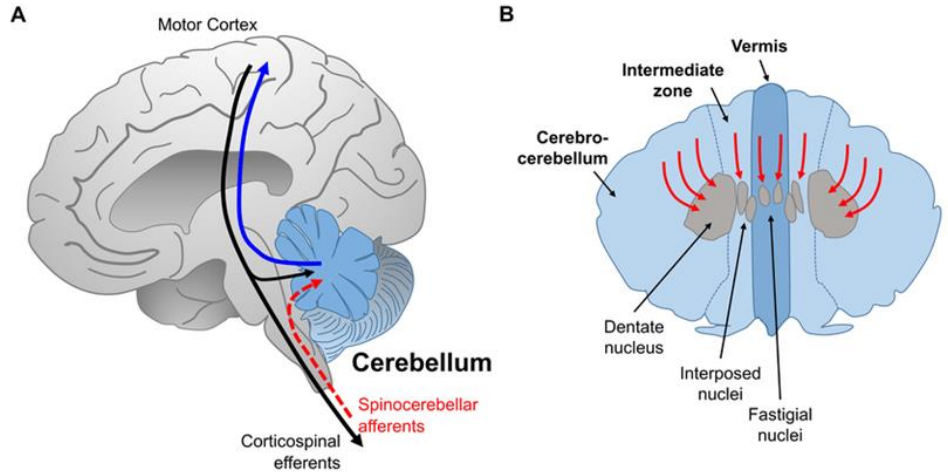
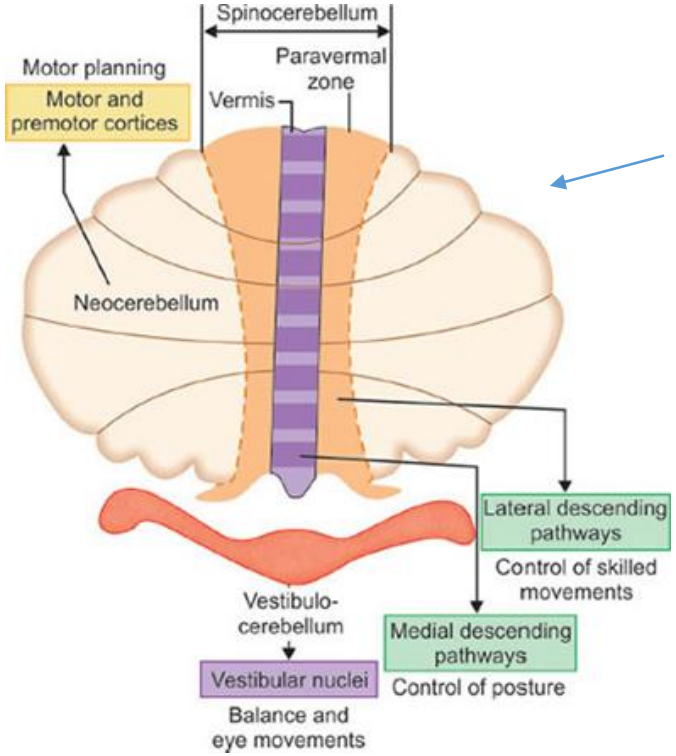
How is cerebellum integrated into the control of movement - why we need it?

- 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
  - **coordination** of voluntary multi-joint movements to improve stability
    - necessary for maintenance of balance and posture
    - subsequent balance disorders require postural strategies to compensate for this problem (e.g., a wide-based stance)
  - motor **learning** to **improve motor performance**
  - cognitive functions

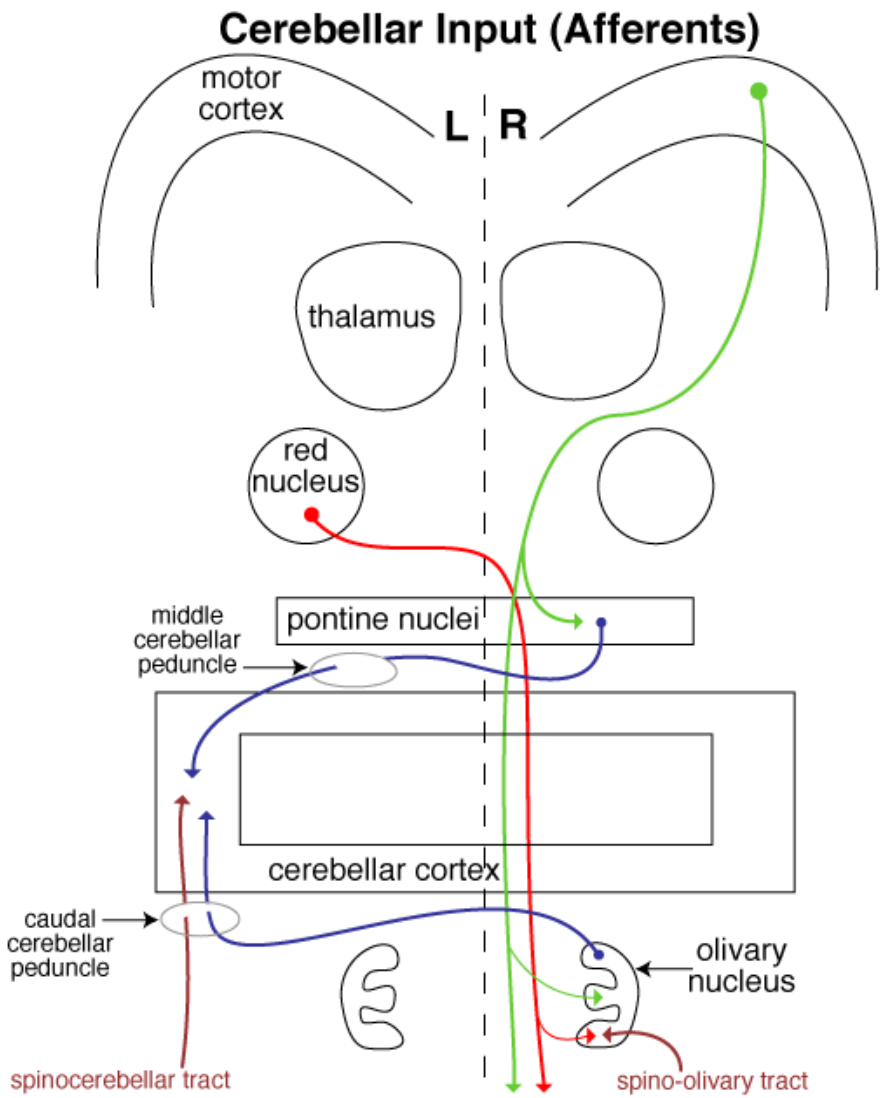




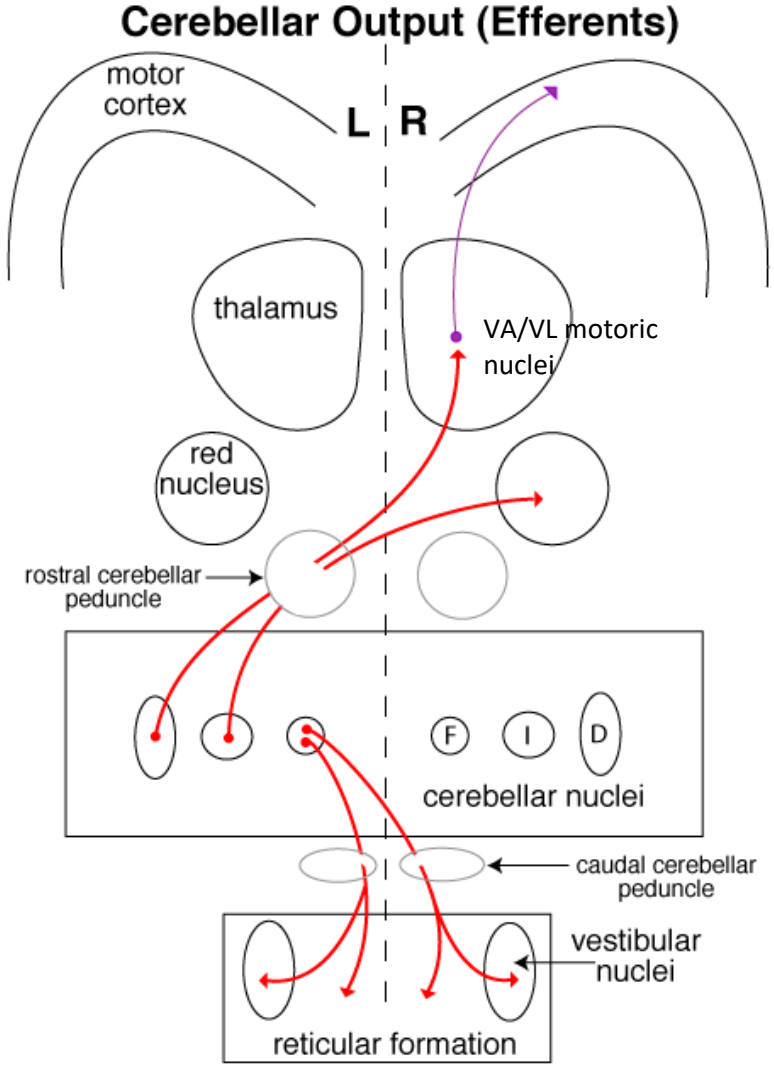
Functional divisions of cerebellum

Inputs and outputs of the cerebellum

note: given side of the body is represented contra- laterally in the cerebral hemisphere but ipsi-laterally in cerebellum



conveying info on proprioception and position of the head



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Disorders of cerebellum

- 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
      - susceptibility to oxidative damage
    - neurological symptoms combined with sensory loss, diabetes 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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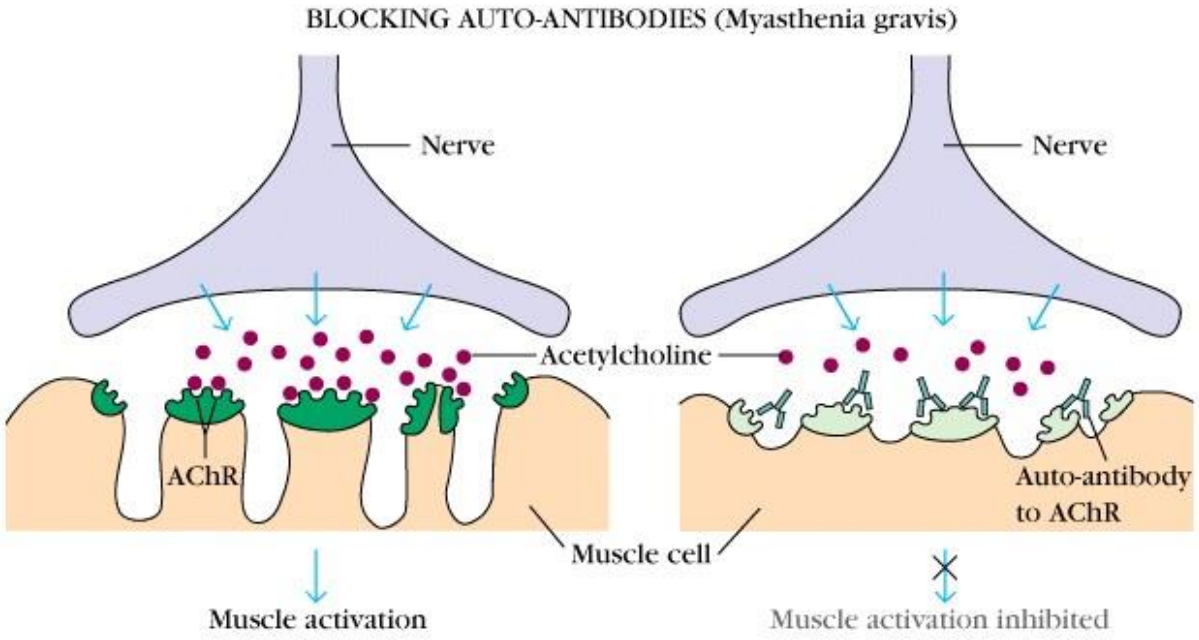
Disorders of neuromuscular junction

- 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)



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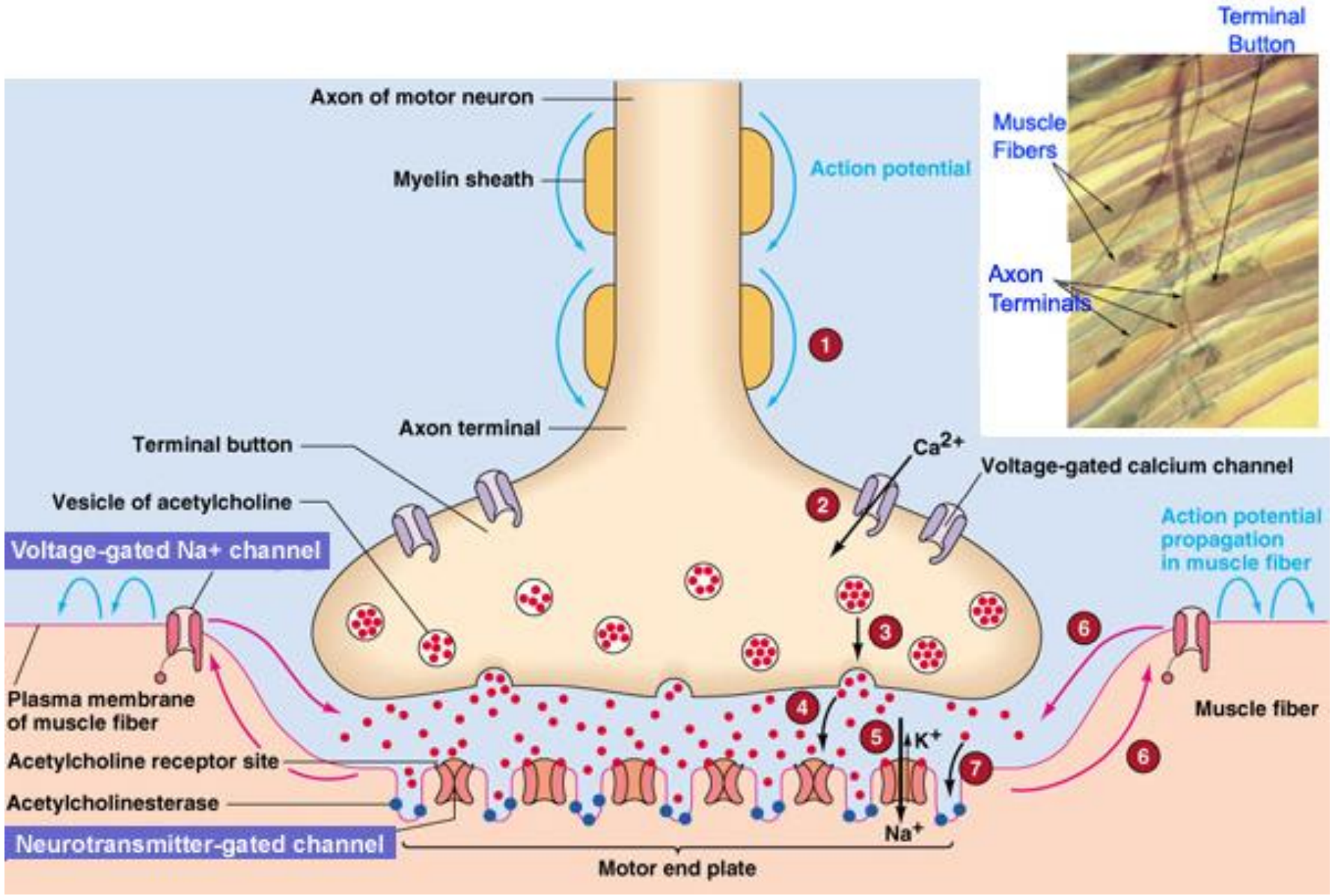
Disorders of neuromuscular junction



Muscular diseases

- (A) Muscular dystrophies
  - characterised by muscle degeneration and weakness
  - there are about 60 different forms of muscular dystrophy, ranging from the most common Duchenne MD, which often causes death by the age of thirty, to rarer, more slowly-progressing or later-onset forms
  - All types of MD are caused by mutations in genes implicated in muscle structure and function
    - dystrophinopathies (most common) – Duchenne and Becker MD (different type of mutation)
      - dystrophin is actually part of a complex of molecules situated in the membrane encircling muscle cells
- (B) Mitochondrial myopathies

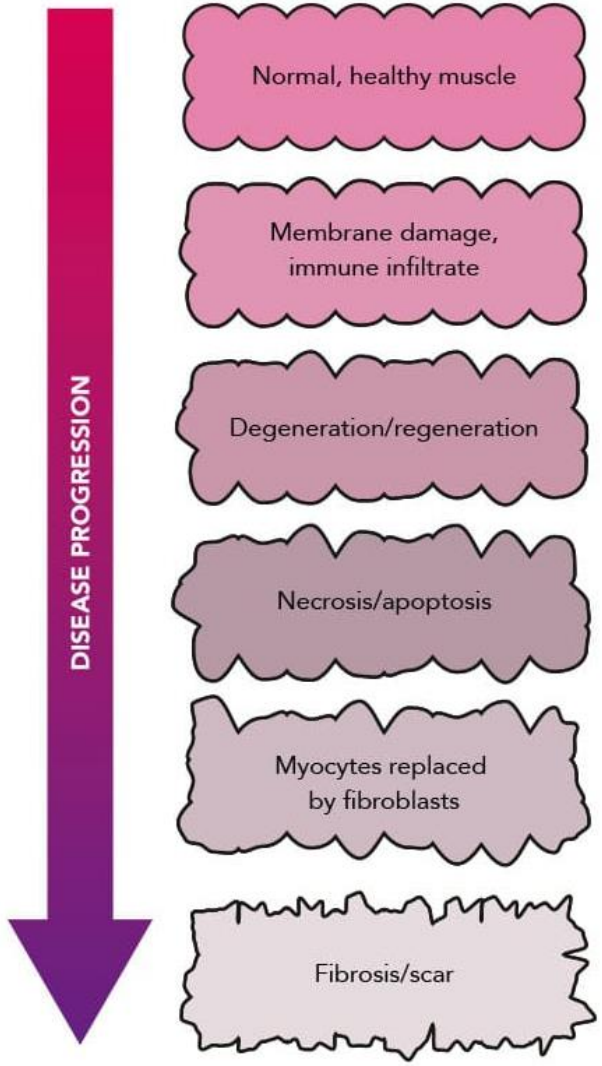
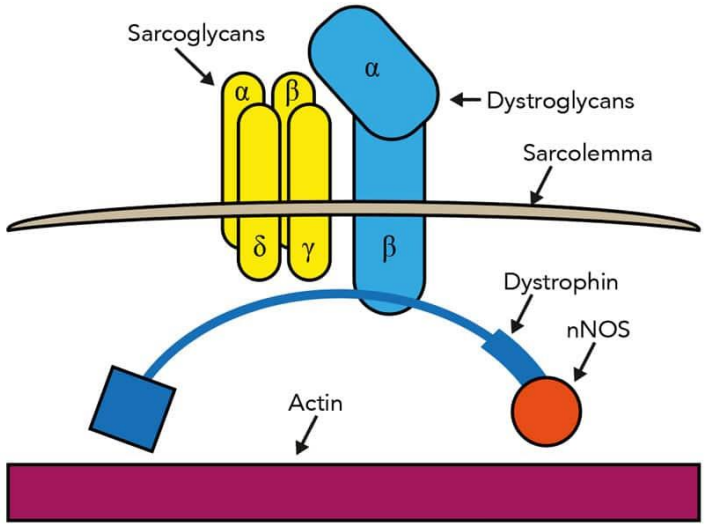


TABLE 1 DMD Versus BMD

	DMD	BMD
Dystrophin protein	Absent	Partially functional
Incidence	1:5,000 male births	1:19,000
Mean age at onset, yrs	3-5	12
Mean age of becoming nonambulatory, yrs	~12	~27
Mean life expectancy, yrs	Mid to late 20s	40s
Onset of cardiomyopathy, yrs	16-18	Variable; cardiomyopathy may precede skeletal symptoms

BMD = Becker muscular dystrophy; DMD = Duchenne muscular dystrophy.



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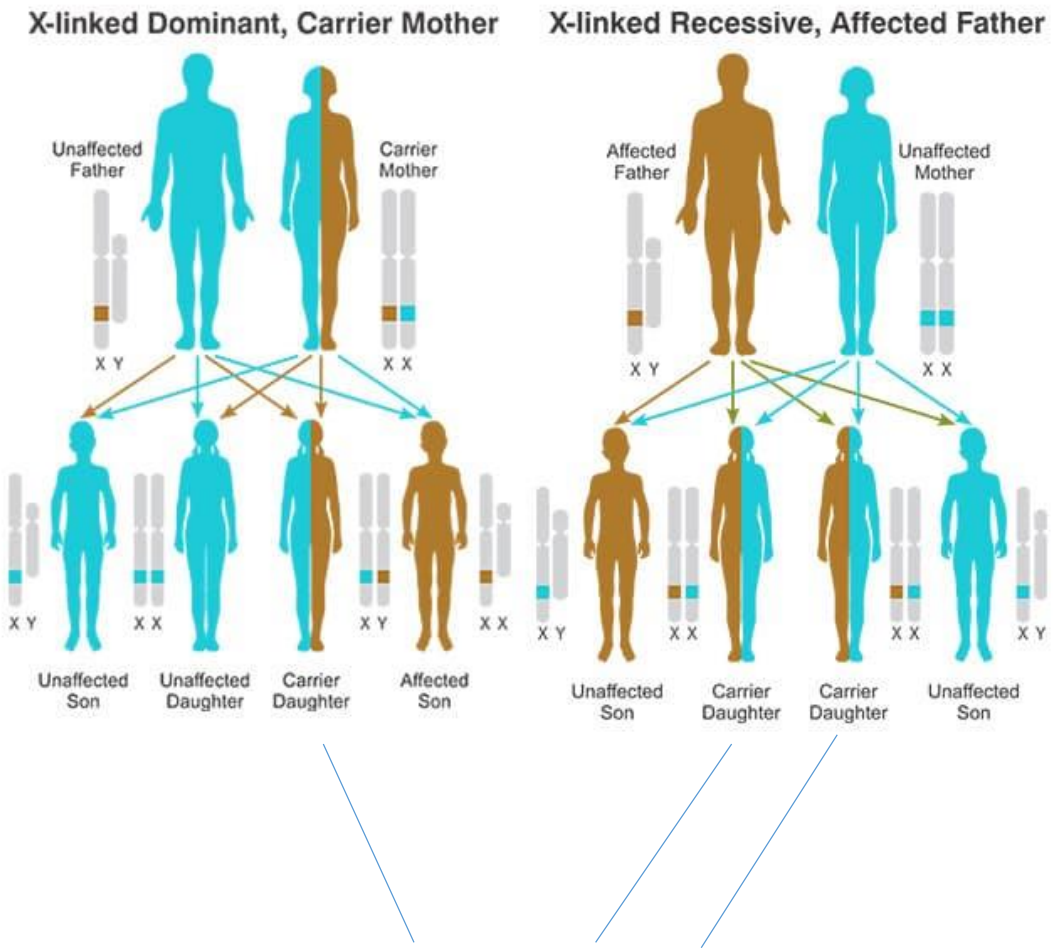
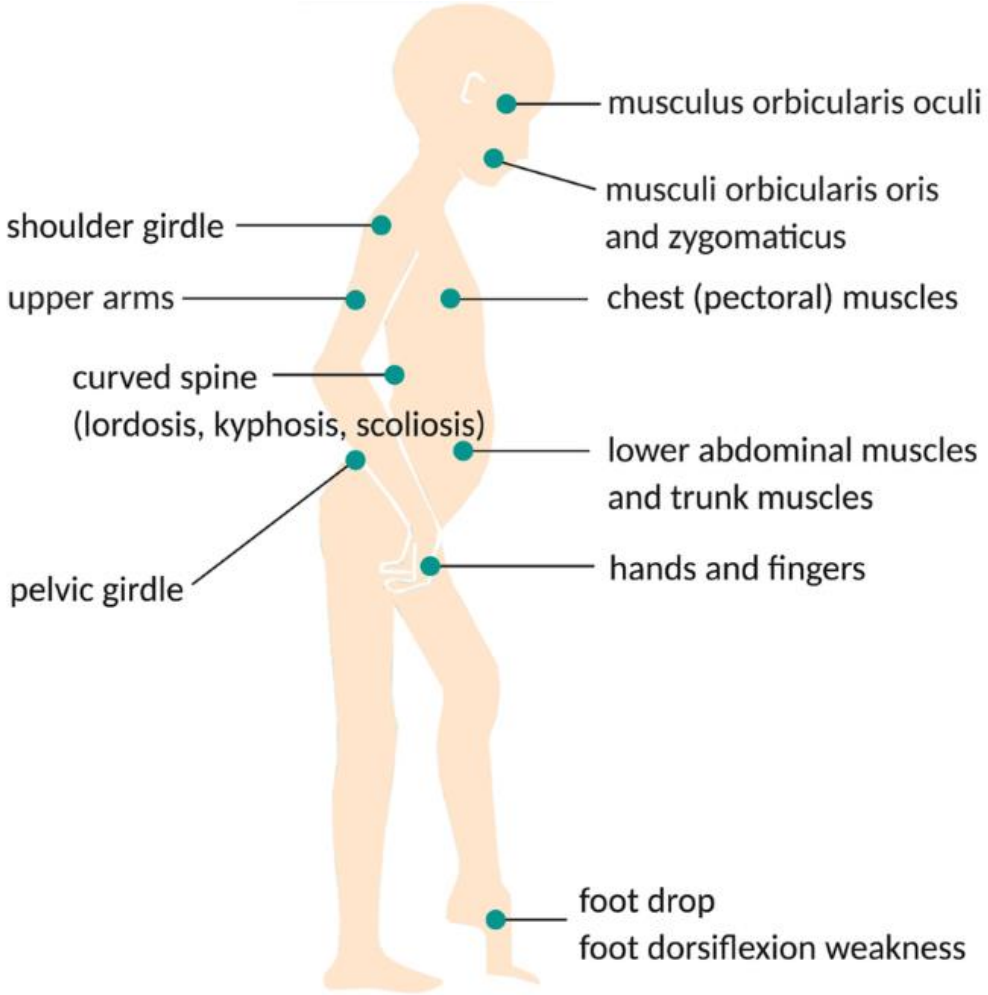
Muscular dystrophies



NOTE: women could be manifesting carries since one copy of X ch gets inactivated (lyonisation) and if this happens with majority of non-mutated X ch. symptoms develop in a carrier female



Affected muscles are generally involved asymmetrically regarding the left-right body axis

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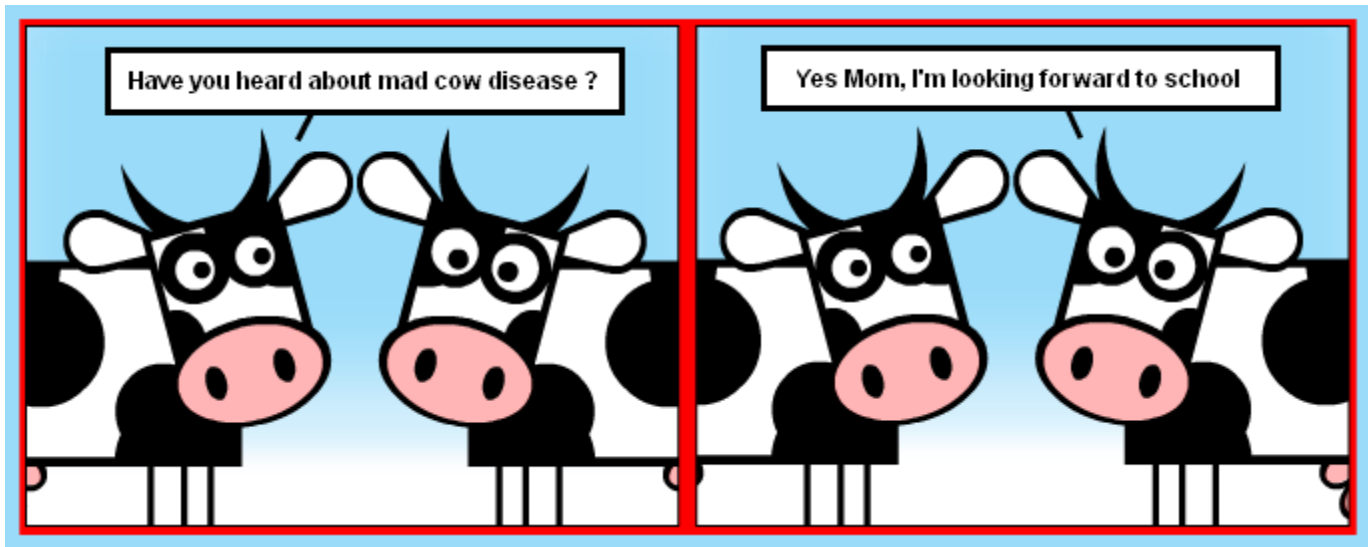
Have you heard about mad cow disease ?
Yes Mom, I'm looking forward to school

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