NX 423

Translational Neuroengineering

Parkinson’s disease

February 29, 2024 // Olaf Blanke

Parkinson's disease

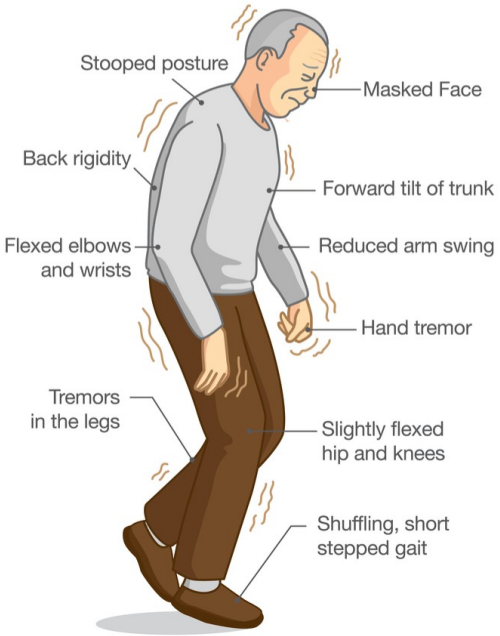
Described clinically 200 years ago by James Parkinson ('*An essay on the shaking palsy*' - 1817).
Linked to substantia nigra and Lewy body pathology 100 years ago.
Linked to nigro-striatal neurons and pathway, striatal dopamine depletion & dopamine replacement therapy 60 years ago.

But, definitive clinical tests and procedures to diagnose PD remain a major unmet goal: Diagosis still relies only on clinical features à la James Parkinson

Diagnosis can be challenging, because there are many different symptoms. Not only motor symptoms, but also many non-motor syptoms (depression, loss of smell, cognitive decline, hallucinations, sleep disruption, …)

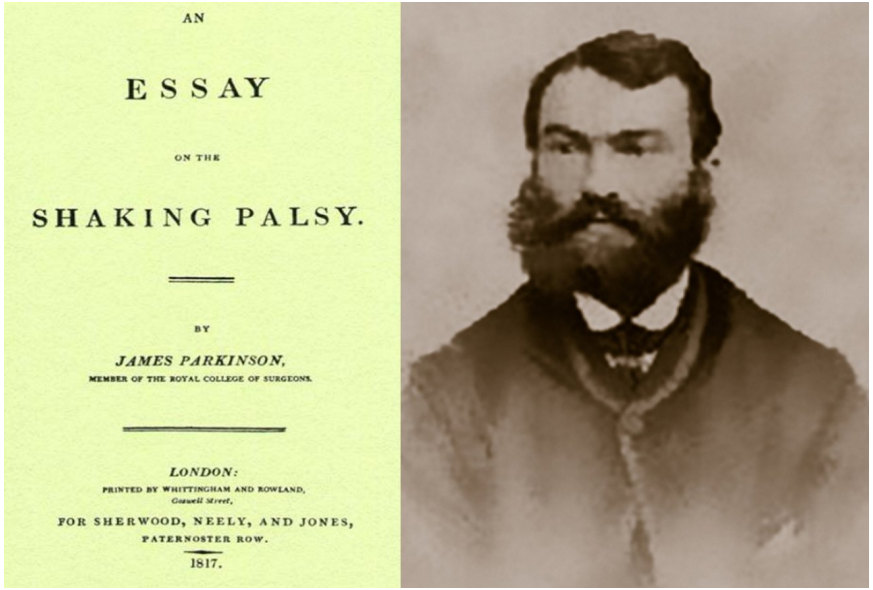
Powerful treatments (dopamine, deep brain stimulation) exist, but they are symptomatic and are not efficient for many of the non-motor symptoms & do not halt the progression of the disease.
→ Current research searches for early markers for PD & disease-altering therapies to stop PD progression.

(Genetic and molecular causes of PD are starting to be uncovered; these are not covered in this class).



James Parkinson

first clinical description of PD



James Parkinson (1755-1824)

1817 paper is based on 6 cases (he only examined 3; the others were «observed» by J. Parkinson in the streets of London.

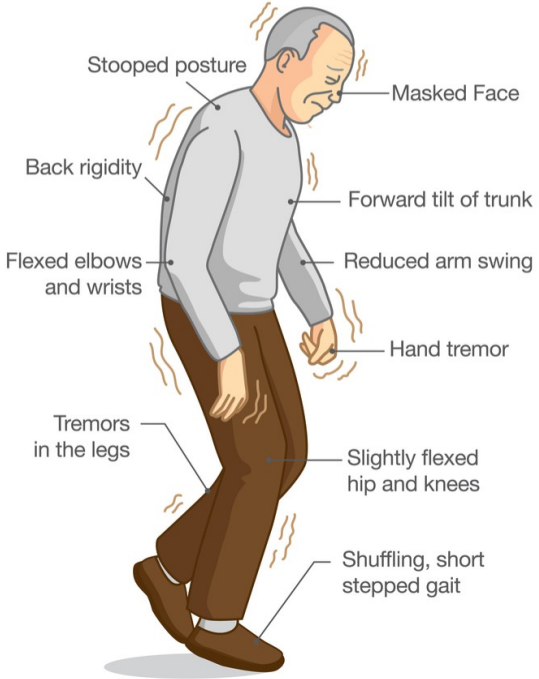
»...involuntary tremolous motion (...) not in action and when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and the intellect being uninjured.»

also describes long duration and progressive nature of PD

Wrote on many topics: medicine, politics, mental health, social reform, chemistry

Parkinson's disease

4 cardinal motor symptoms



4 cardinal motor symptoms

Bradykinesia (slowness of movements)
Resting tremor (shaking)
Rigidity (stiffness)

Axial symptoms (posture & gait)

… but also …
speech deficits (dysarthria)
swallowing problems (dysphagia)
Handwriting (dysgraphia)
…as well as many more motor symptoms

Resting tremor

Bloem et al., 2021

Bradykinesia

Bloem et al., 2021

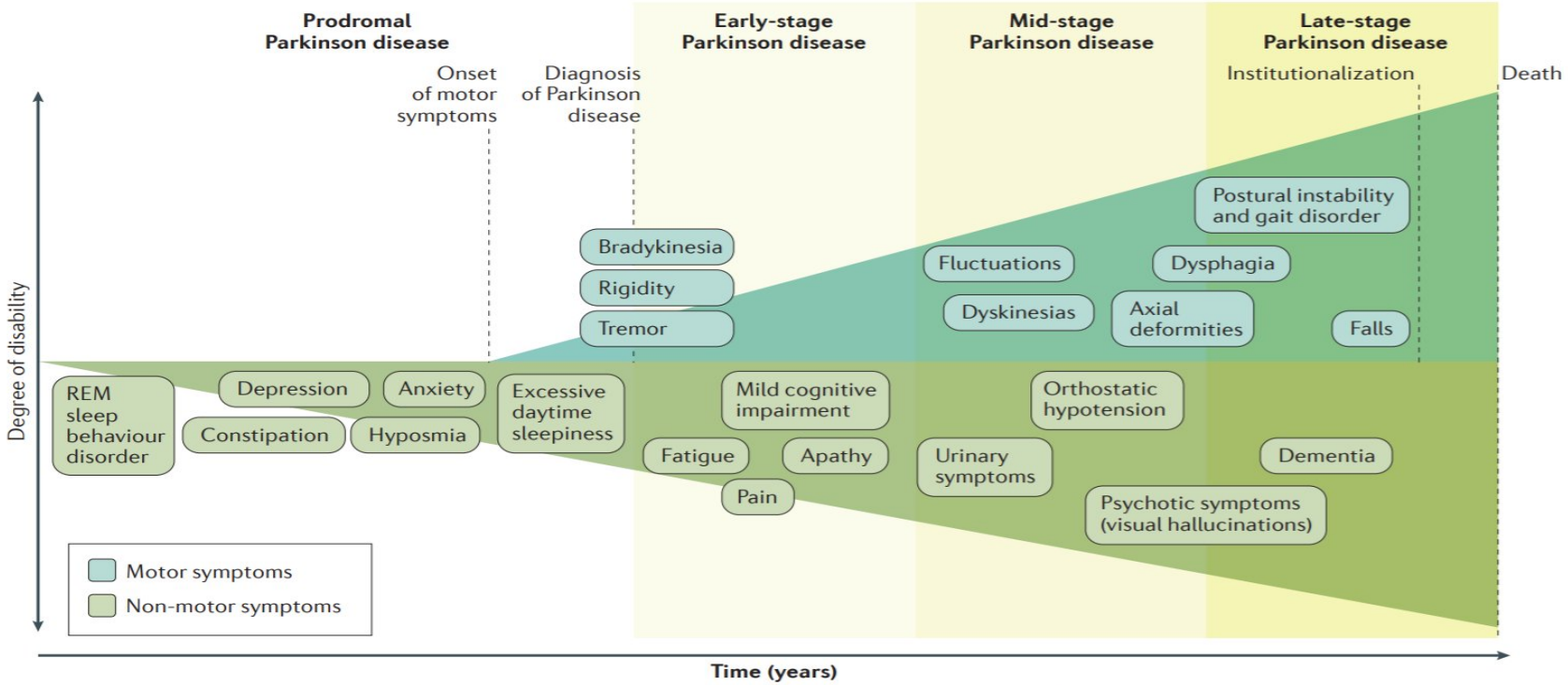
Rigidity

- see website at Lancet, also for second patient video

Bloem et al., 2021

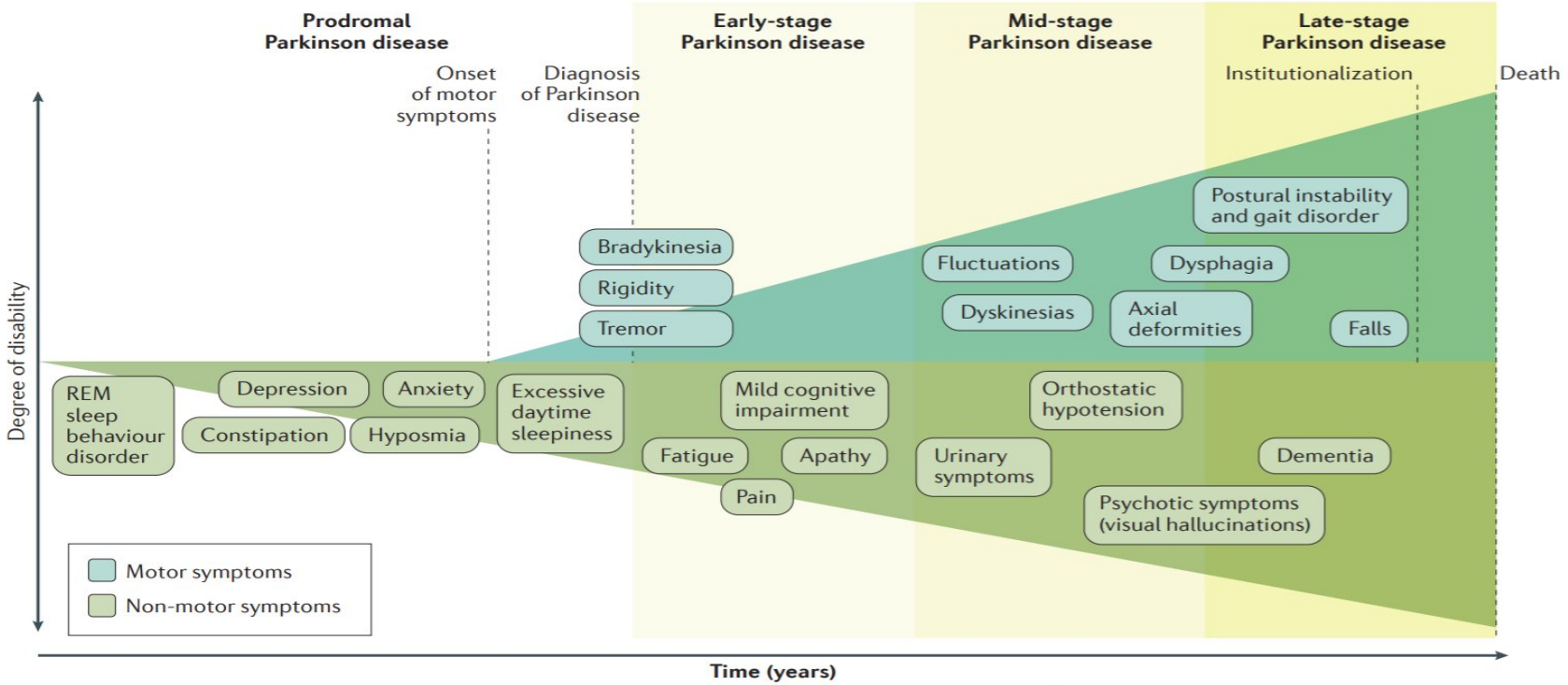
Parkinson's disease

Motor and non-motor symptoms



Parkinson's disease

Stages of the disease defined by symptoms



Parkinson's disease

Non-motor symptoms

Many non-motor symptoms

Depression-anxiety
Fatigue
REM sleep behavioral disorder (RBD)
Hyposmia (loss of smell)
Orthostatic hypotension
Dementia
Psychosis
Apathy
Urinary symptoms
…

In another lecture on PD we will focus on 3 major non-motor symptoms

Hallucinations & Psychosis

Mild cognitive decline & Dementia

REM sleep behavior disorder

Parkinson's disease

Epidemiology

PD in numbers
over 10 Mio individuals affected by PD, worldwide
(Europe: >1 Mio, CH: 15'000)

100'000 new PD cases/year (Europe)

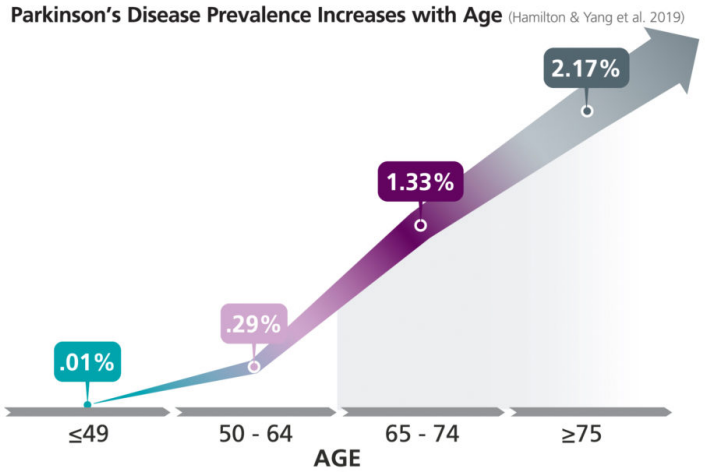
Estimates for 2040: 20 Mio PD patients (= fastest rising neurodegenerative disease)

Slow progression, starts with minor symptoms and accumulating disability, spans decades, but has highly variable patterns of PD and patterns of progression

Life expectancy is decreased, but most PD patients live a long life (many for decades after the diagnosis)

Stress for patient, but also for caregiver

Enormous socio-economic burden (disability burden has doubled in last 20 years)



PD is a disease of older people (>2-3% of people over 65 years of age).

Fastest growing neurological disorder: aging population, efficient symptomatic therapies !

PD can also occur in younger people (25% of cases before 65yo; 5-10% of cases are younger then 50yo)

Parkinson's disease

Epidemiology

Mortality (death) is higher if …

… dementia
… hallucinations
… poor response to dopamine therapy
… male sex
… no tremor

Parkinson's disease

Etiology

Genetic origin
Genetic causes account for about 10% of PD
(90% sporadic PD)

About 10 PD-related genes have been defined and lead to early-onset PD

SNCA, *LRRK2*, *PRKN*, *PINK1*, *GBA*.

α-synuclein
(SNCA)

Michael J. Fox (Foundation)

Environmental origin
-Pesticides
-Head injury (soccer, boxing)

Mohamed Ali

Negative associations:
Smoking
Coffein
Physical exercise

Many factors described, not always replicated across studies

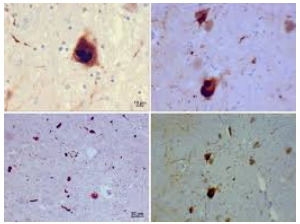
Neurodegenerative disorders

PD is the second most frequent neurodegenerative diseases

Alzheimer's disease (40 Mio cases worldwide; 80 Mio by 2040)
(cortical degeneration, temporal cortex)

PD (subcortical neurodegeneration)

Dementia with Lewy bodies (5-10 Mio cases worldwide)
(Lewy body pathology in neocortex)



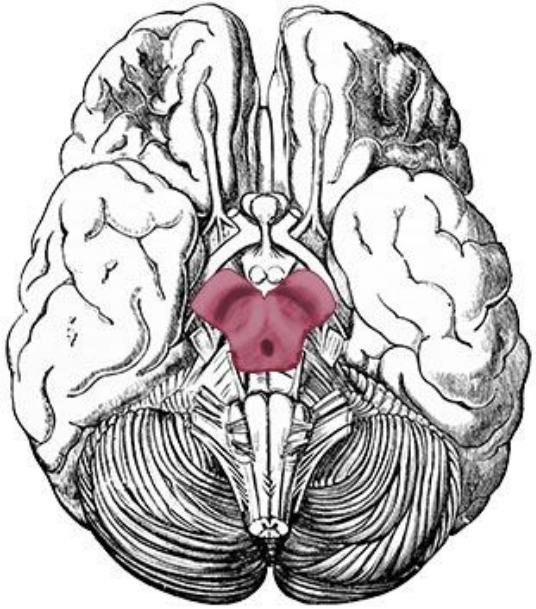
Stephen Hawking

Amyothrophic lateral sclerosis
(motor neuron degeneration)

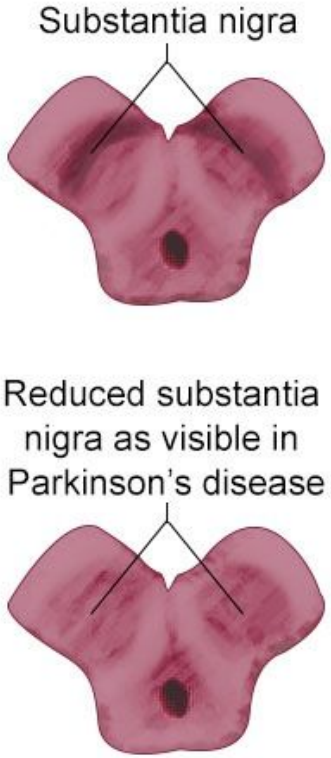
Corticobasal degeneration
Other
…

Parkinson's disease

Neuropathology

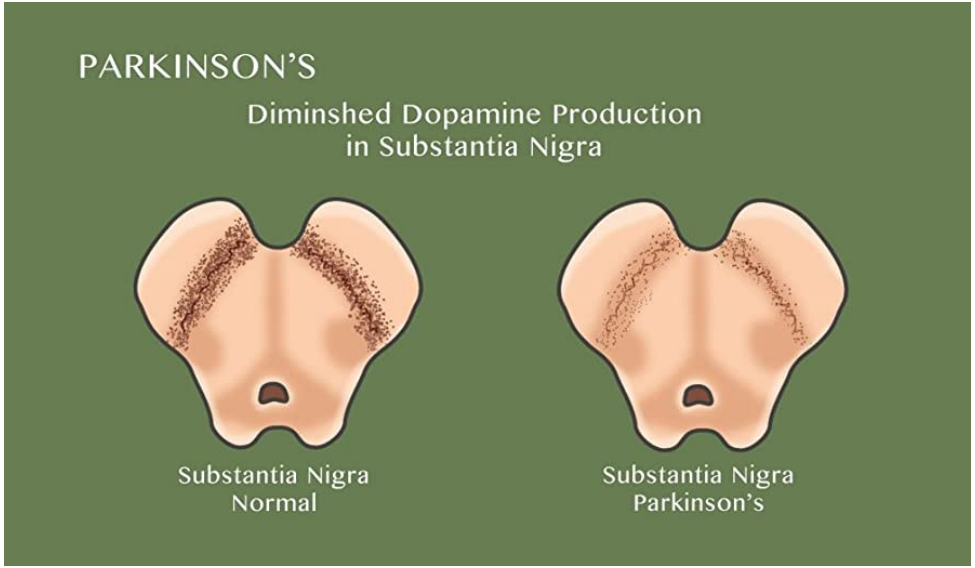


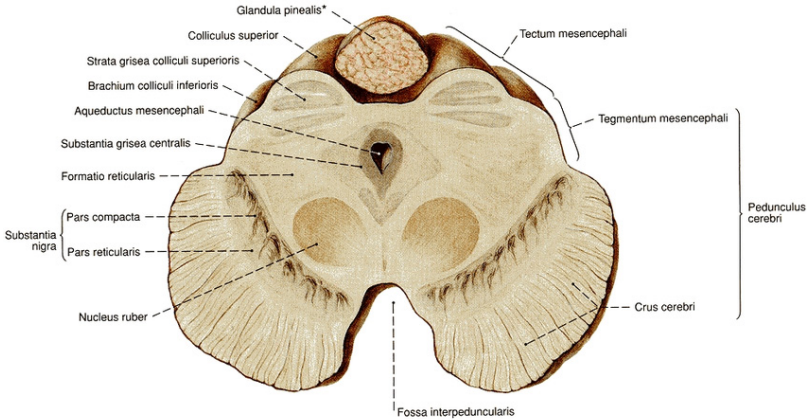
Cut section of the midbrain where a portion of the substantia nigra is visible



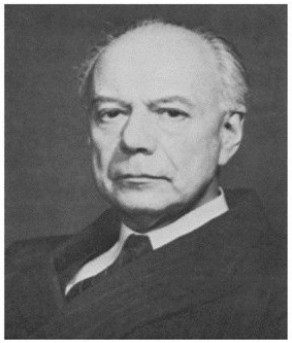
Parkinson’s disease

Cell loss in the substantia nigra pars compacta

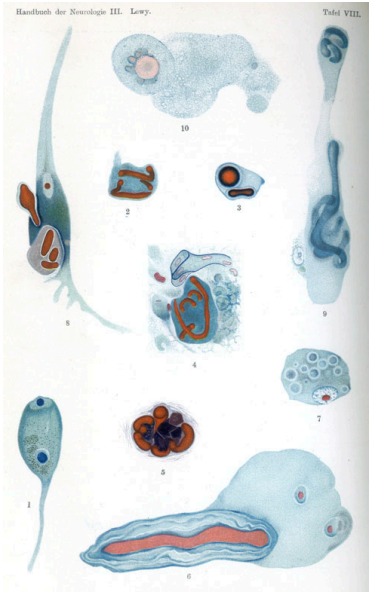




Loss of dopamine neurons affects the Pars compacta of the substantia nigra (not the Pars reticulata of the substantia nigra).



Fritz Lewy
(1885-1950)



Parkinson's disease (history)

Lewy body pathology in PD was discovered in 1912

Lewy was first to detail the pathological anatomy of PD in the brains of 25 patients with PD

Described eosinophilic cytoplasmatic concentric inclusion bodies (Lewy bodies) in brainstem, globus pallidus, and thalamus; linked Lewy bodies to PD (but did not link these changes to the substantia nigra)

Formation of Lewy pathology is central to the neurodegenerative process of PD

Central role of Lewy pathology only became known in 1997 (!) due to the discovery of the protein alpha-synuclein and its role in PD: mutation in SNCA (alpha-synuclein gene) causes familial form of PD; Lewy bodies are immunoreactive to alpha-synuclein.

Pathology can also be found in other disease (i.e., Lewy body dementia)

1912, in the Lab of Alois Alzheimer
(Lewy on far right)

Parkinson's disease

Lewy bodies in PD in the substantia nigra (1919)

Konstantin Tretiakoff (1892-1958)

CONTRIBUTION A L'ÉTUDE

DE

l'Anatomie pathologique du Locus Niger

DE SŒMMERING

avec quelques déductions relatives à la pathogénie des troubles du tonus musculaire

ET

DE LA MALADIE DE PARKINSON

Working in Paris after the Russian revolution

His PhD work was in histology/pathology and he studied the substantia nigra in 54 brains including several with PD.

In the PD cases he discovered the loss of pigmented substantia nigra neurons and swelling of cell bodies. Some surviving cells contained inclusion bodies (which he termed Lewy bodies).

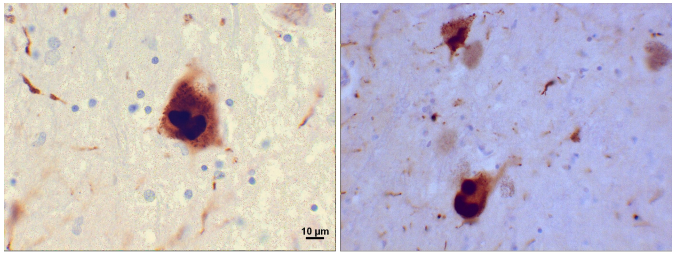
Linked substantia nigra (SN) to PD, including post-encephalitic forms of Parkinsonism (encephalitis lethargica).

Published in 1919, his first study in neurology, was one of the most important neuropathological discoveries of the 20th century (like Lewy he never worked on PD again).

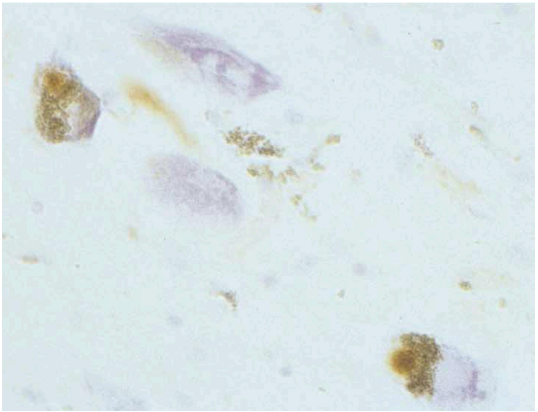
Lees AJ et al. (2008) Mov Dis

Parkinson's disease

Pathology: Lewy bodies & α-synuclein



Wikipedia



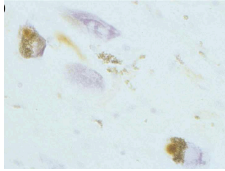
Godaert, Science 2015

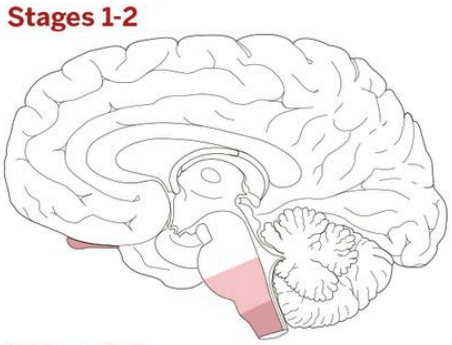
Definitive diagnosis of PD can only be established on the basis of post-mortem identification of hallmark neuropathological changes in the brain, especially the pars compacta of the Substantia nigra

Pathologically, Parkinson's disease is defined by the accumulation of α-synuclein in so-called Lewy bodies. Lewy pathology is characterised by aberrant α-synuclein aggregation, dysfunction of mitochondria, lysosomes or vesicle transport, synaptic transport issues, and neuroinflammation.

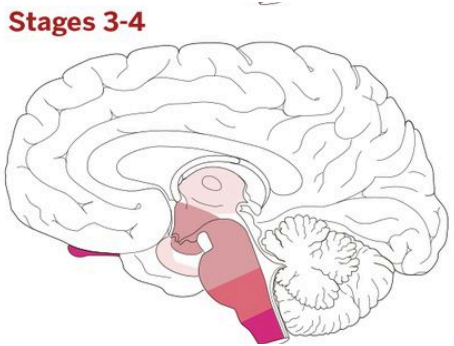
Parkinson’s disease

Braak stages (histology/pathology)
(based on presence of Lewy bodies across the brain)

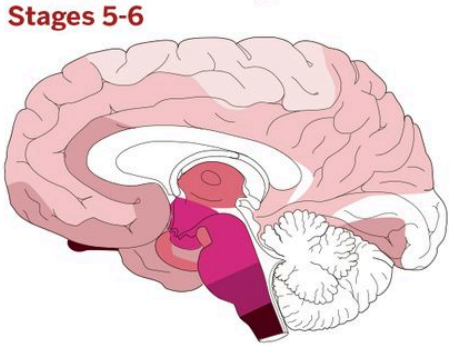




Motor *pre-symptomatic
prodromal phase



Motor symptomatic
Phase with diagnosis

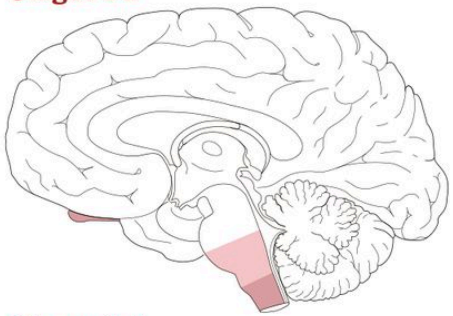


Advanced phase of PD

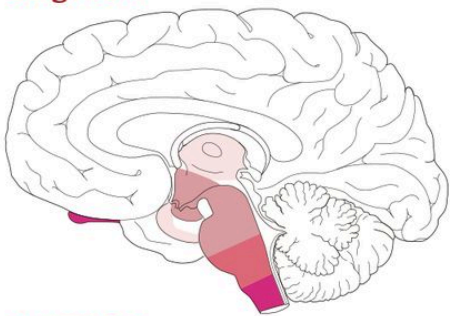
Parkinson's disease

Braak stages
(based on presence of Lewy bodies across the brain)

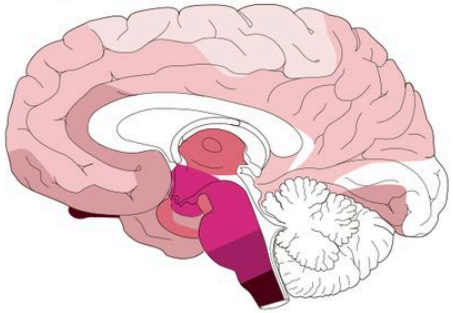
Stages 1-2



Stages 3-4

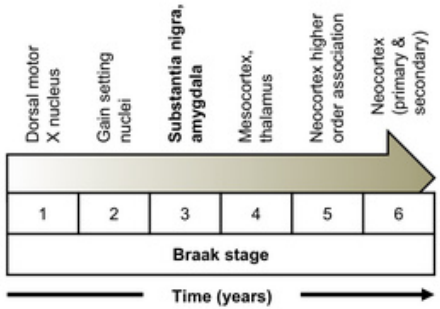


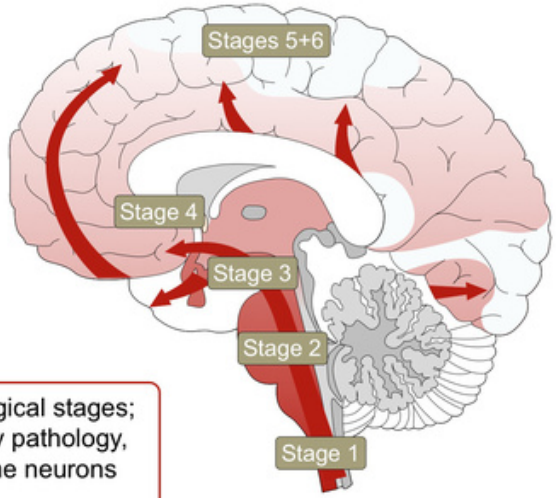
Stages 5-6



Braak staging of Parkinson's disease

The ascending pathological process within the PD brain[1]





PD is hypothesised to progress in six neuropathological stages; all of the affected neurons eventually develop Lewy pathology, but, despite the presence of inclusion bodies, some neurons survive for a long period of time[1]

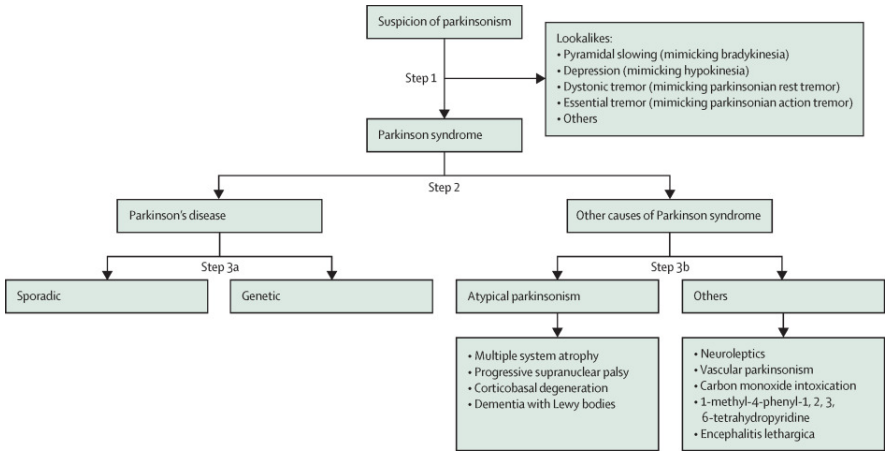
1. Braak et al. Cell Tissue Res 2004;318(1):121–134

Lundbeck Institute Campus

Parkinson's disease

Making the diagnosis & measuring disease progression & efficacy of treatment

Diagnosis



Progression

Internationally accepted rating scales to measure and quantify the progression of the disease and the efficacy of anti-parkinsonian treatments.

UPDRS (unified PD rating scale) is the most commonly used scale

4 sub-scales
Part I: Mentation, Behavior, Mood
Part II: Activities of Daily Living
Part III: Motor Examination
Part IV: Complications of Therapy

Questions


2

Parkinson’s disease

Anatomy
Physiology
Pathophysiology
… of the basal ganglia

Basal ganglia
Anatomy-Function

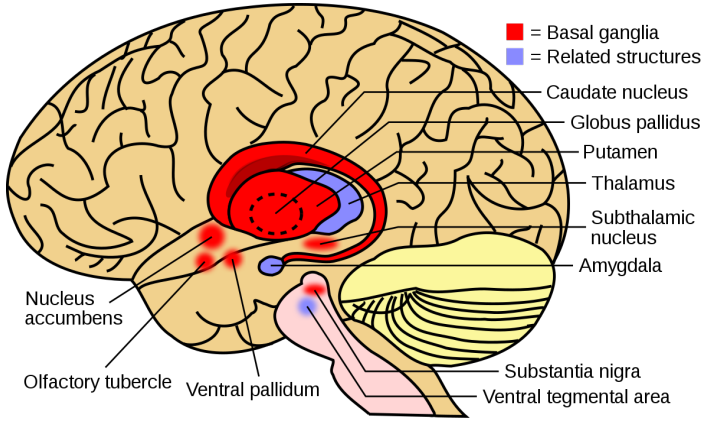
Basal ganglia (BG) are bilateral subcortical key structures for motor, cognitive, and affective functions.

Include subcortical nuclei in diencephalon, mesencephalon and telencephalon.

BG are connected to all cortical regions, especially to frontal cortex.

BG function is best studied/known for motor function:
BG are key structures for motor learning, selection of movements and inhibition of competing movements.

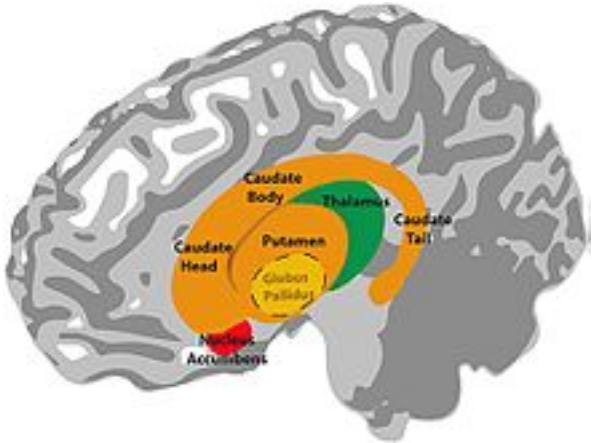
4 main anatomical structures:
1 - Striatum (caudate, putamen, nucleus accumbens)
2 - Globus pallidus (GPe, GPi, central pallidum)
3 - Subthalamic nucleus
4 - Substantia nigra (SNpc, SNpr)

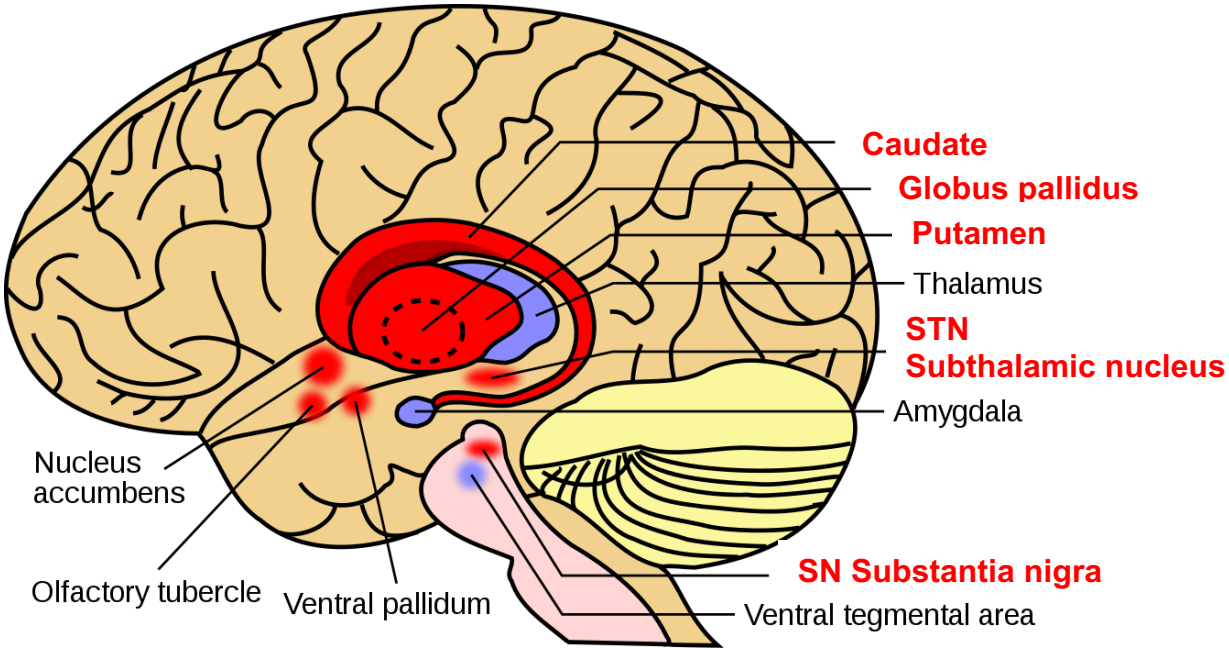


The majority of input into BG arrives from cortex (and thalamus) to the striatum (the input is excitatory input)

Output nuclei are GPi and SN (pars reticulata) and send their projections to thalamus and brainstem/spinal cord (the output is inhibitory output)

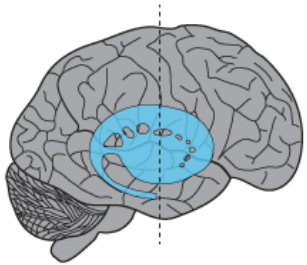
Basal ganglia

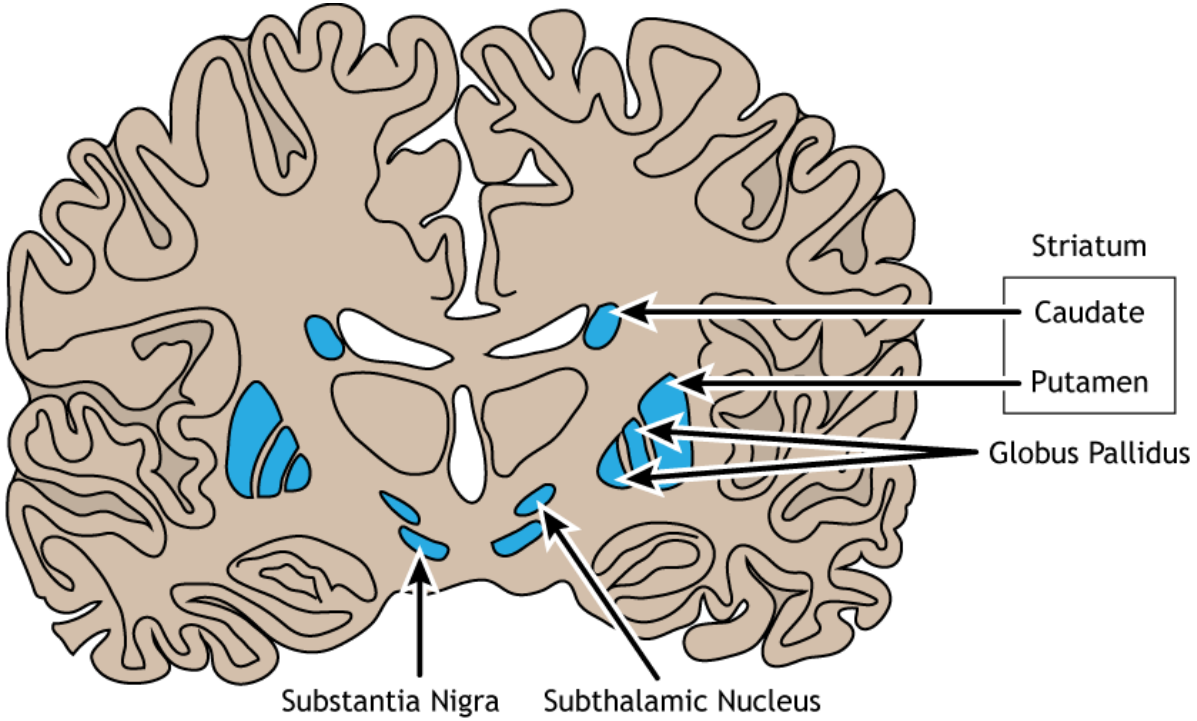




RED = strutures covered in class

Basal ganglia



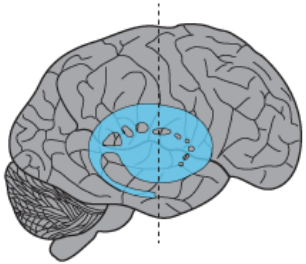


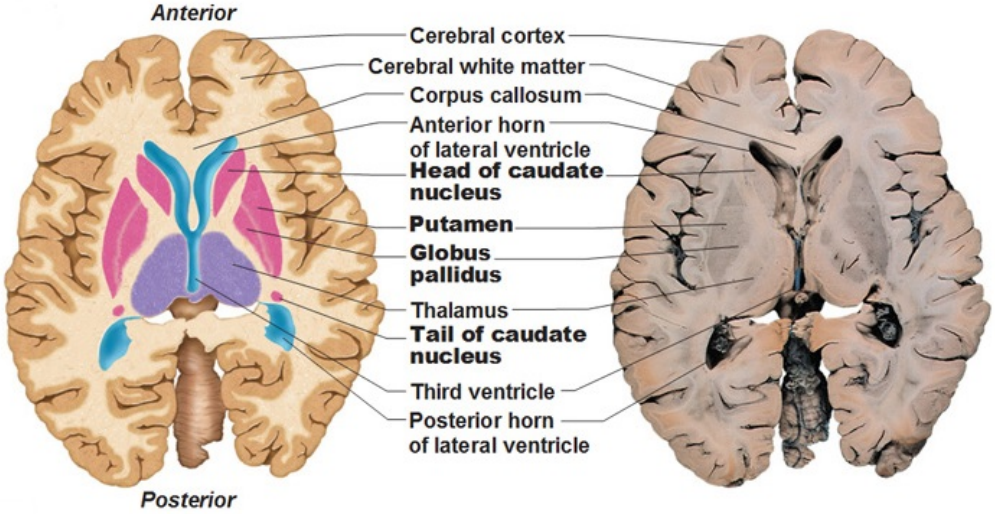
Coronal section/view

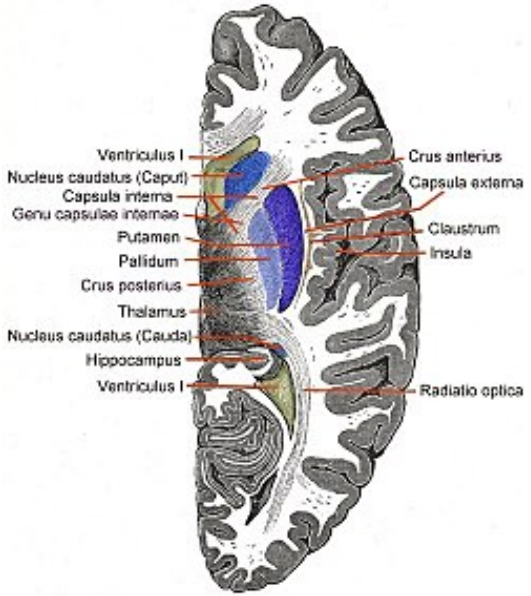
Striatum:

Caudate nucleus, Putamen: dorsal striatum

(Nucleus accumbens & olfactory tubercule = ventral striatum not discussed)



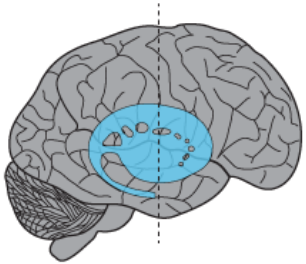




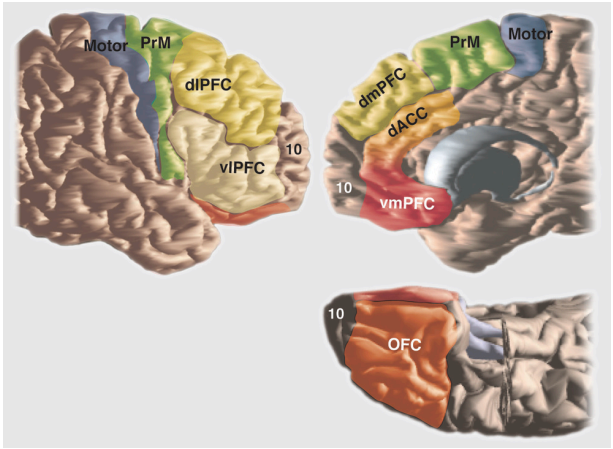
Striatum receives input from cortex (and thalamus)

Striatum:

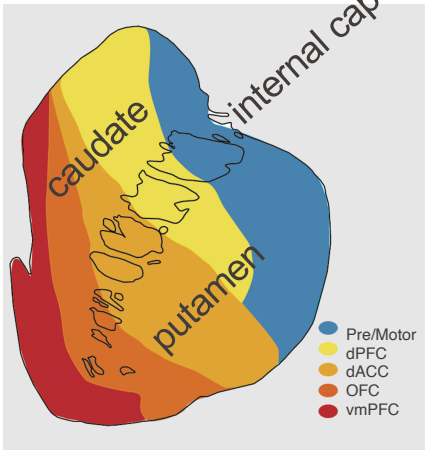
Dorsal striatum: Caudate nucleus, Putamen



Frontal cortical subregions



Striatum



(Haber, 2016)

Putamen and caudate are part of the telencephalon (together with cerebral cortex)

Striatum is connected with all cortical regions

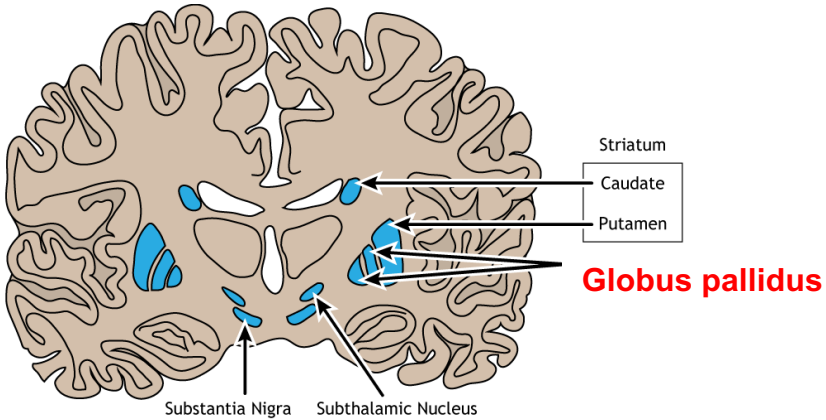
Most densely connected with frontal cortex (M1, premotor cortex, supplementary motor cortex, prefrontal cortex)

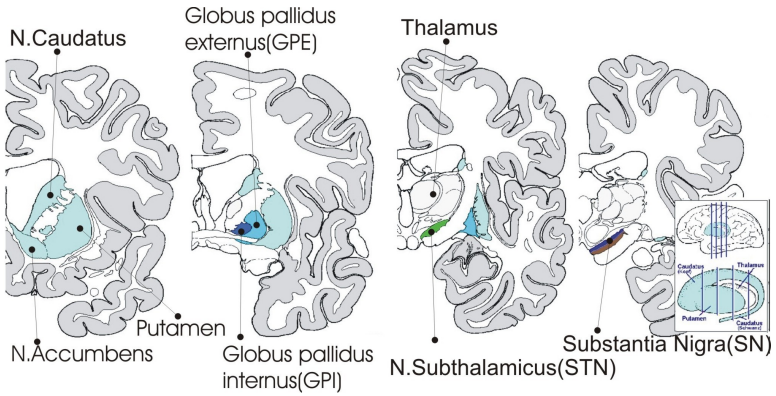
Interareal connectivity shows topography (i.e. most premotor connections are in the same region), but also mixing/divergence of connections (premotor fibers project to different parts of the striatum)

Pallidum:

Globus pallidus internal segment (GPi), Globus pallidus external segment (GPe)

(ventral pallidum, not covered)

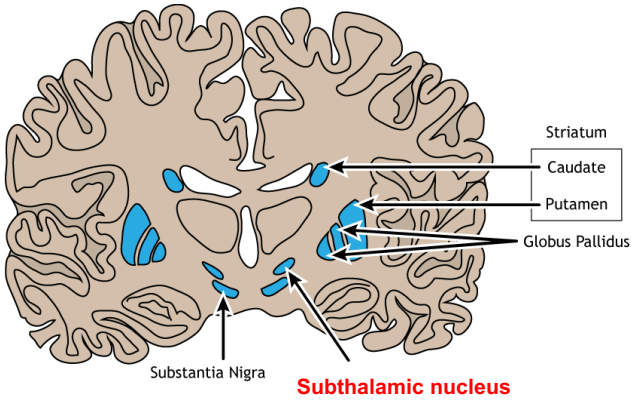


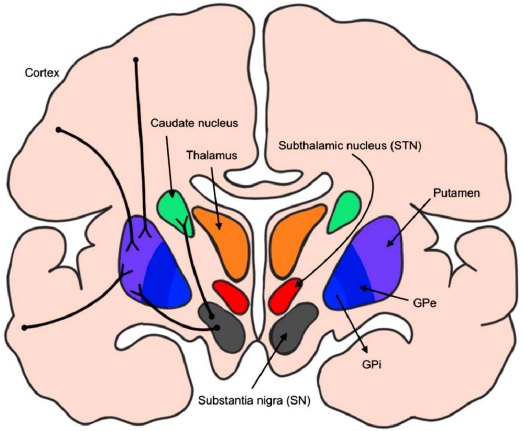


GPi is important output nucleus of the basal ganglia.

GPe receives input from striatum and sends it to GPi and STN.

Subthalamic nucleus (STN)





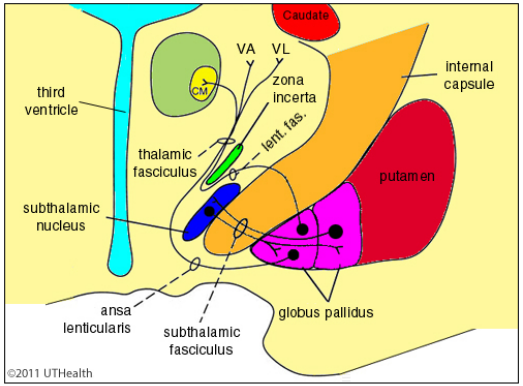


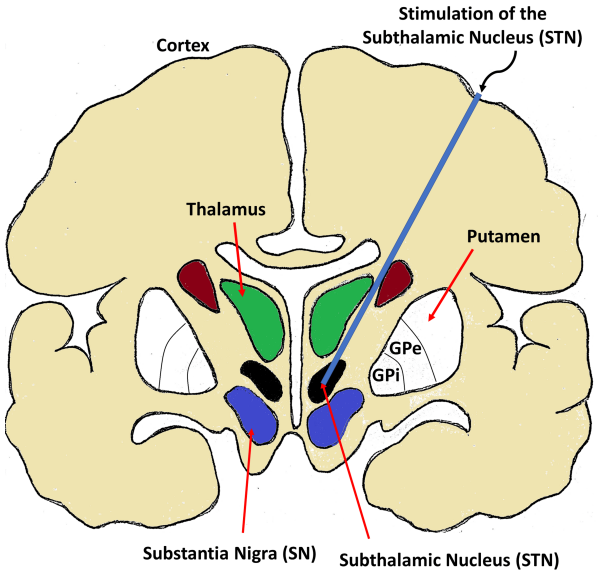
Figure 1

Oval shaped
Located in diencephalon

STN receives input from GPe and sends it to GPi and sends feedback to GPe.

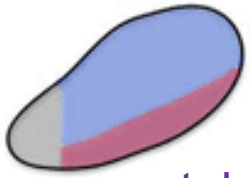
Also note that many fiber tracts are close to the basal ganglia (internal capsule, medial lemniscal tract, others).

Subthalamic nucleus (STN)



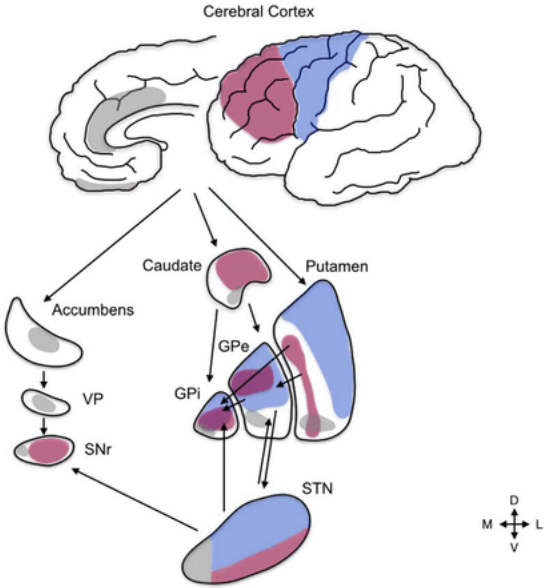
Key structure for deep brain stimulation (DBS) in PD

dorsal-lateral
(sensorimotor part)



rostral
(limbic)

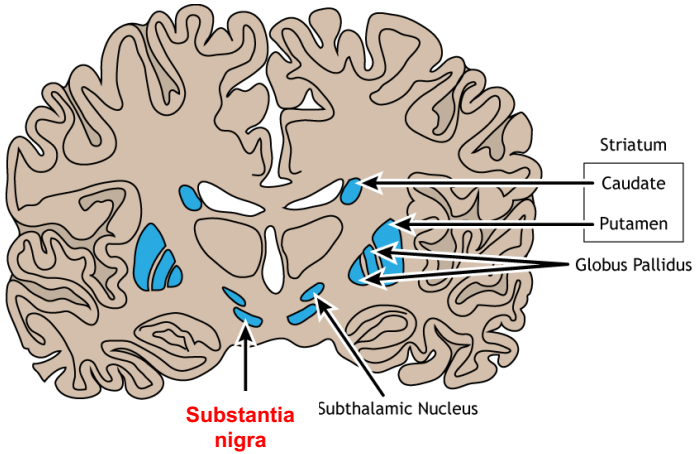
ventral
(associative part)

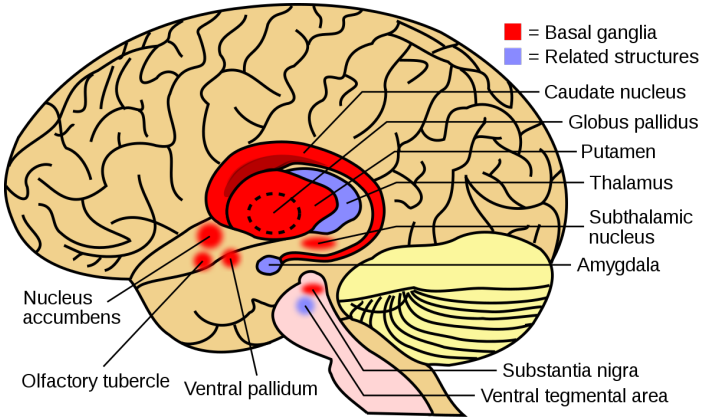


dorsal-lateral part of STN is targeted for DBS

Hamani et al., 2017

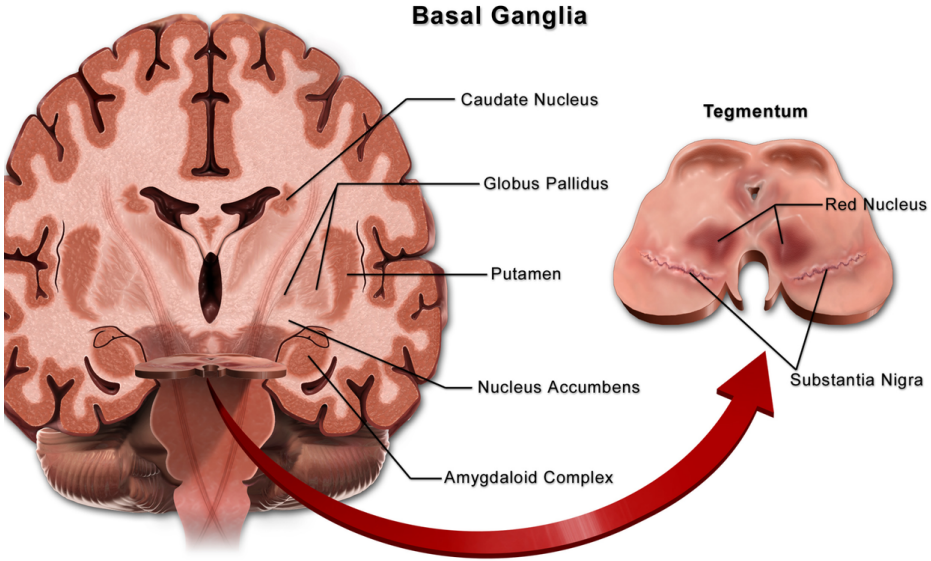
Substantia nigra

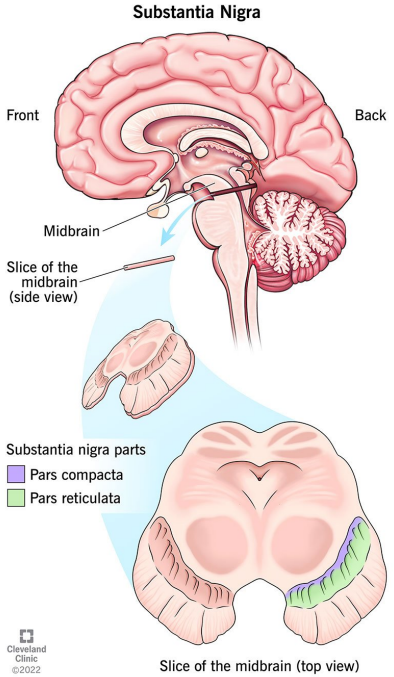




Located in mesencephalon, not di- or telencephalon as other basal ganglia nuclei

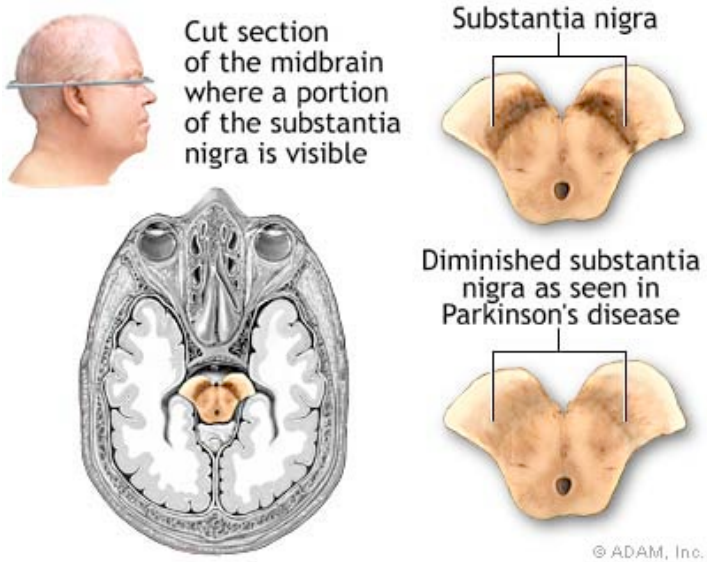
Substantia nigra:
SN pars compacta, SN pars reticulata

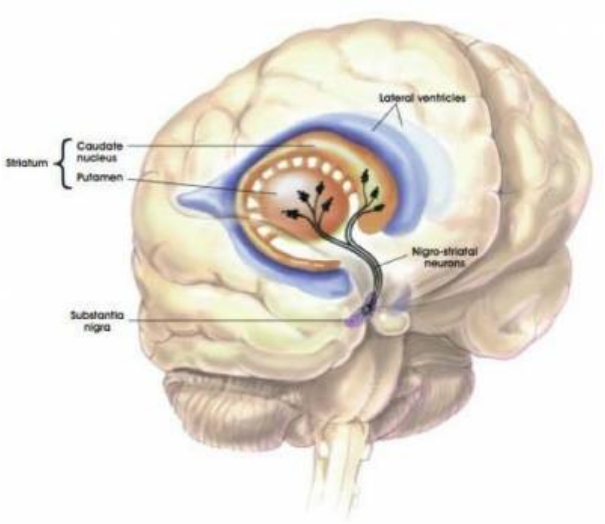




Substantia nigra

SN pars compacta is the key pathological structure in PD with loss of dopaminergic nigro-striatal neurons

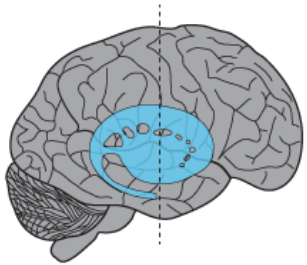


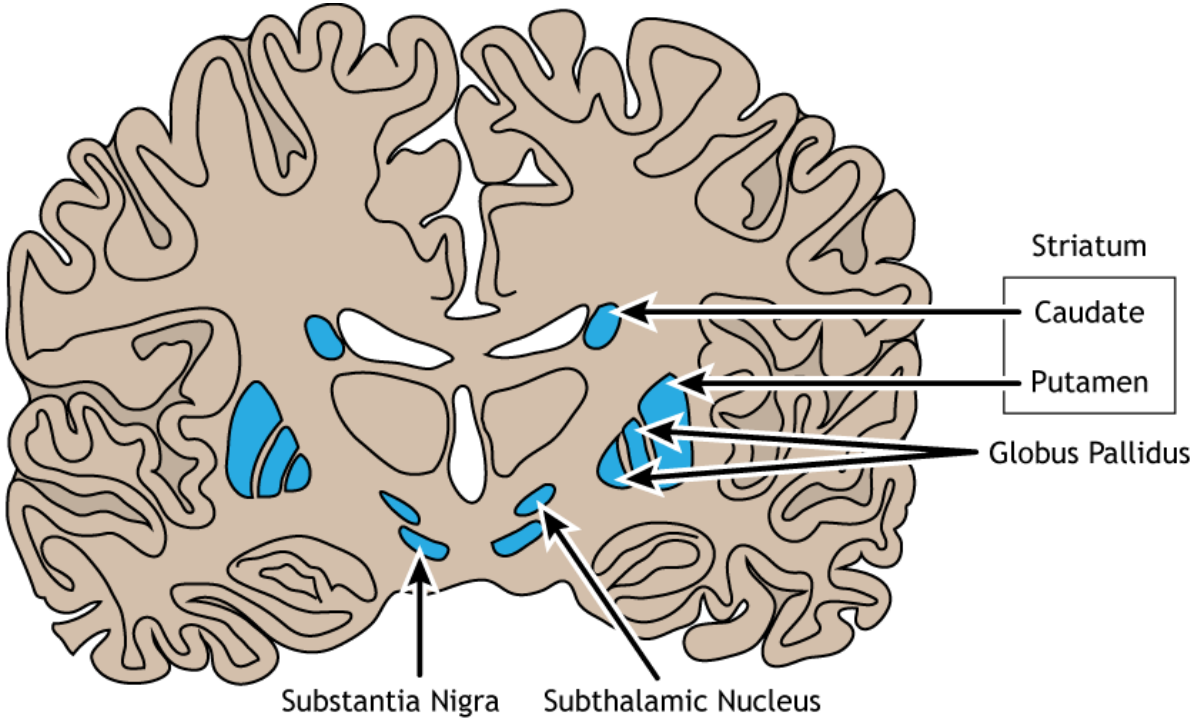


Depigmentation of SN pars compacta is caused by degeneration of nigro-striatal neurons and loss of melanin from these neurons

Basal ganglia

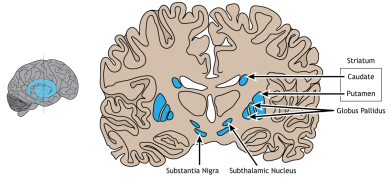
Functional circuits for movement control





Basal ganglia

Functional circuits for movement control



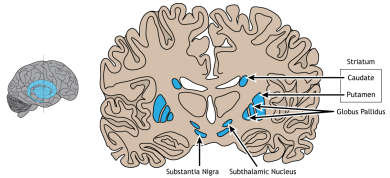
Cerebral cortex

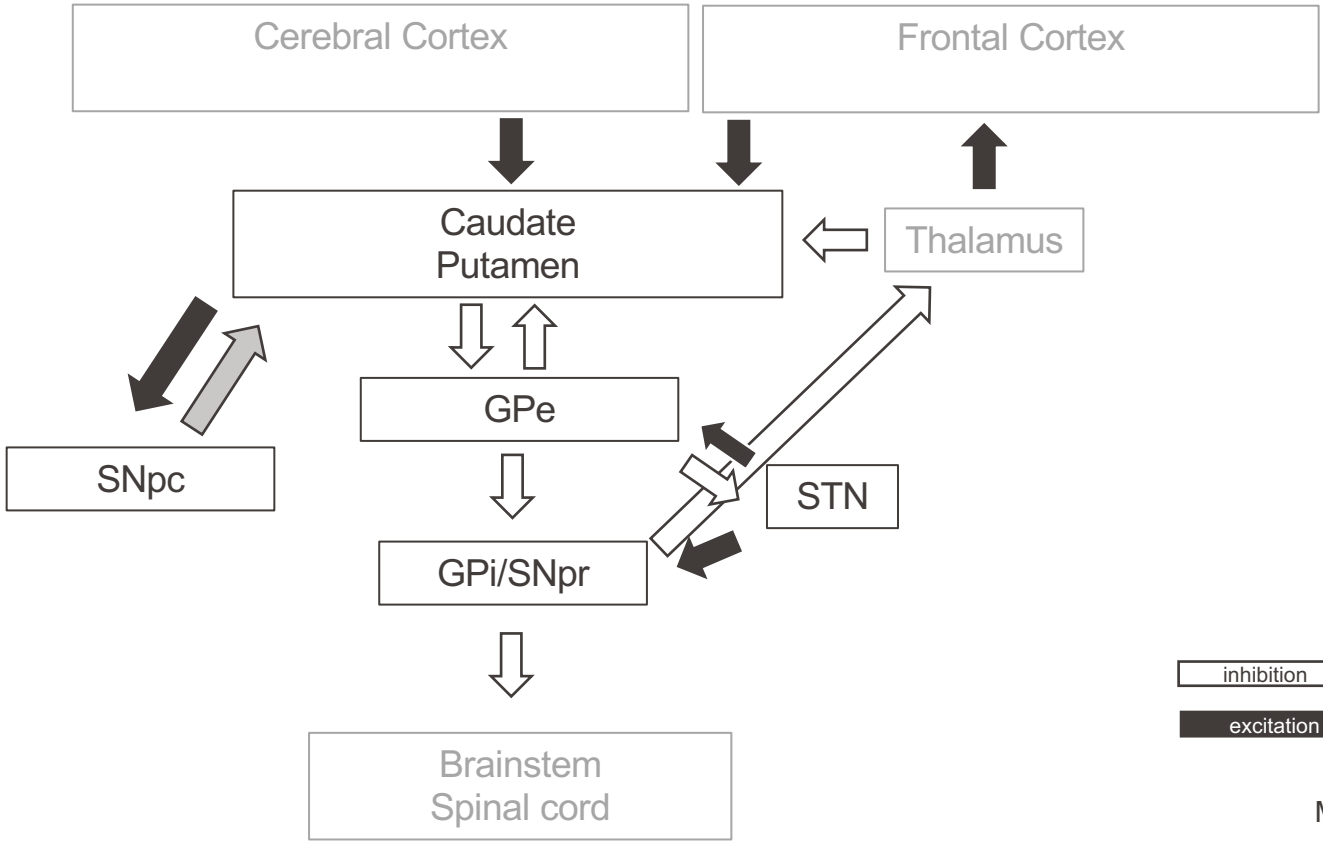
Basal ganglia

Thalamus

Basal ganglia

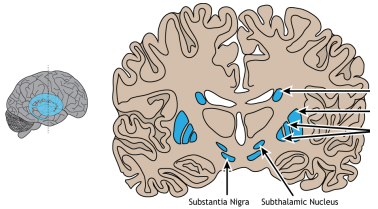
Functional circuits for movement control





Mink, 2015

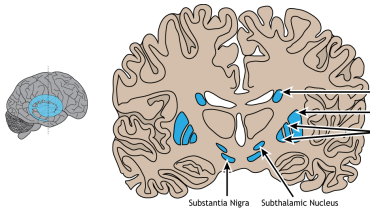
Two primary di-synaptic pathways from the cortex to basal ganglia output structures (PGi/SNpr) and from there via thalamus back to cortex are fundamental for BG motor function



Direct pathway (from cortex to striatum to GPi)

Hyperdirect pathway (from frontal cortex to STN to GPi)

Two primary di-synaptic pathways from the cortex to basal ganglia output structures (Pgi/SNpr) and from there via thalamus back to cortex



Cerebral Cortex

Frontal Cortex

Caudate
Putamen

Thalamus

GPe

SNpc

STN

GPi/SNpr

Brainstem
Spinal cord

inhibition

excitation

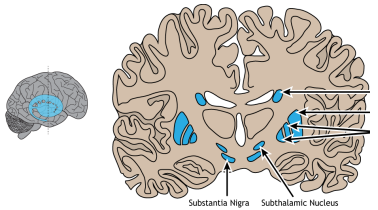
Direct pathway (from cortex to striatum to GPi)

- input from all cortical regions
- slow
- inhibitory
- focussed

Hyperdirect pathway (from frontal cortex to STN to GPi)

- only frontal input
- fast
- excitatory
- divergent

Two primary di-synaptic pathways from the cortex to basal ganglia output structures (Pgi/SNpr) and from there via thalamus back to cortex



Cerebral Cortex

Frontal Cortex

Caudate
Putamen

STN

GPi/SNpr

Broad excitation (via STN) and focussed inhibition (via striatum) of GPi/SNpr

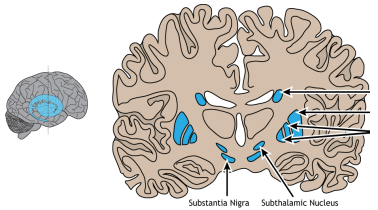
Direct pathway (from cortex to striatum to GPi)
- input from all cortical regions
- slow
- inhibitory
- focussed

Hyperdirect pathway (from frontal cortex to STN to GPi)
- only frontal input
- fast
- excitatory
- divergent

inhibition

excitation

Two primary di-synaptic pathways from the cortex to basal ganglia output structures (Pgi/SNpr) and from there via thalamus back to cortex



Cerebral Cortex

Frontal Cortex

Caudate
Putamen

Thalamus

STN

GPi/SNpr

Broad excitation (via STN) and focussed inhibition (via striatum) of GPi/SNpr

Brainstem, Spinal cord

Direct pathway (from cortex to striatum to GPi)

- input from all cortical regions
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- inhibitory
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Hyperdirect pathway (from frontal cortex to STN to GPi)

- only frontal input
- fast
- excitatory
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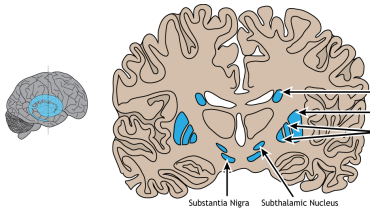
inhibition

excitation

Two primary di-synaptic pathways from the cortex to basal ganglia output structures (Pgi/SNpr) and from there via thalamus back to cortex



Cerebral Cortex

Frontal Cortex

Caudate
Putamen

Thalamus

STN

GPi/SNpr

Broad excitation (via STN) and focussed inhibition (via striatum) of GPi/SNpr

Because GPi/SNr output is inhibitory → this leads to broad/surround inhibition of unintended movements and focussed dis-inhibition (facilitation) of intended movement (via thalamus and brainstem)

Brainstem, Spinal cord

Direct pathway (from cortex to striatum to GPi)
- input from all cortical regions
- slow
- inhibitory
- focussed

Hyperdirect pathway (from frontal cortex to STN to GPi)
- only frontal input
- fast
- excitatory
- broad/divergent

inhibition

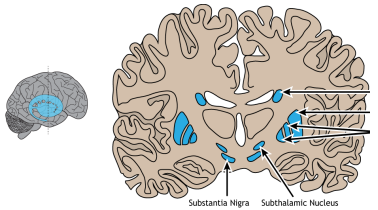
excitation

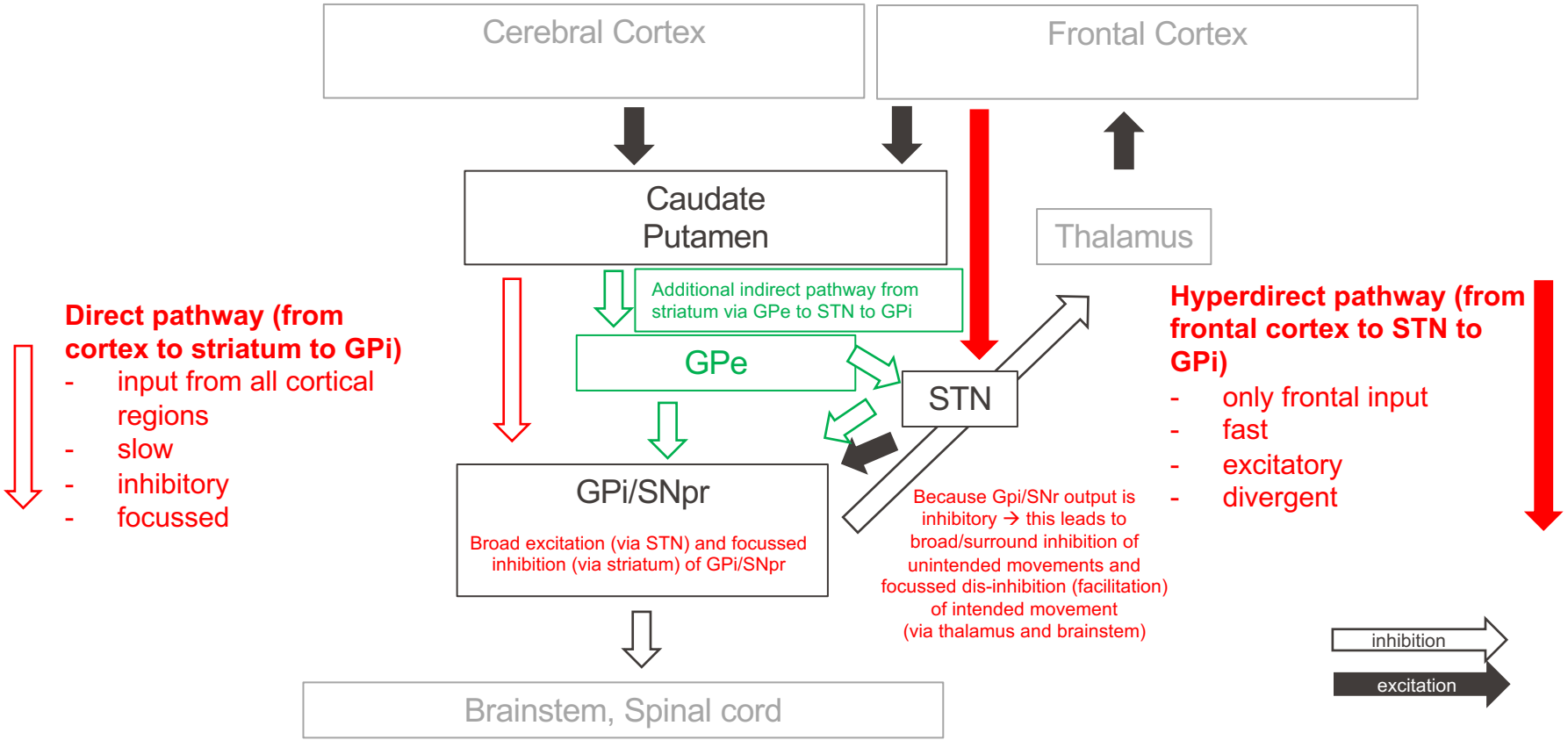
Because output of GPi/SNpr, in general, is inhibitory (output to thalamus-cortex and to brainstem) the net result of the broad excitation of GPi/SNpc via the **hyperdirect pathway** is broad inhibition or supression of unintended movements.

Because output of GPi/SNpr in general is inhibitory (to thalamus-cortex and brainstem) the net result of the focussed inhibition of GPI/SNpc via the **direct pathway** is dis-inhibition or facilitation of selected-intended movement.

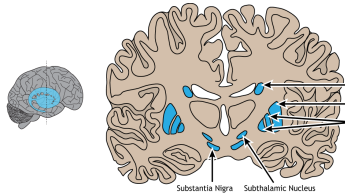
Functional center-surround organization
Selection of the intended movement and prevention of unintended movements, mediated via the hyperdirect and the direct pathways, through a cortical-basal ganglia-thalamus-cortical loop.

This organization of action selection is additionally fine-tuned through the indirect pathway



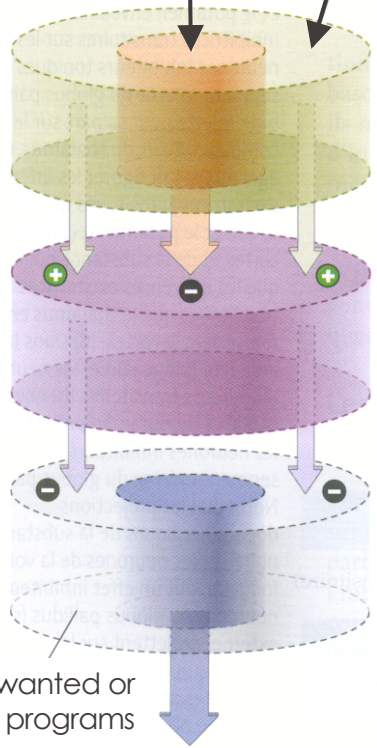


Action selection by basal ganglia circuits



Direct pathway
(inhibitory via striatum)

Hyper-direct pathway
(excitatory via STN)



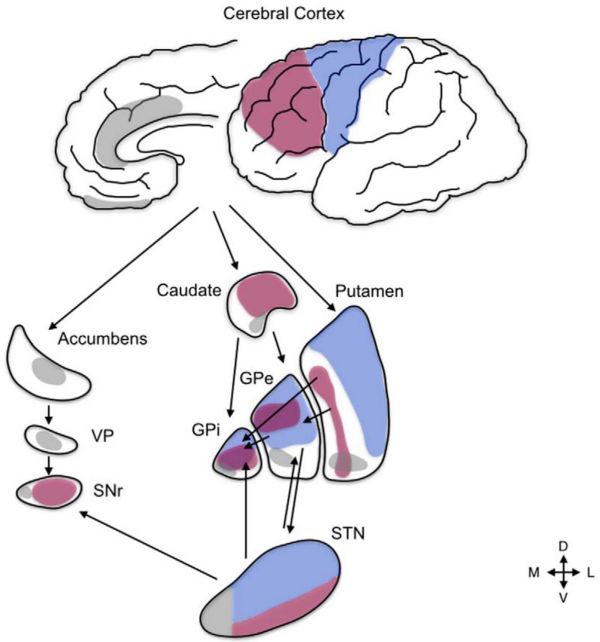
GPi/SNr

Thalamus (back to cortex)
and brainstem

Suppression of unwanted or
involuntary motor programs

Activation of desired motor programs

Motor/premotor basal ganglia circuit: Movement
Lateral prefrontal basal ganglia circuit: Cognition
Medial prefrontal-limbic basal ganglia circuit: Emotion



Many other functions of the basal ganglia:

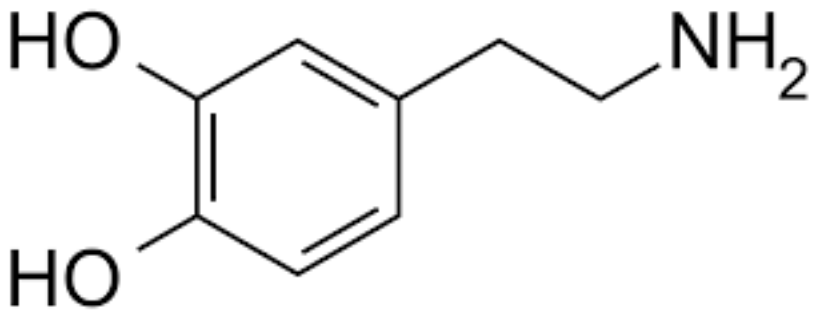
Complex action selection
Decision making
Learning
Working memory
Motivation
Reward processing
…

- Hamani et al 2017

Questions

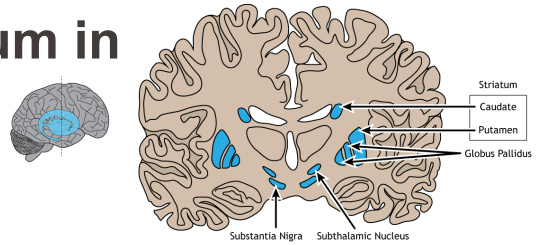

3

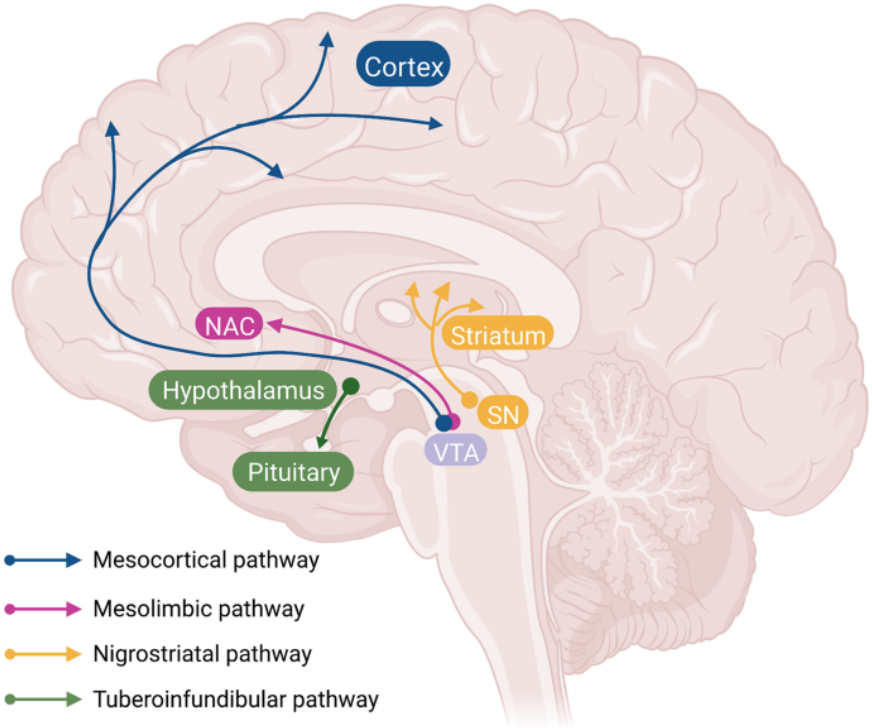
Dopamine & PD



Dopamine, the substantia nigra & the striatum in Parkinson's disease

Dopamine pathway in PD



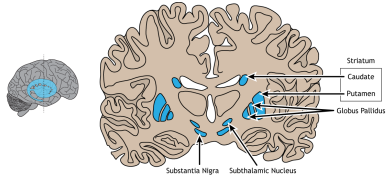


Several dopamine pathways

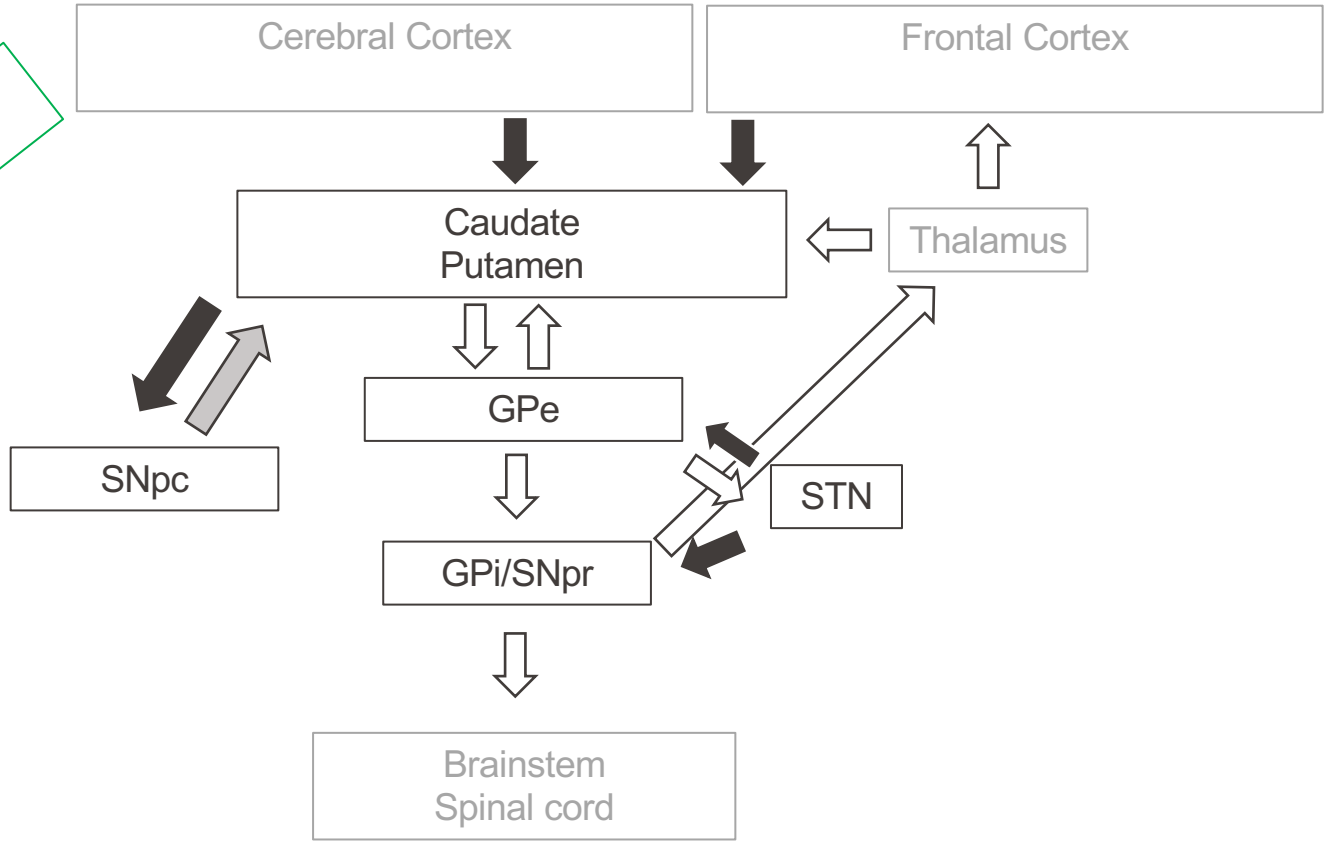
Nigrostriatal pathway between substantia nigra and striatum is affected in PD and the key neuropathological hallmark of PD

Basal ganglia

Functional circuits for movement control

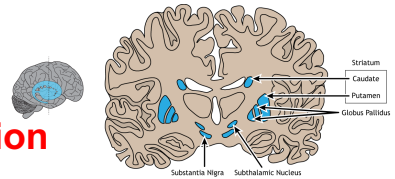


Reminder



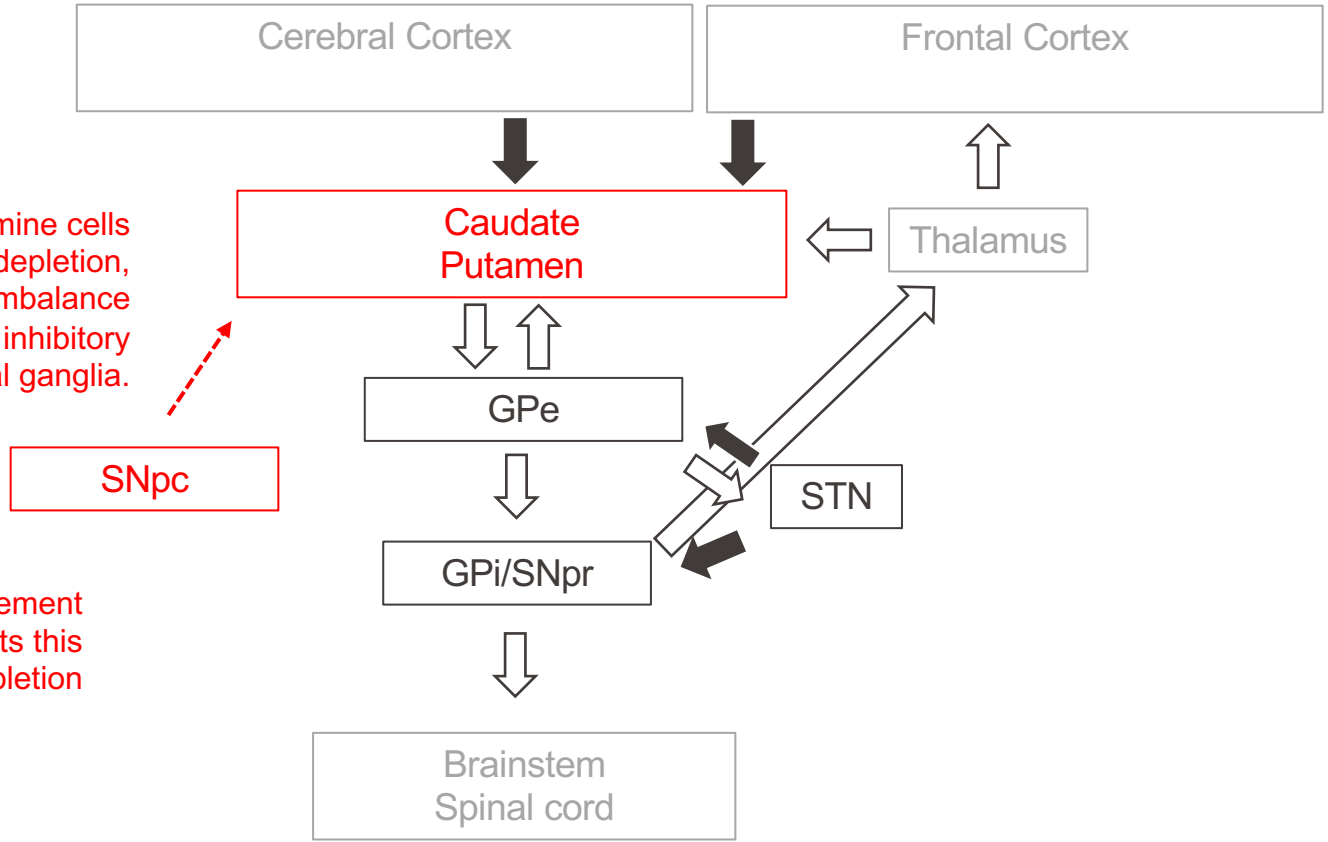
Basal ganglia

Loss of nigrostriatal neurons in PD leading to dopamine depletion in striatum



Loss of nigrostriatal dopamine cells causes striatal dopamine depletion, which results in an imbalance between excitatory and inhibitory pathways through the basal ganglia.

Dopamine replacement therapy corrects this depletion



Parkinson's disease

Linking neuronal loss in SNpc to dopamine loss in the striatum in PD

Oleh Horneykiewicz
(1926-2000)

Arvid Carlsson
(1923-2018)

Neurochemical properties of the substantia nigra neurons that Tretiakoff discovered were unknown, when Horneykiewicz performed his experiments

Horneykiewicz measured dopamine in post-mortem brains of PD patients and healthy controls and found selective dopamine depletion in caudate and putamen in PD patients and proposed nigrostriatal pathway theory (1960)

Also proposed that dopamine replacement therapy may relieve PD symptoms and tested this with i.v. injections of dopamine (1961)

Showed in several animal experiments that levodopa antagonized the effect of reserpine (which induces PD-like symptoms such as immobility) (1957)

Showed that reserpine depleted brain dopamine and that L-dopa restored it (1958)

Showed that dopamine is highest in the striatum, proposed dopamine is a neurotransmitter and plays an important role in motor function

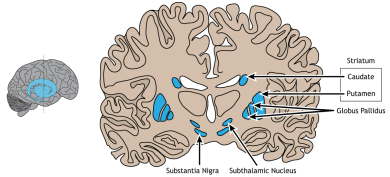
Received Nobel prize in 2000

Lees AJ et al. (2008) Mov Dis

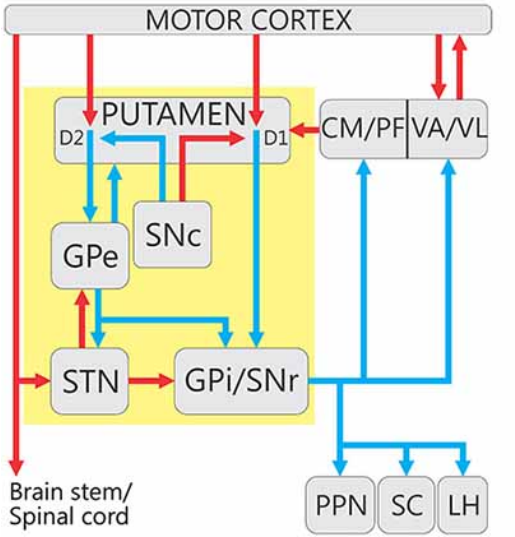
Carlsson Science 2001
AJ Lees (2015) Mov Dis

Basal ganglia

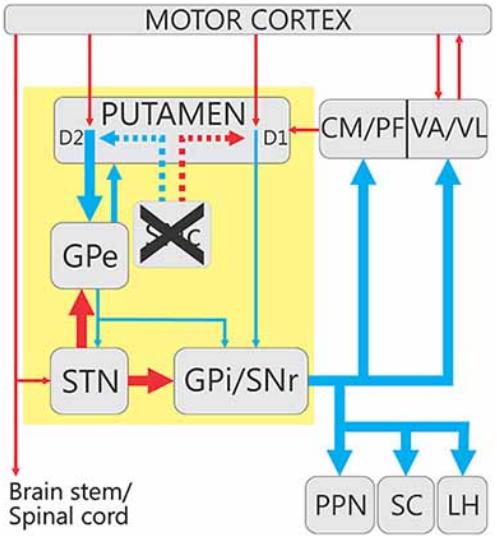
Loss of nigrostriatal dopamine leads to circuit changes beyond SN pars compacta and Putamen



Normal



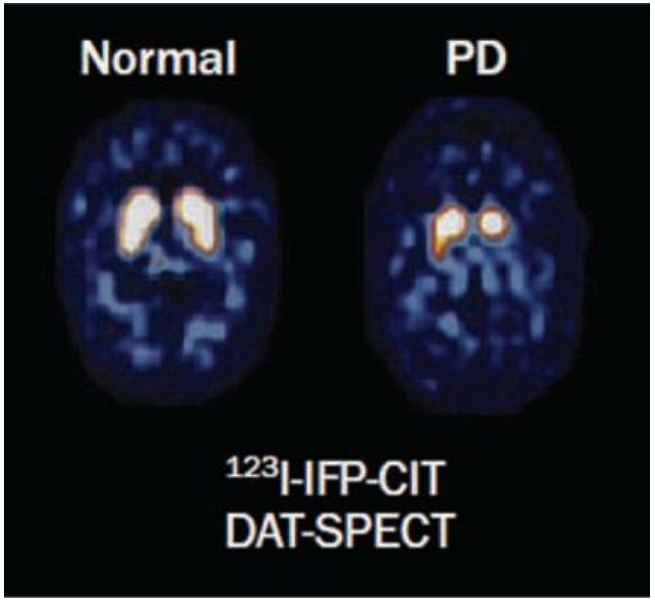
Parkinson's



excitatory

inhibitory

Radioactive tracer detects loss of dopaminergic neurons in striatum



For the DaT-scan (DopAmine Transporter scan) procedure a radioactive tracer is injected into the blood (Ioflupane 123I).

Ioflupane 123I attaches to the dopamine transporter in dopaminergic neurons.

Detects presynaptic dopaminergic neurons, especially those of the nigrostriatal pathway in the striatum.

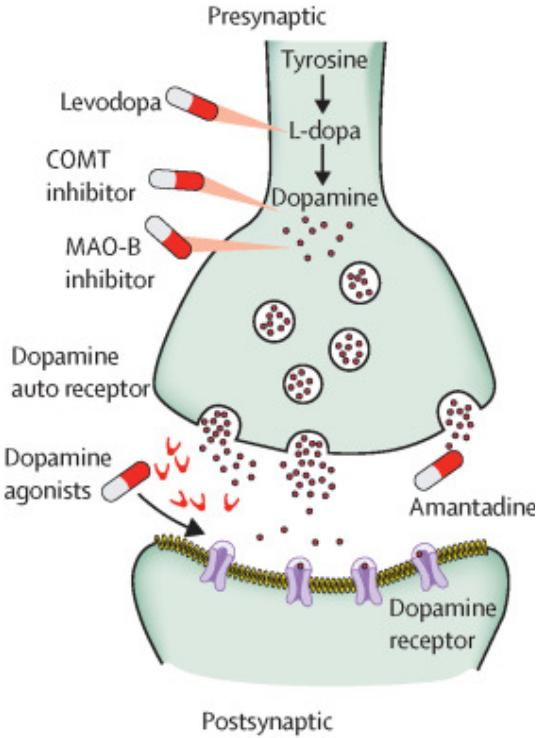
Complements the clinical testing for diagnosis.

Current MRI does not help in detecting Parkinson's disease.

DaT-scan is abnormal in PD (but also in other diseases with Parkinsonism; i.e. DLB, corticobasal degeneration, etc) = DaT-scan is not a specific marker.

Treatments for Parkinson's disease

Pharmacology & Dopamine therapy



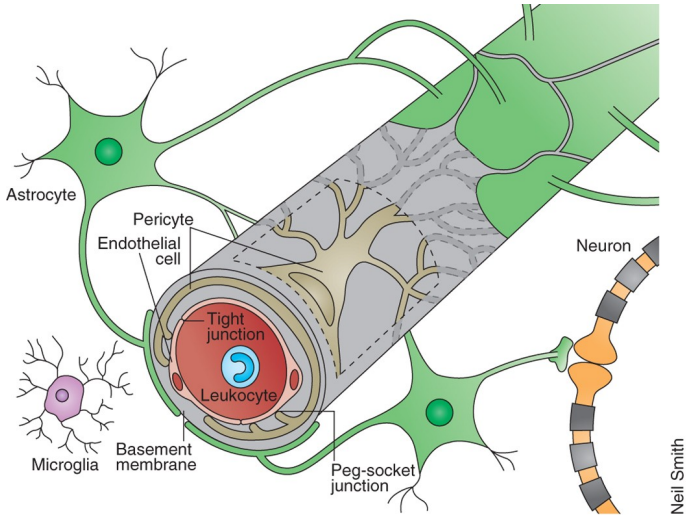
Dopamine is a neurotransmitter and the main therapy in PD. In dopamine replacement therapy, orally administered dopamine replaces dopamine in the central nervous system, especially in dopamine-depleted neurons (in striatum and elsewhere)

DA agonists are another treatment in PD: they also act directly on the DA receptor

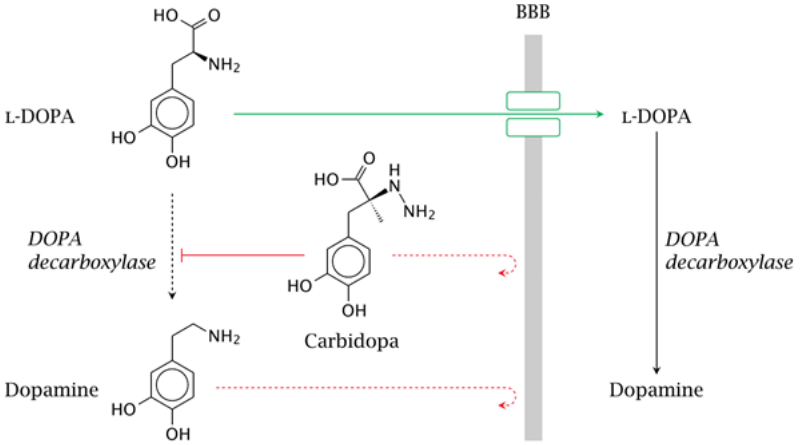
Amantadine is another treatment in PD: it increases presynaptic DA release and blocks DA reuptake.

Treatments for Parkinson's disease

Levodopa crosses BBB (blood-brain-barrier), dopamine not



BBB prevents dopamine in blood from entering the brain



Levodopa is able to cross the BBB, but dopamine not

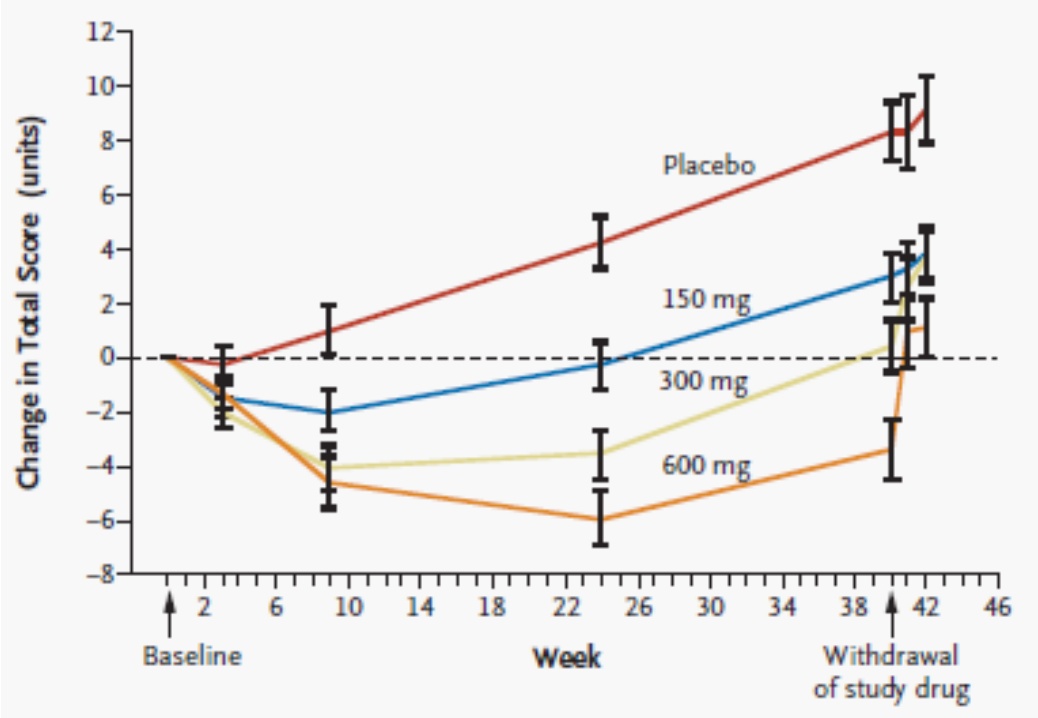
DOPA decarboxylase changes most of levodopa rapidly to dopamine (in brain and blood)

Adding a decarboxylase inhibitor (Carbidopa) to levodopa avoids this and sufficient dopamine arrives in the brain

(interesting research on opening the BBB by focussed ultrasound in Alzheimer's disease)

Dopamine replacement therapy

Early versus late levodopa therapy most effective and protective



(ELLDOPA) Parkinson's study group (NEJM, 2004)

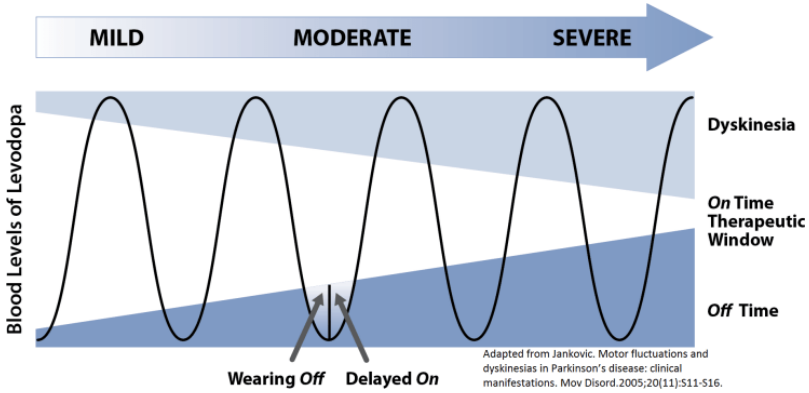
Treatments for Parkinson's disease

other observations

ON-OFF fluctuations are an important complication of dopamine replacement therapy and disease progression

ON: when the symptoms of Parkinson's disease are relatively well controlled because of the medication
OFF: when the symptoms of Parkinson's disease (bradykinesia, rigidity, etc) are pronounced and the patient develops a disability because the dopaminergic medication is providing insufficient relief
SIDE EFFECTS: dopamine dosage too high (ON++; i.e. dyskinesias)

Initial replacement therapy is characterized by mild fluctuations and a larger therapeutic window); as the disease progresses and dosage increases, fluctuations increase and may require addition of other treatments (deep brain stimulation).



Next to motor symptom fluctuations, many non-motor symptoms of Parkinson's disease do not respond adequately to optimal pharmacotherapy.

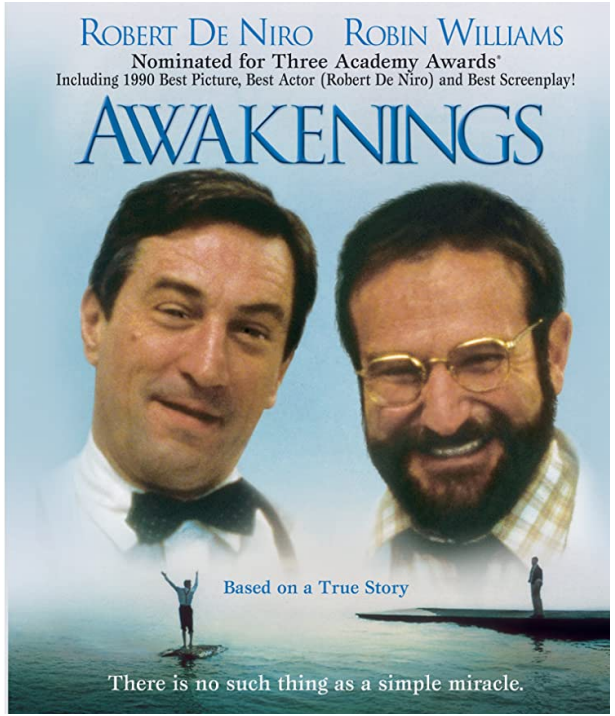
These adverse effects increase with disease progression (neurodegeneration also involves non-dopaminergic brain areas) and because dose-limiting side-effects hamper a successful deployment of pharmacotherapy.

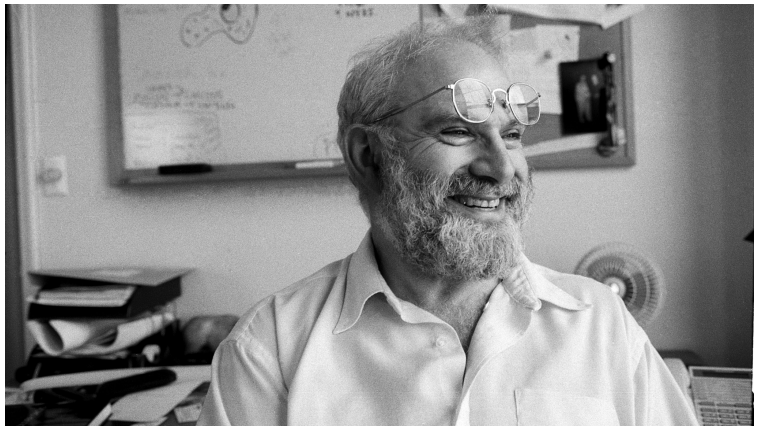
→ multidisciplinary management approach including regular exercise, day-night rhythm, appropriate diet.

→ Deep brain stimulation

Awakenings

Movie “Awakenings” by Penny Marshal, based on book by Oliver Sacks





based on effects of levodopa in patients with encephalitis lethargica, which also affects the dopamine system and the substantia nigra and leads to complete paralysis

Questions