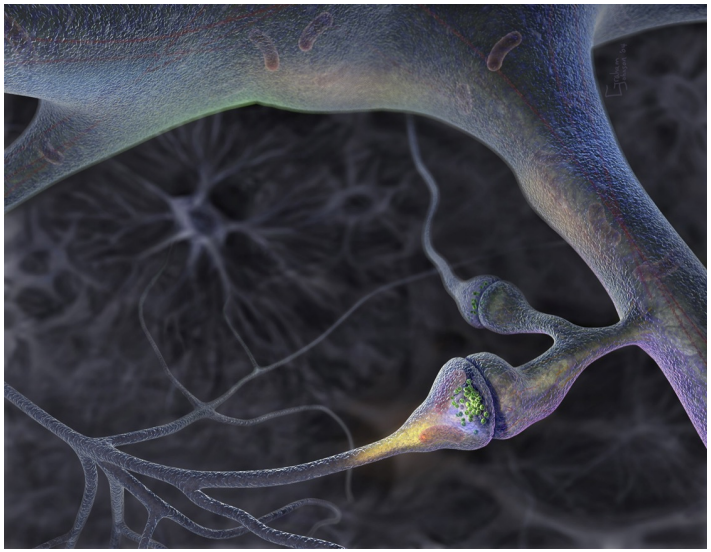
Parkinson's Disease

Basal ganglia: function and pathology

Bernard Schneider

November 2025



Lecture plan

1. Basal ganglia circuitry

2. Nigrostriatal degeneration and symptomatic treatments
   - Motor symptoms → dopamine replacement
   - Deep brain stimulation

3. Neuronal degeneration / Lewy body pathology
   - Selective vulnerability of neuronal subtypes
   - Spreading of the α-synuclein pathology

4. PD etiology: organelle quality control
   - Recessive forms: parkin, PINK1 and mitochondrial turnover

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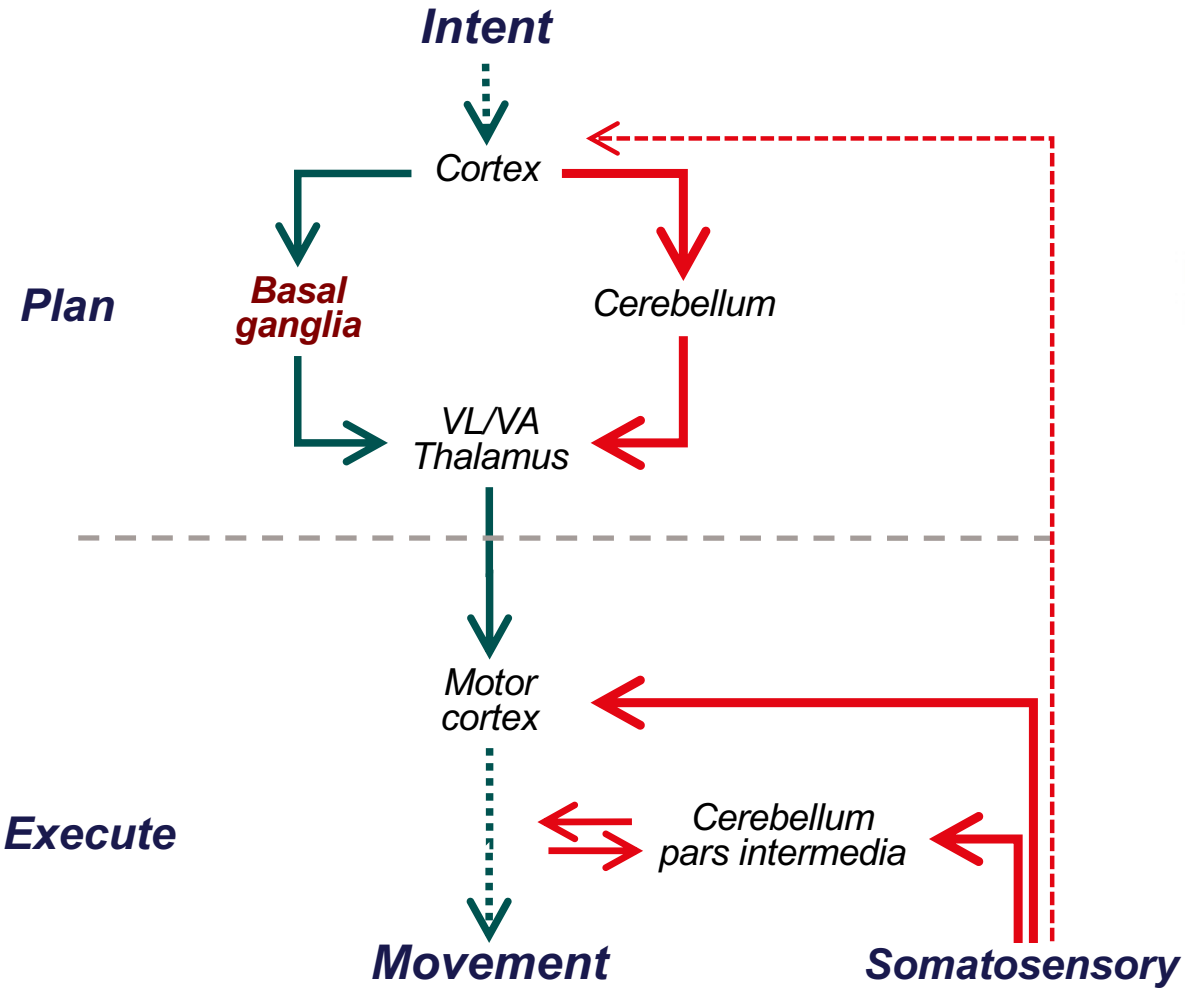
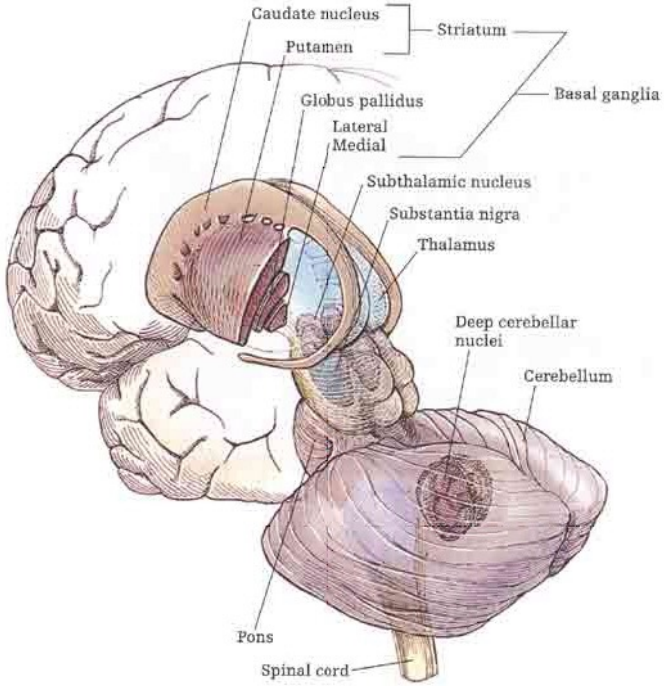
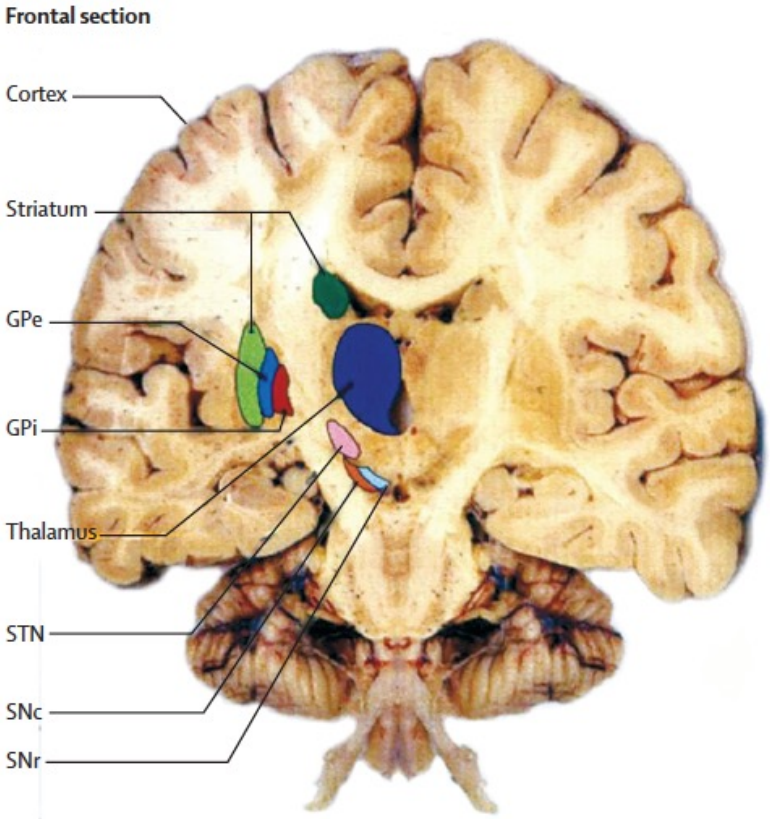
Basal ganglia: movement control





Basal ganglia: structure

Basal ganglia:

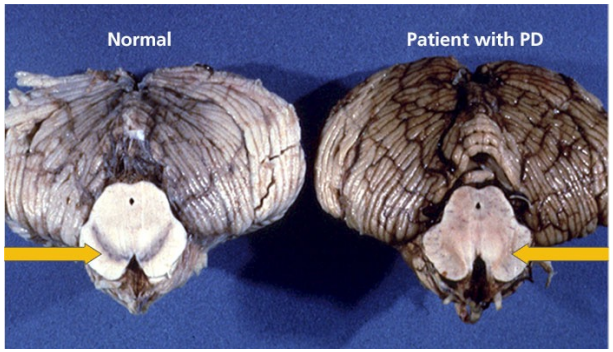


striatum *caudate*
putamen

globus pallidus *interna*
externa

subthalamic nucleus

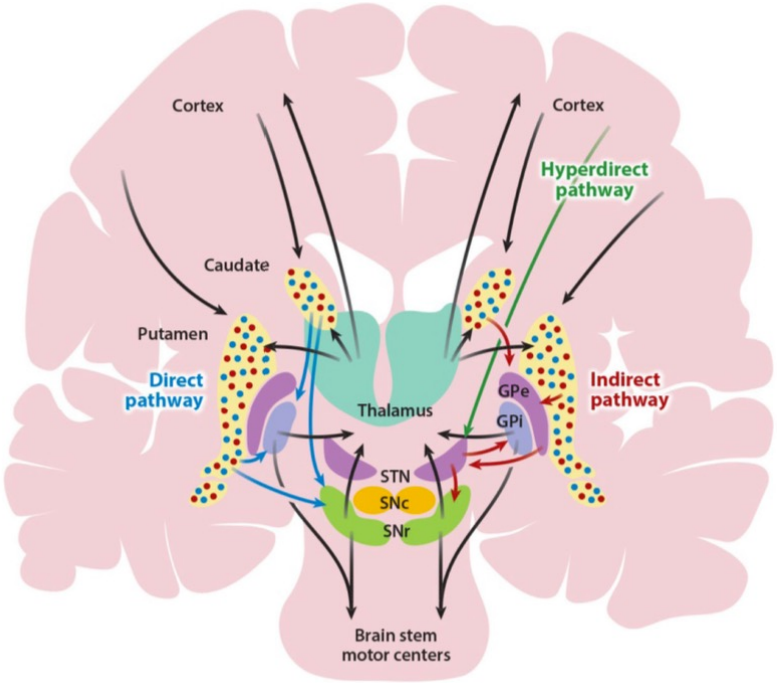
substantia nigra *pars compacta*
pars reticulata



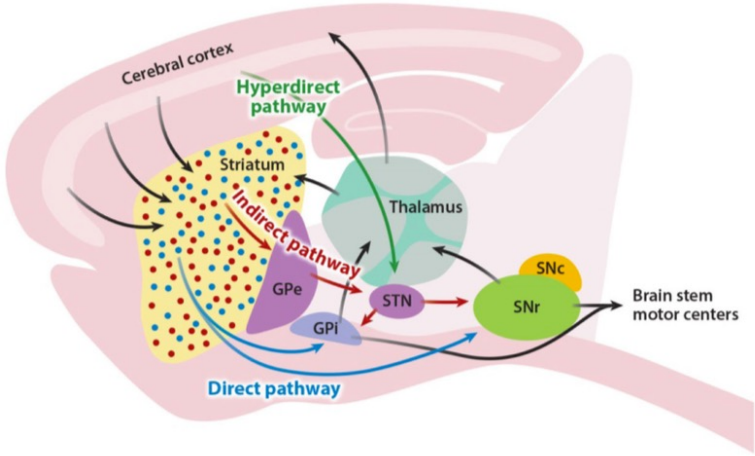
Stoessl AJ, Lancet 2014
Obeso JA, Lancet 2014

Basal ganglia: circuit for motor control

Human brain



Rodent brain

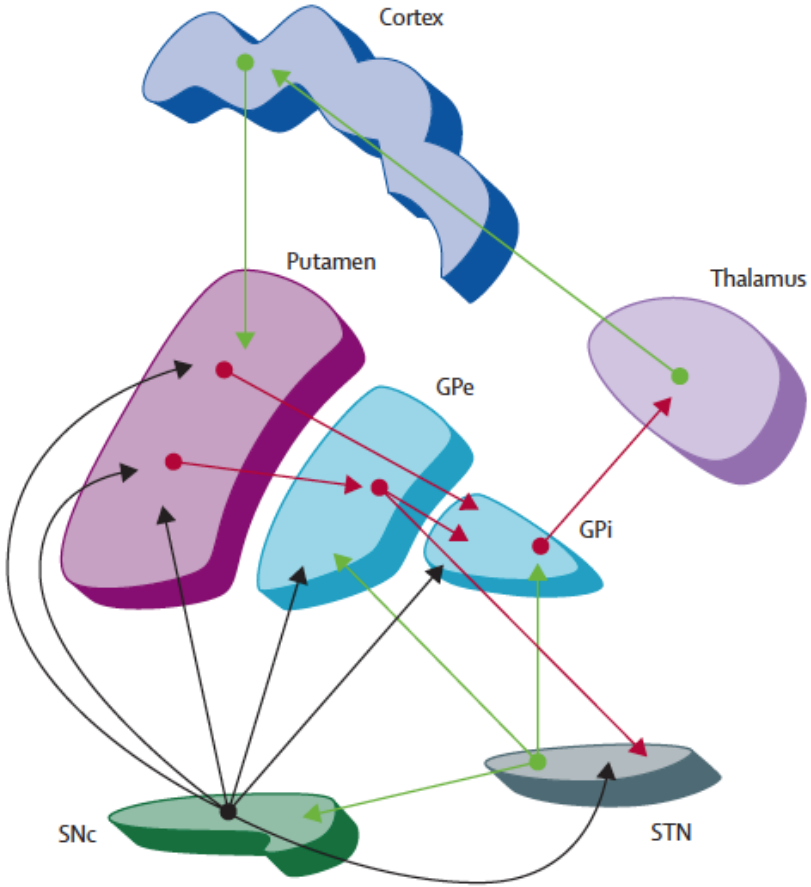


- **Input nuclei of the Basal Ganglia:**
  striatum
  STN
- **Output nuclei of the Basal Ganglia**:
  SNr
  GPi

- Nelson AB & Kreitzer AC, Ann Rev Neurosci 2014

Basal ganglia: circuits / neurotransmitters

Motor circuit: associated neurotransmitters



Glutamate

GABA

Dopamine

GP: globus pallidus
STN: subthalamic nucleus
SN: substantia nigra

- Stoessl AJ, Lancet 2014

Basal ganglia: movement disorders

Tremor/bradykinesia: Parkinson's disease

Dyskinesia/hyperkinesia:
Huntington's disease/chorea

Dystonia:
abnormal sustained muscle contraction
co-activation of normally antagonistic muscle groups

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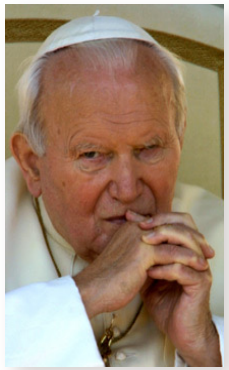
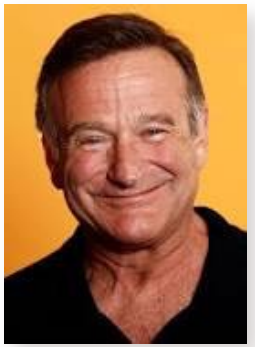
Parkinson's disease

Epidemiology

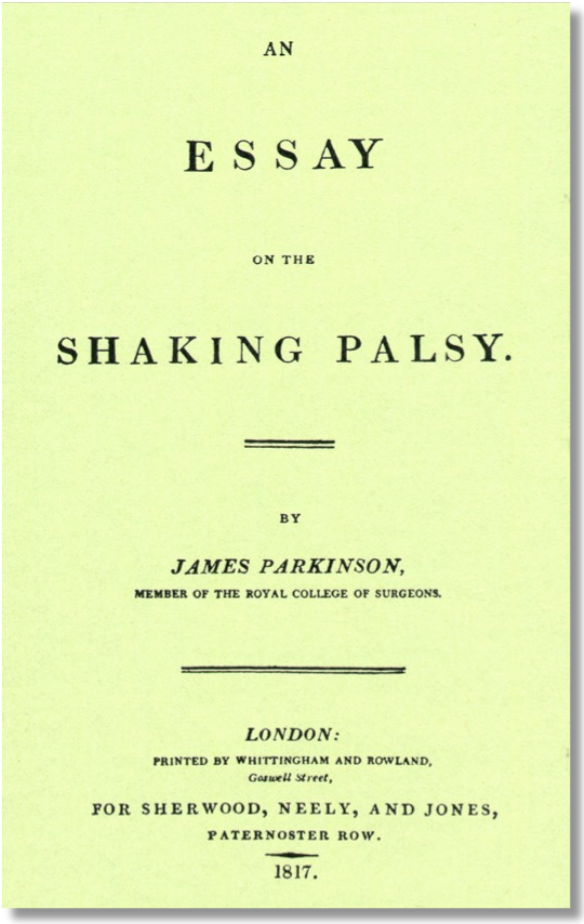
- 1-2% of the population over the age of 65 years (4-5% by the age of 85)
- Average age of onset typically between 58-65 years
- Found world-wide, more common in industrialized countries
- Symptom severity increases over time
- Men ≥ women





Parkinson's disease

First clinical description


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,
Gaswell Street,

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

James Parkinson, 1817

" *...involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace, the senses and the intellects uninjured*."

- rhythmic tremor at rest
- rigidity
- bradykinesia / akinesia

Parkinson's disease: symptoms

Shuffling

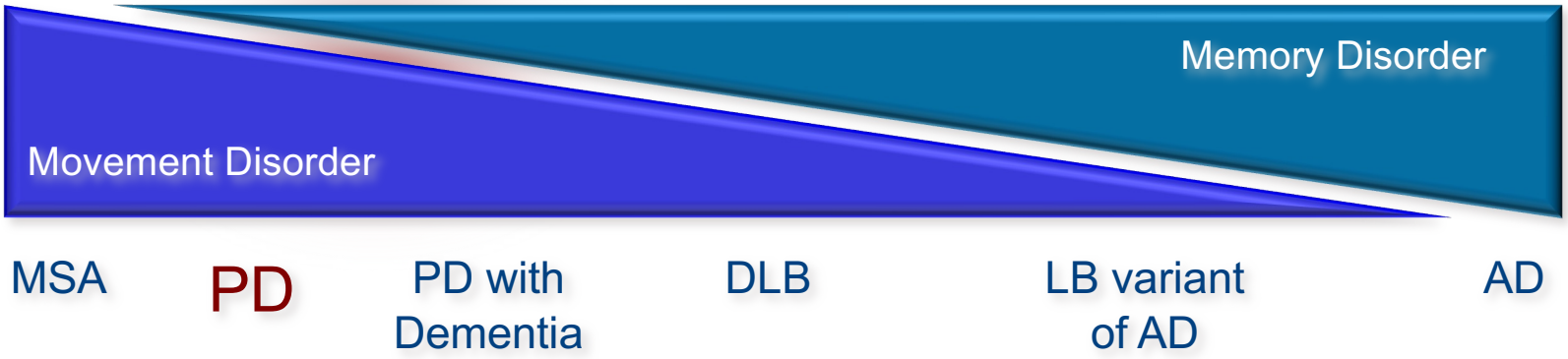
Postural instability

Tremor at rest

Initiation of movement

Parkinsonism: a syndrome

Parkinsonism: a syndrome not clearly delineated



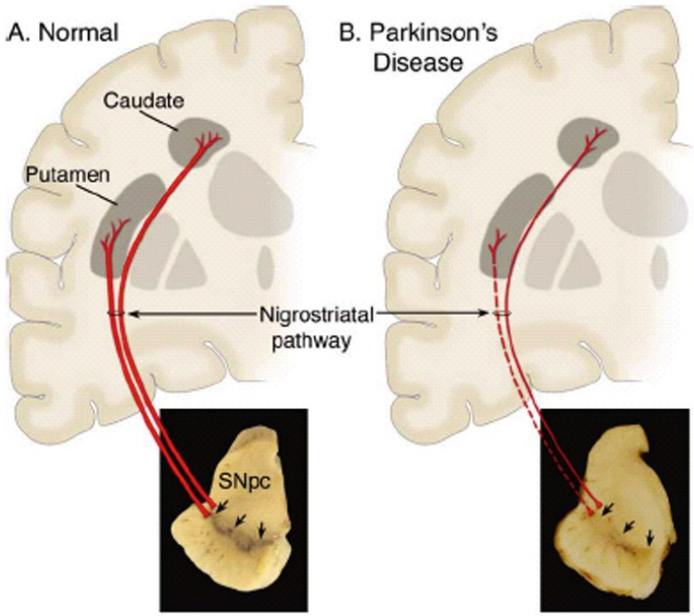
MSA	Multiple System Atrophy
PD	Parkinson's disease
DLB	Dementia with Lewy bodies
AD	Alzheimer's disease

- *Modified from Arch Neurol 2001; 58:186*

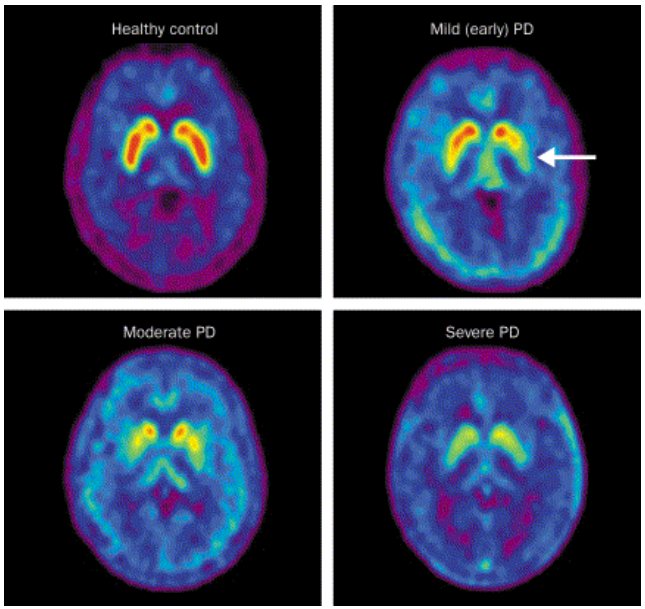
Parkinson's disease: pathology

Loss of pigmented neurons residing in the *Substantia Nigra pars compacta* and innervating the striatum

- Late 50s: dopamine is present in the mammalian brain, mainly in the striatum
- 1960: Ehringer & Hornykiewicz discover the decrease in striatal dopamine content
- <50% striatal dopamine loss ⇒ no symptoms
- **>70% striatal dopamine loss ⇒ Parkinsonian symptoms**
- At death, >90% loss of dopamine



18-fluorodopa PET scan



Parkinson's disease: loss of dopamine

Dopamine in Parkinson's disease: a few milestones…

1967: Cotzias: oral high dose **l-DOPA as a symptomatic treatment**

1961: **first trials of l-DOPA**

1960: Hornykiewicz & Ehringer: **lack of dopamine in PD**

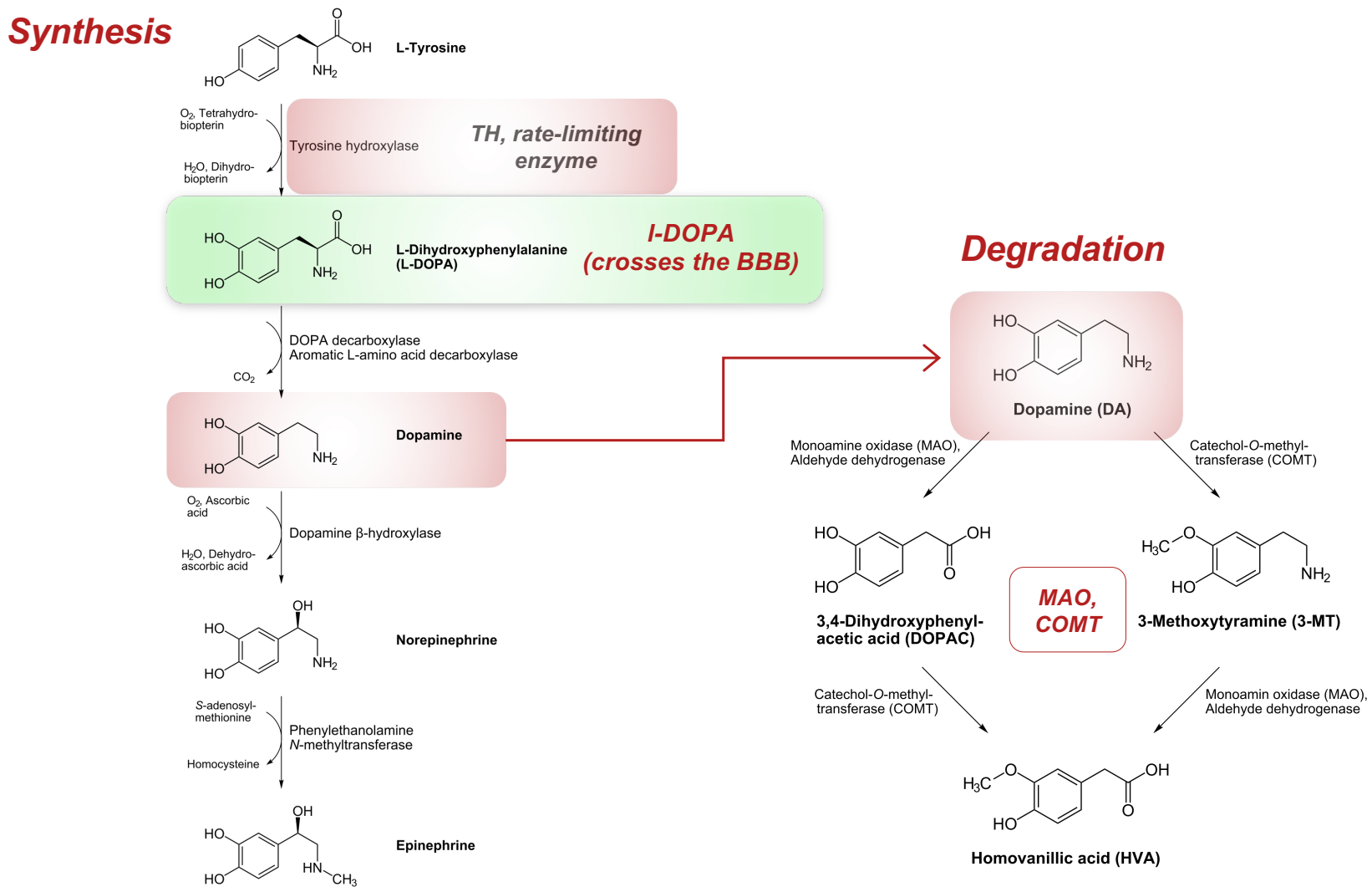
1959: Carlsson (Nobel prize) et al.: **dopamine = neurotransmitter**

1919: K. Tretiakoff: **degeneration of the *S. nigra***

1912: **description of Lewy bodies**

1817: **description of symptoms by James Parkinson**

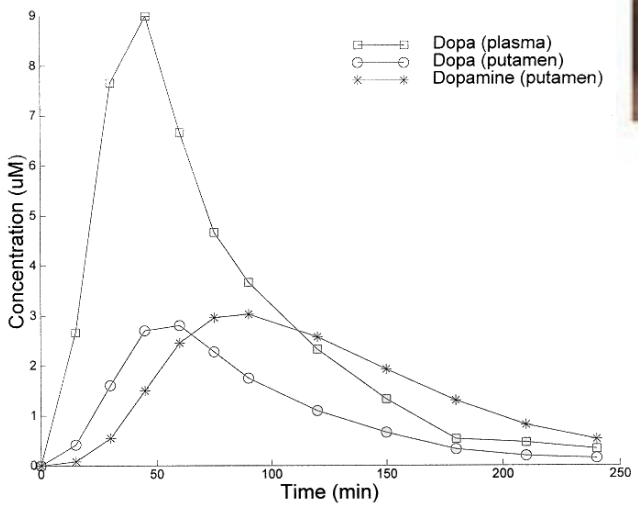
Dopamine biosynthesis (catecholamines)



L-DOPA: a therapeutic precursor for dopamine biosynthesis

L-DOPA (levodopa)

- L-DOPA: first synthesis in 1911 (Casimir Funk)
- L-DOPA has poor pharmacokinetic properties:
  - blood half-life of approximately 1 hour.
  - absorbed in the upper small intestine.
  - metabolized to dopamine in the periphery.
  - metabolized rapidly in the CNS.



EPFL

Parkinson's disease - Question 1

1913: Marcus Guggenheim (Hoffmann-la Roche) isolated the L-DOPA enantiomer from Vicia faba. He ingested the compound and immediately started vomiting as L-DOPA was converted to dopamine, which induces nausea via the medulla oblongata, a CNS region accessible to peripheral dopamine. L-DOPA is now an effective drug for PD, why?

(1 correct answer)

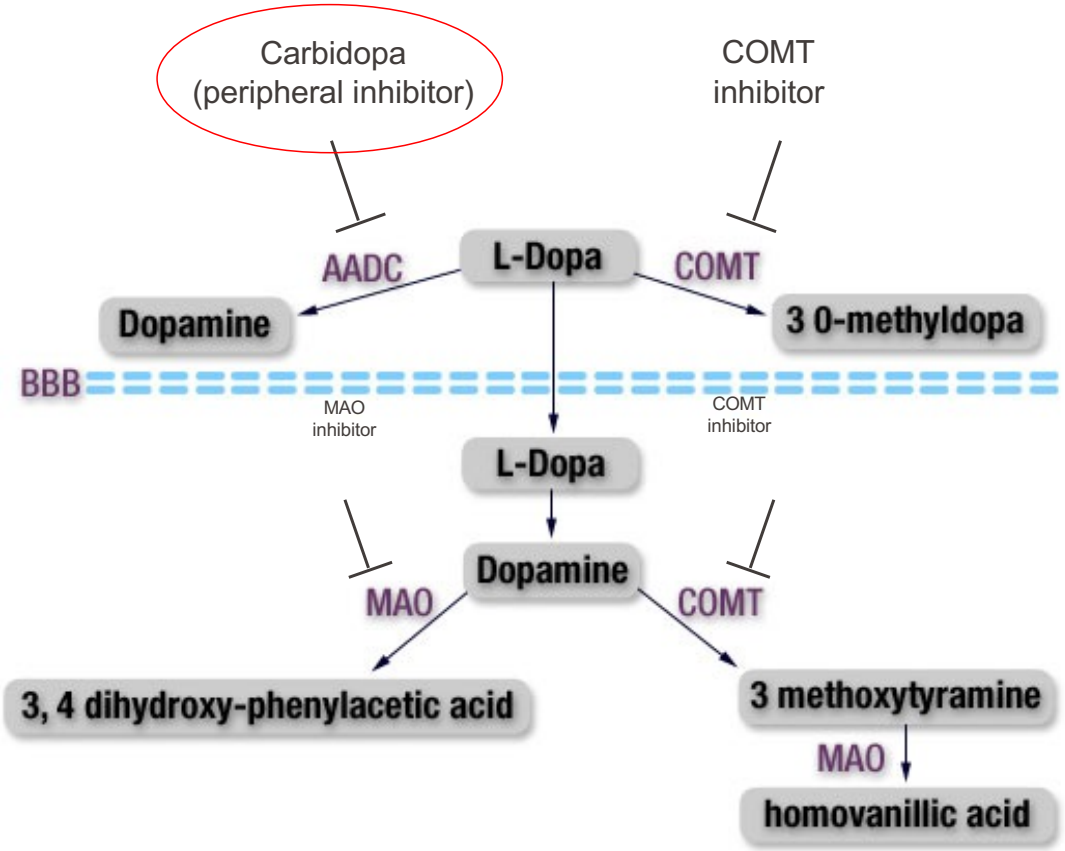
A. L-DOPA is injected in the brain

B. A compound is co-administered to block L-DOPA to dopamine conversion in the periphery

C. A modified form of L-DOPA is used that accumulates only in the brain

D. The dose of L-DOPA was adapted to prevent this side effect

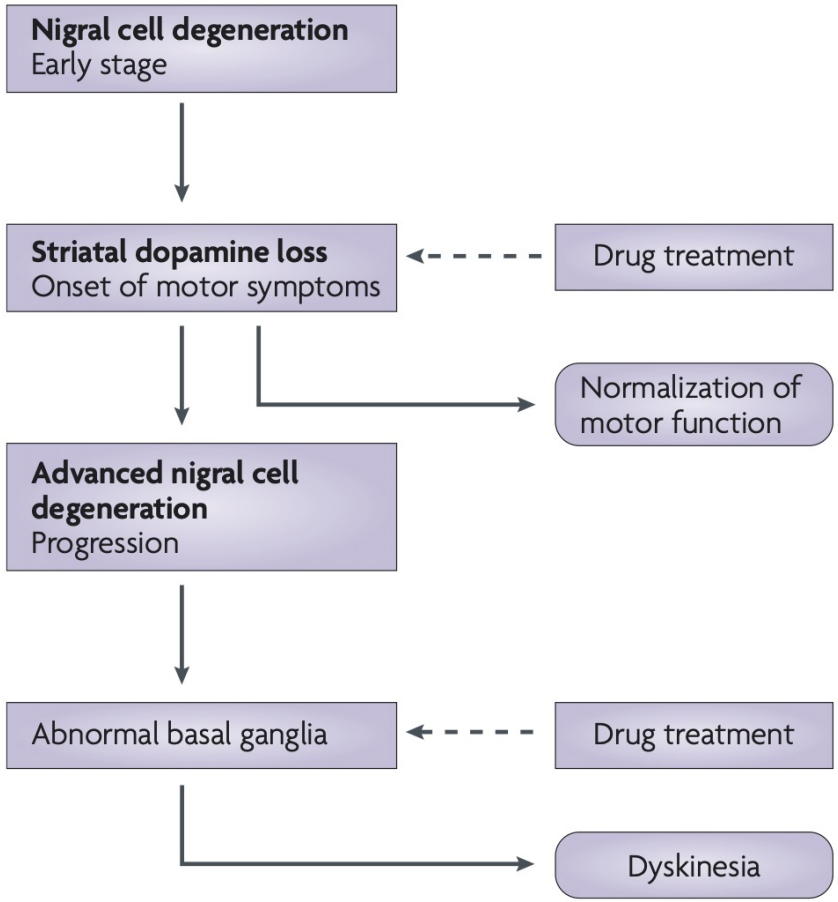
Pharmacological symptomatic treatment: L-DOPA



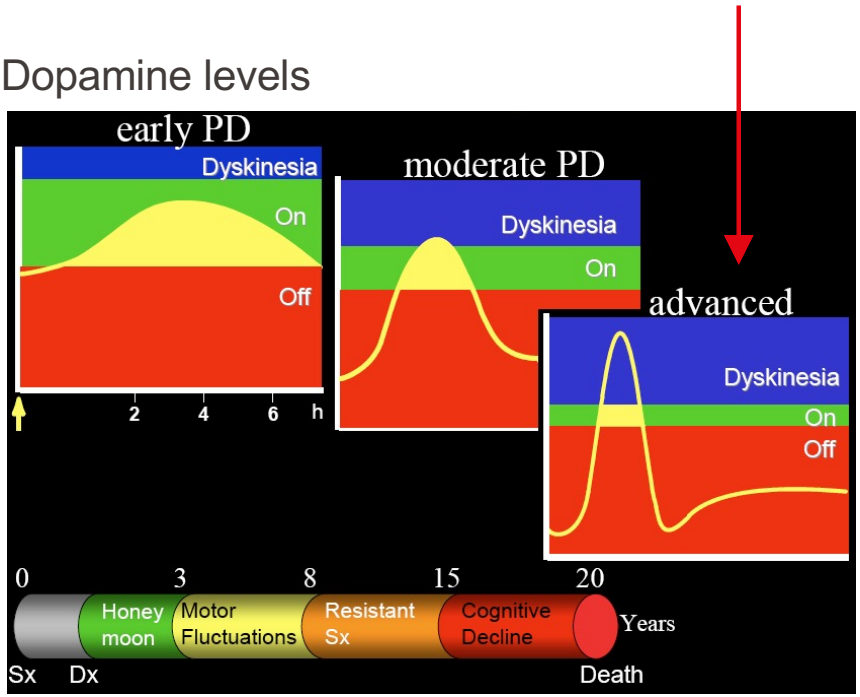
Therapeutic options to enhance dopamine function:

- Provide a dopamine precursor (l-DOPA) able to pass the blood-brain barrier and blocks dopamine synthesis in the periphery.
- Administer inhibitors of dopamine degradation (early phase of the disease): MAO and COMT inhibitors.

L-DOPA treatment: dyskinesia as a severe side-effect



- ***No more buffering capacity in presynaptic vesicles.***
- *DA levels in the brain reflect blood pharmacokinetics.*



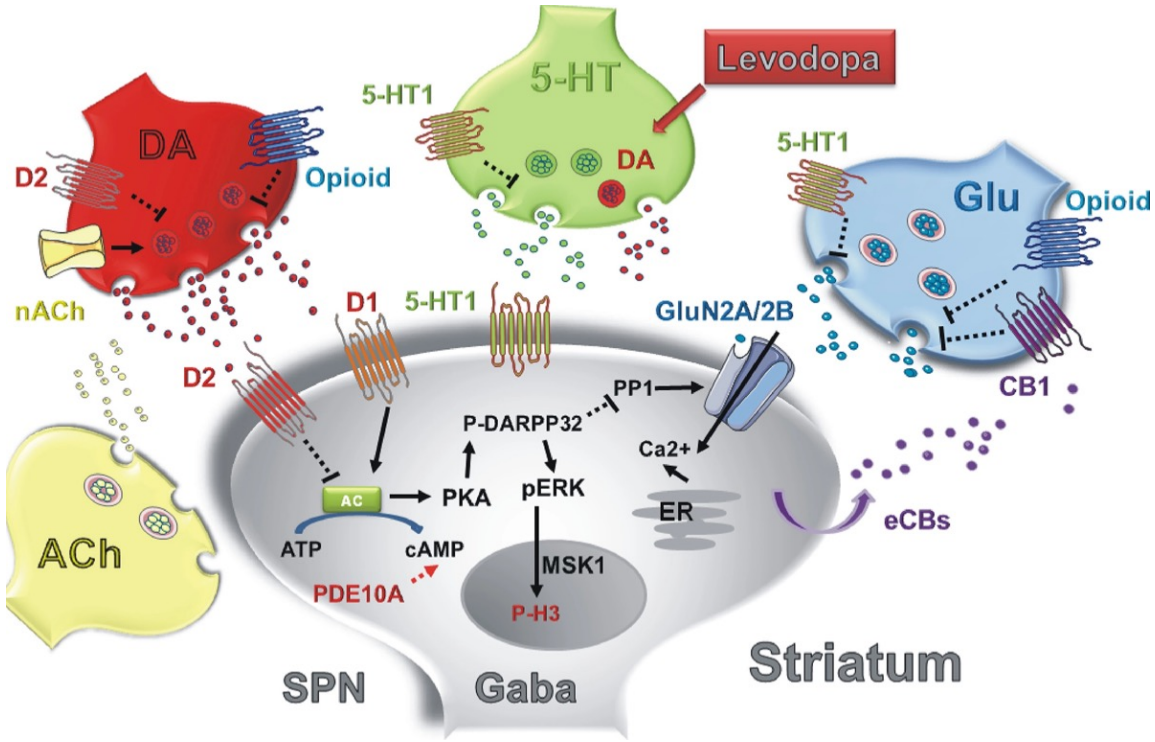
Sx: symptoms; Dx: diagnosis

- *doi:10.1038/nrn2471*

Dyskinesia: involuntary movements as a side effect of l-DOPA
Dyskinesia likely due to pulsatile l-DOPA exposure

L-DOPA treatment: dyskinesia as a severe side-effect

Example of dyskinesia mechanism: faulty dopamine neurotransmission



Serotoninergic neurons take up L-DOPA ⇒ dopamine (DA)

DA is then released in a non-physiological, unregulated manner in the extrasynaptic cleft ⇒ **'false transmitter'** causing abnormal and pulsatile activation of striatal DA receptors.

- *https://doi.org/10.1002/ana.25364*

Parkinson's disease - Question 2

L-DOPA treatment is poorly effective in late-stage PD patients because… (indicate all correct answers)

A. L-DOPA does not cross the BBB

B. Dopamine can no more be synthesized from L-DOPA

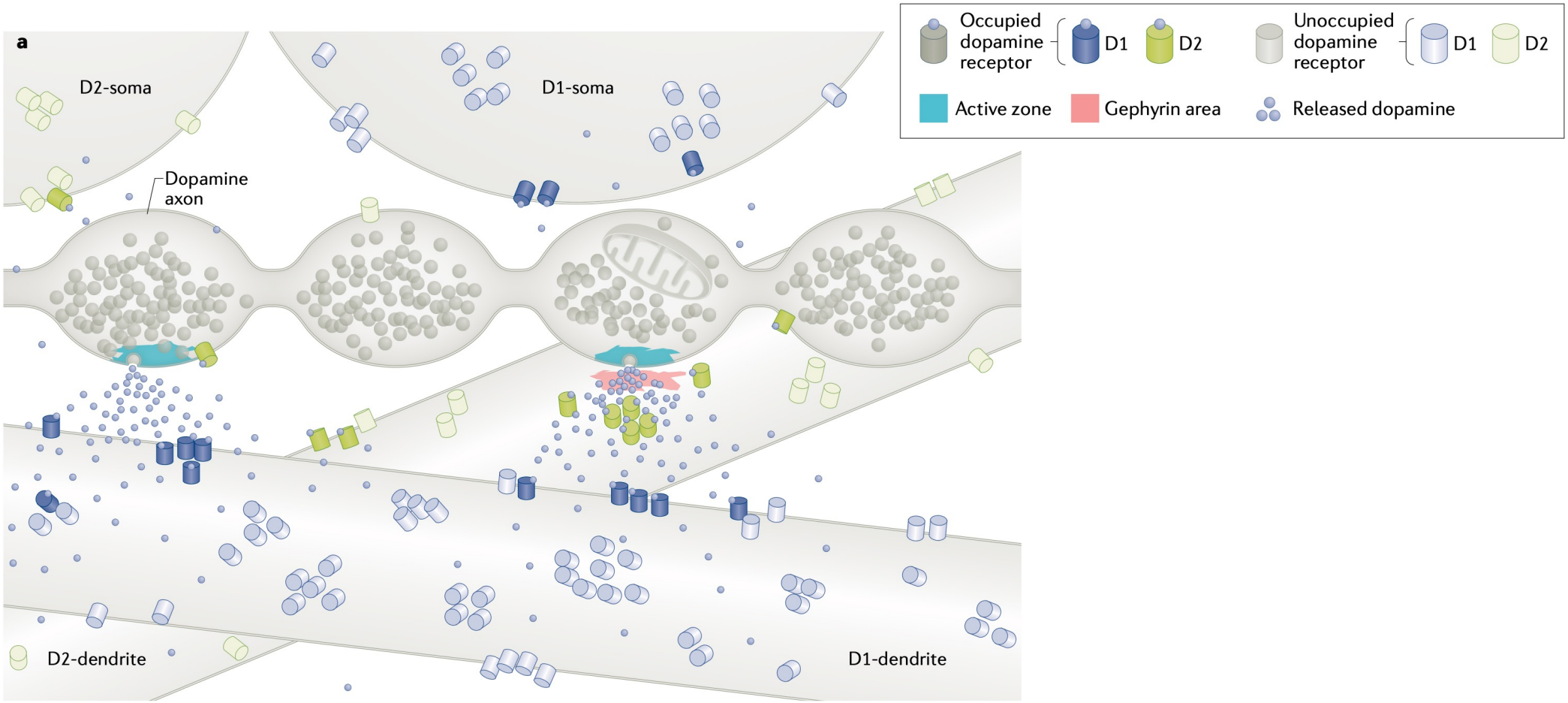
C. There is not enough presynaptic vesicles to store dopamine in the striatum

D. There is not enough dopamine transporter to recapture dopamine

E. Striatal neurons have degenerated

F. Other symptoms appear that do not respond to L-DOPA

Parkinson's disease: dopamine signaling in the striatum



- https://doi.org/10.1038/ s41583-021-00455-7

Parkinson's disease: dopamine signaling in the striatum

Medium-sized spiny neurons

~ 95% of all neurons in the striatum

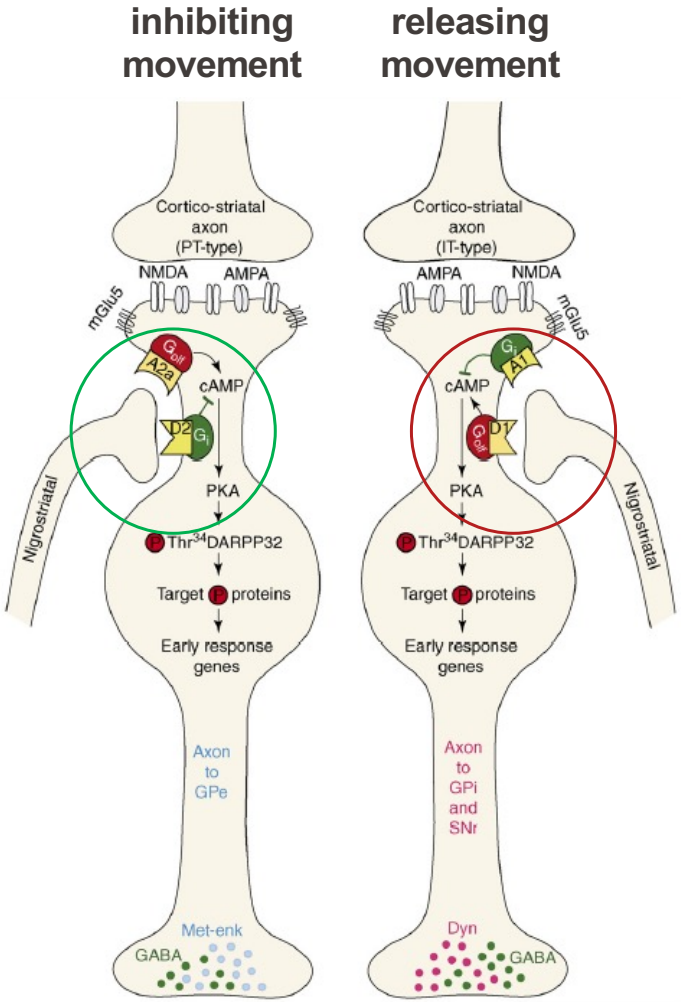
Push-pull system to release or inhibit movement

« **Direct pathway** » MSNs

D1 receptor ➔ activation

« **Indirect pathway** » MSNs

D2 receptor ➔ inhibition

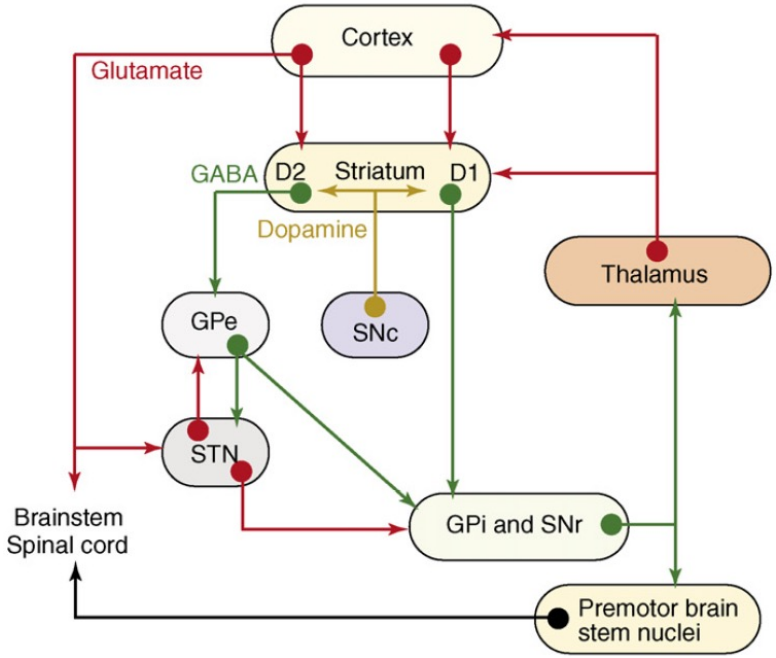


- Cenci MA, TINS 30(5), 2007

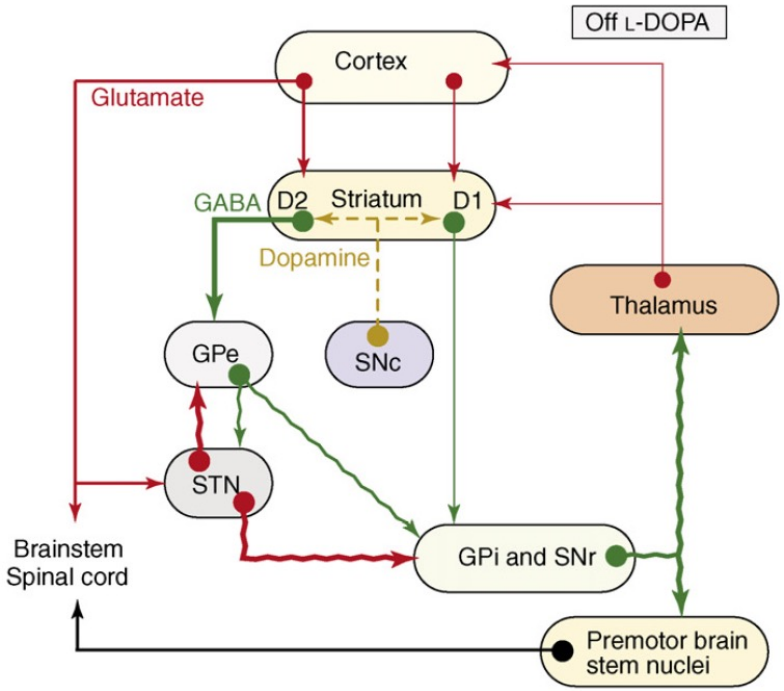
Parkinson's disease: role of dopamine in the basal ganglia

How does PD affect the basal ganglia circuitry ?

Normal basal ganglia



Parkinsonism



Parkinson's disease - Question 3

In multiple system atrophy (MSA), there is degeneration of dopaminergic neurons in the substantia nigra which is similar to PD. However, the disease also affects multiple brain regions including medium spiny neurons in the striatum.

MSA patients have Parkinsonian symptoms that respond well to levoDOPA treatment:

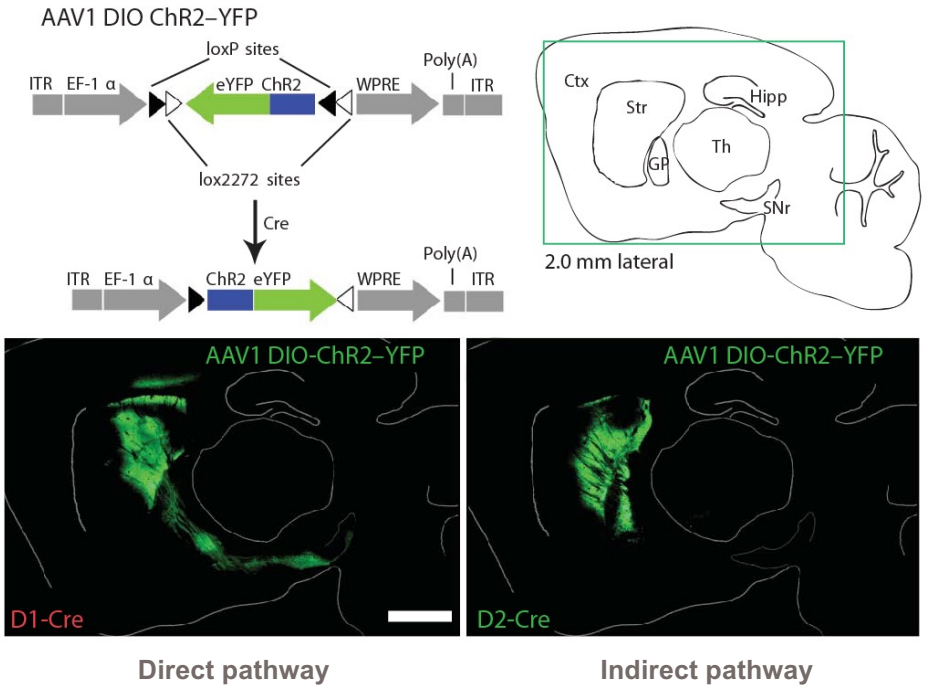
A. Vrai
B. Faux

Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry

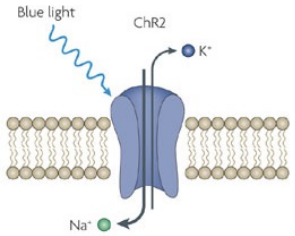
nature 2010

Alexxai V. Kravitz[1], Benjamin S. Freeze[1,4,5], Philip R. L. Parker[1,3], Kenneth Kay[1,5], Myo T. Thwin[1], Karl Deisseroth[6] & Anatol C. Kreitzer[1,2,3,4,5]

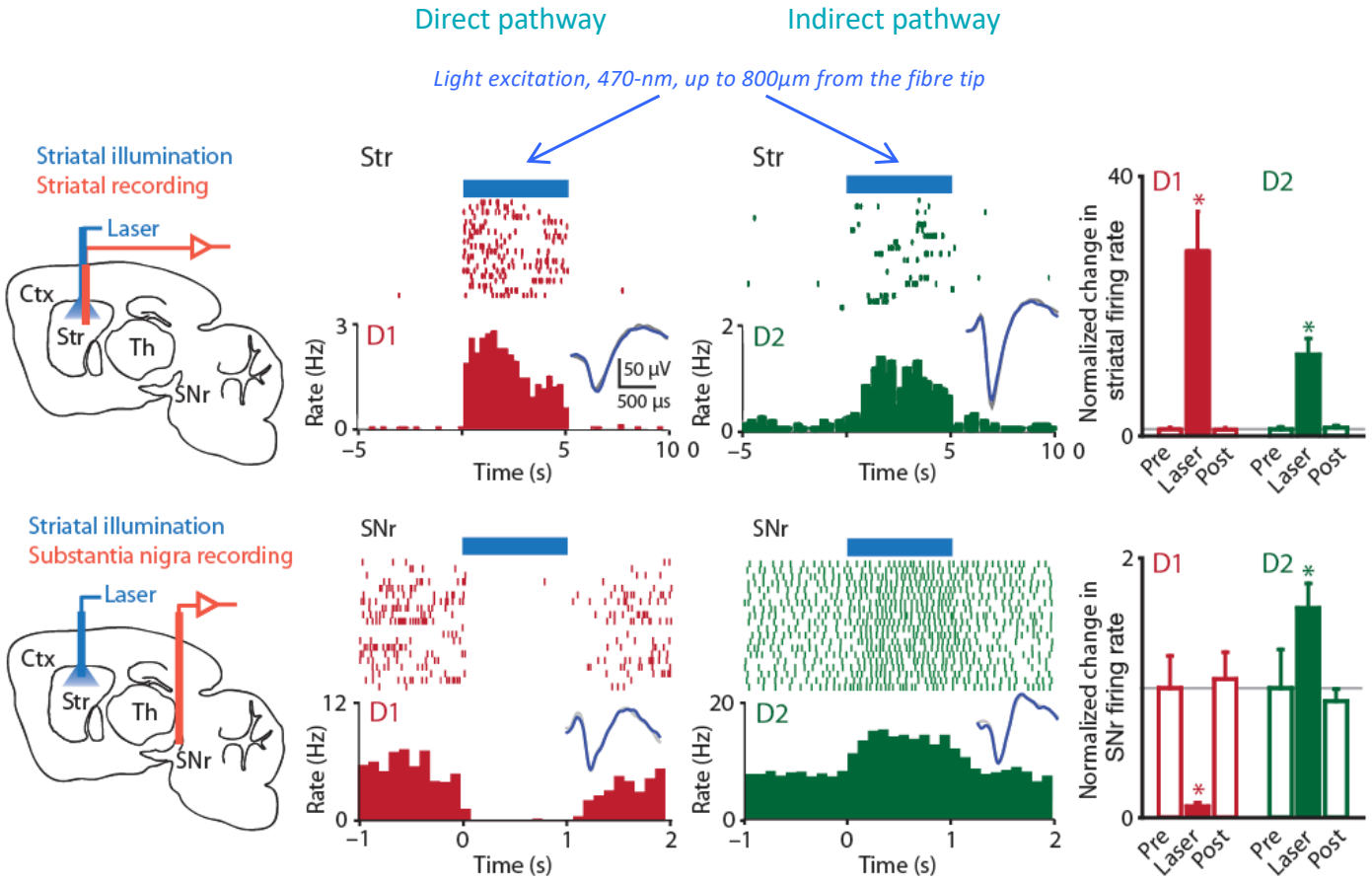
Optogenetics: *modulation of electrical activity by expression of light-activated regulators of transmembrane conductance*



Basal ganglia: role of the striatum in motor control



Optogenetic control of D1 and D2 medium spiny neurons has opposite effects on the output in the *substantia nigra pars reticulata*



Parkinson's disease: question 4

What is the behavioral effect of **light stimulation** in the striatum of D2R-Cre mice injected with AAV-DIO-ChR2 ?

(1 correct answer)

A. No change in animal motor behavior

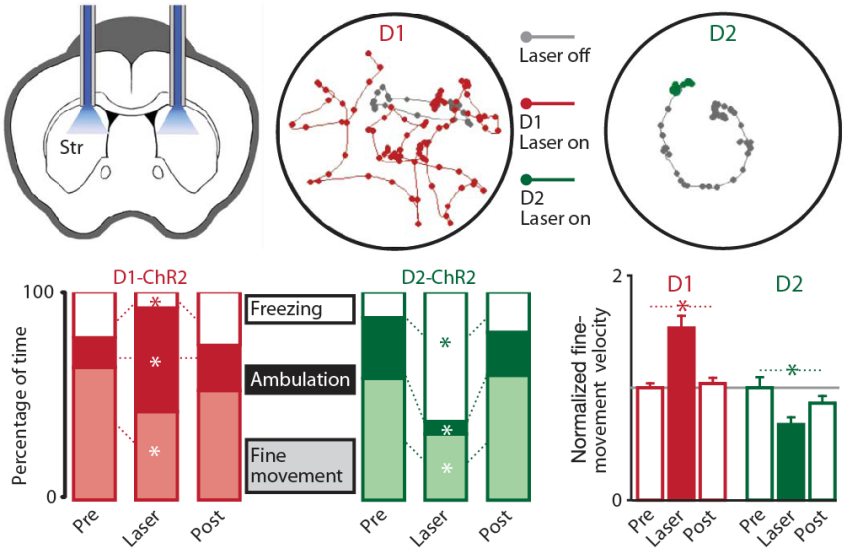
B. Constant hyperactivity

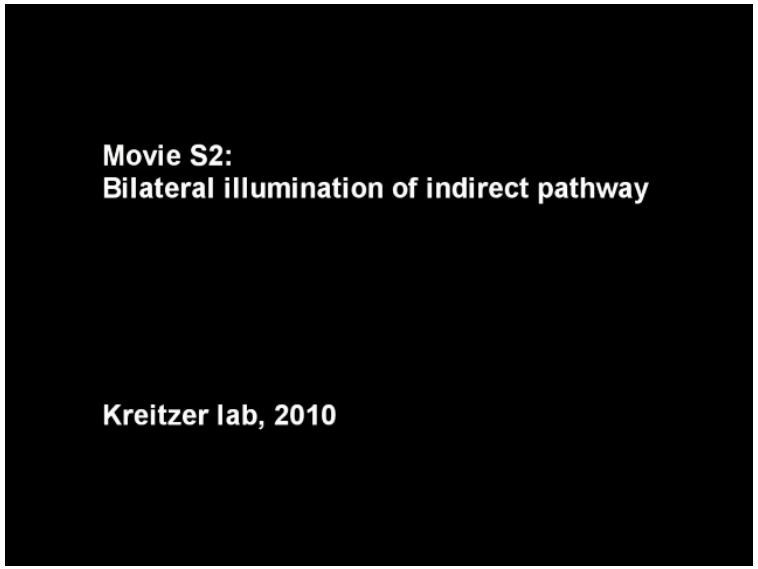
C. Transient hyperactivity

D. Mouse freezing during exposure to light

Basal ganglia: role of the striatum in motor control

- Activation of D1 striatal neurons increases spontaneous motor activity
- Activation of D2 striatal neurons reduces spontaneous motor activity





Light-activation of the « indirect » D2 pathway leads to mouse freezing

Parkinson's disease: question 5

A toxin is injected in the striatum to induce the selective degeneration of nigrostriatal neurons. The experiment is performed in D1R-Cre mice previously injected with AAV-DIO-ChR2.

What is the behavioral effect of light stimulation ?
(1 correct answer)

A. Constant hyperactivity

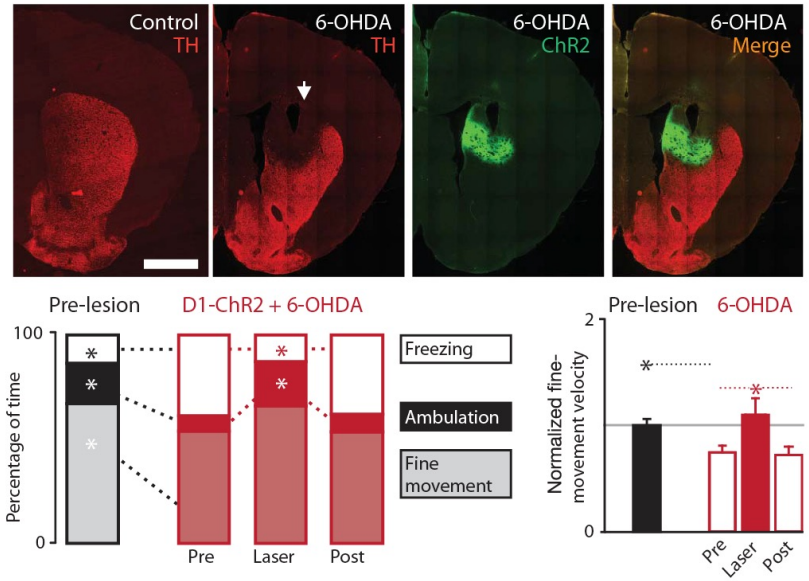
B. Rescue of parkinsonian bradykinesia observed in these mice

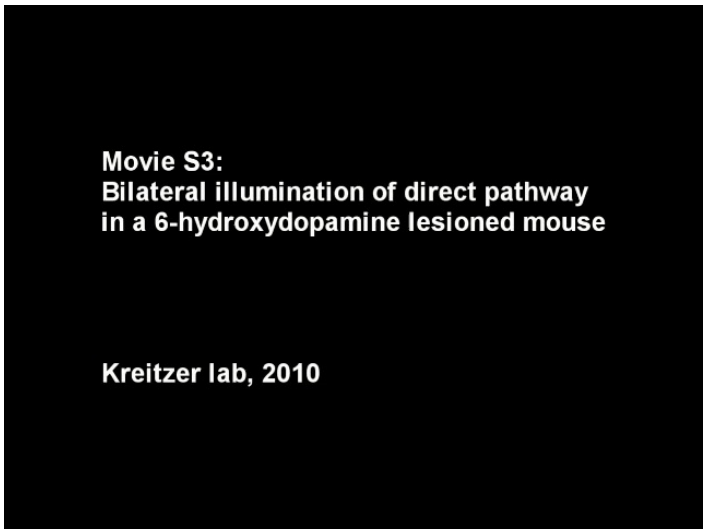
C. No change in motor activity

D. Development of parkinsonian symptoms

Basal ganglia: role of the striatum in motor control

- Activation of D1 striatal neurons increases spontaneous motor activity can correct reduced motor activity due to 6-OHDA-induced lesions of the nigrostriatal system



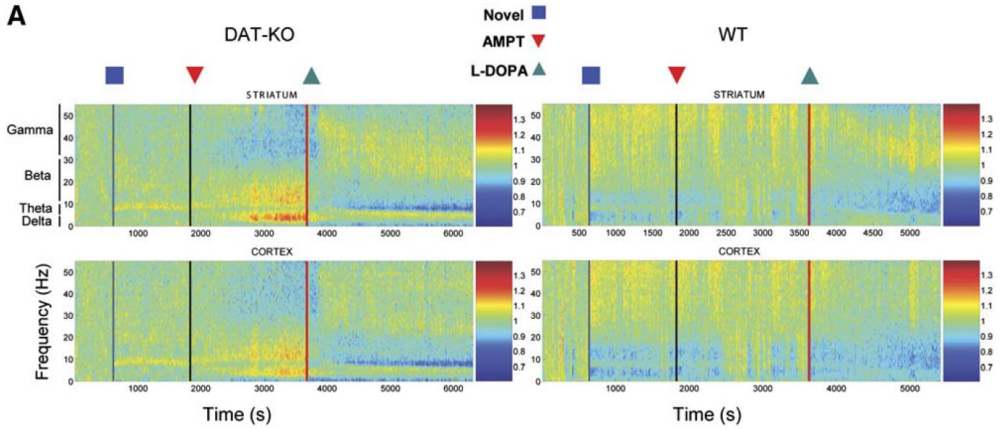


Light-activation of the « direct » D1 pathway restores mouse motor activity

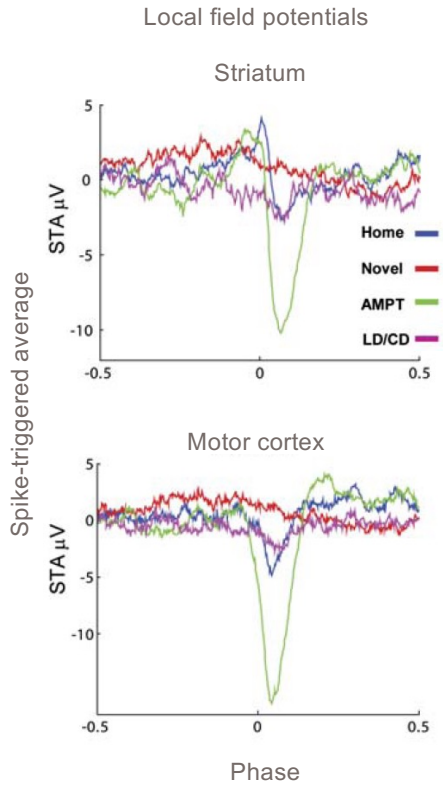
Basal ganglia: brain activity

The synchronicity and activation frequency of motor cortex/striatum is controlled by basal ganglia

Activity frequency (AMPT = TH inhibitor)



Synchronicity



- During the transition between dopamine-related hyperkinesia and akinesia, the overall cortical firing rate remained unchanged
- Change in neuronal oscillations and ensemble activity coordination between cortex and striatum
- Hyperkinesia = asynchronous corticostriatal activity
- Akinesia in response to dopamine-depletion = increased synchronicity

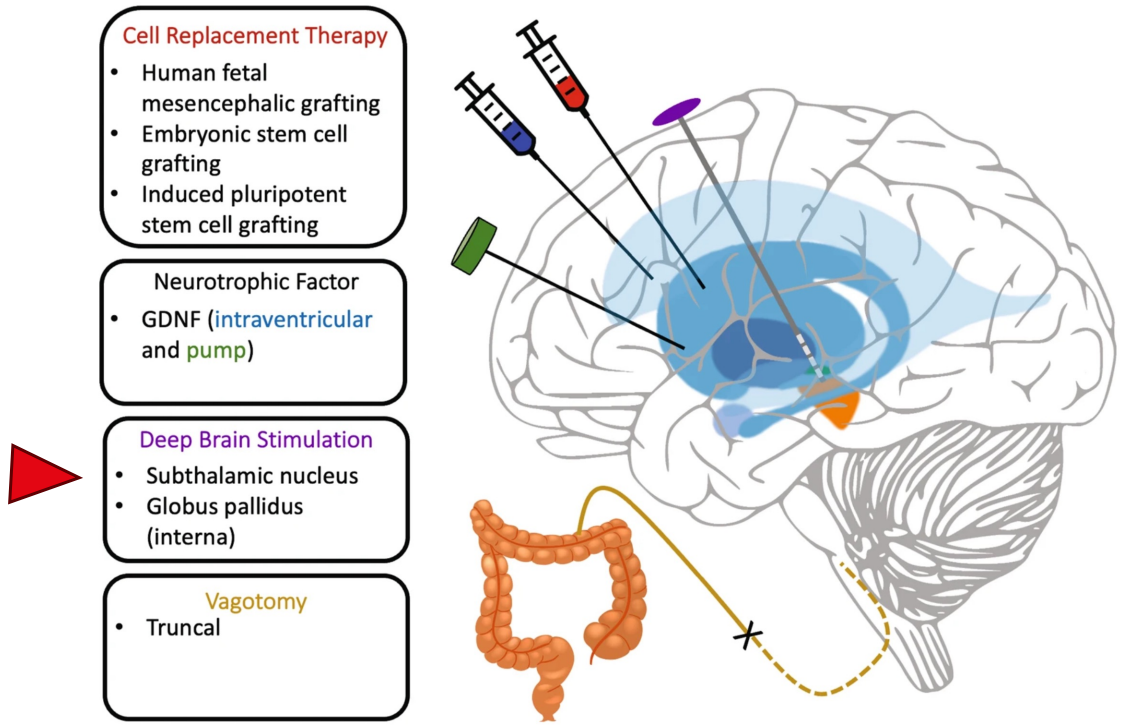
- *Rui M. Costa et al, Neuron 52, 359–369, 2006*

Basal ganglia: symptomatic treatments

Functional interventions on the circuitry of the basal ganglia

- Surgical ablation: pallidotomy, thalamotomy (for tremor only)
- **Functional interference: Deep brain electrical stimulation (DBS)**
- Subthalamic or striatal gene therapy: glutamic acid decarboxylase / AADC / combined enzymes for dopamine synthesis

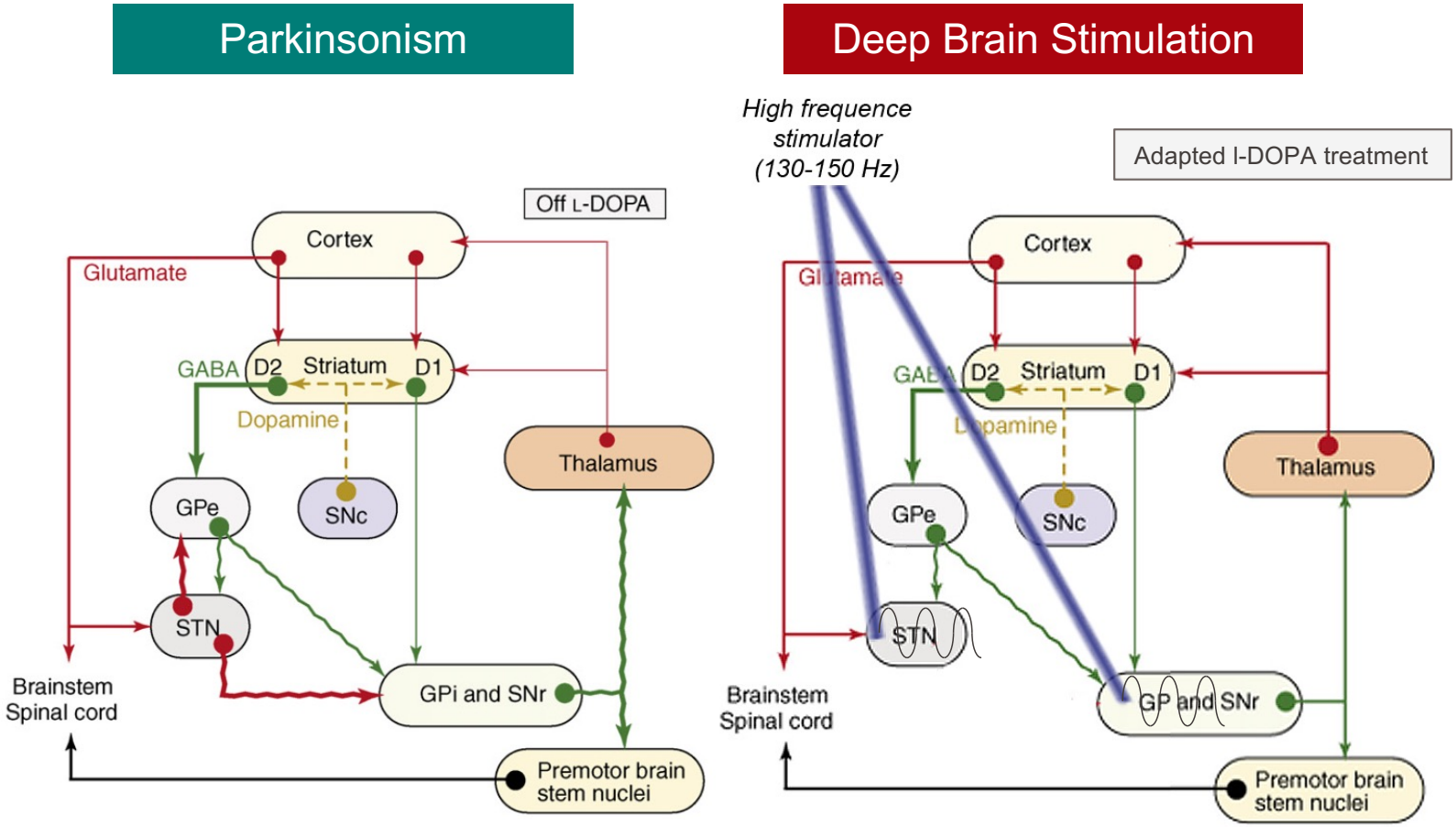
Surgical treatments for Parkinson's disease



- *npj Parkinson's Disease volume 8, Article number: 33 (2022)*

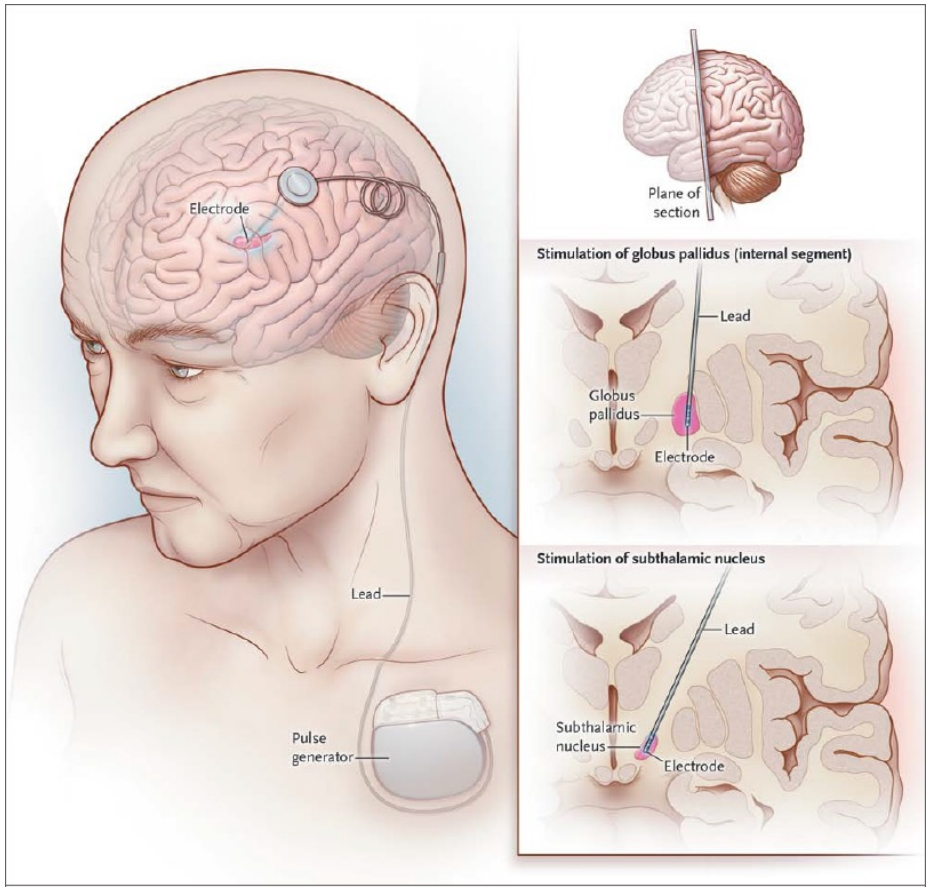
Basal ganglia: deep brain stimulation

- Deep Brain Stimulation targets nodes in the basal ganglia - thalamocortical circuit.



Basal ganglia: symptomatic treatments

Deep Brain Stimulation



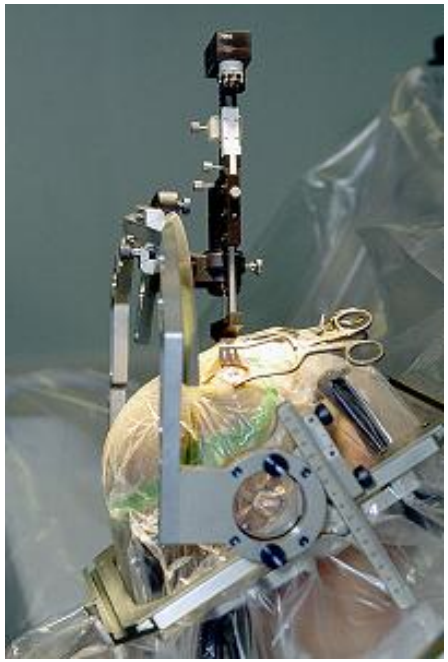
- Developed by Alim-Louis Benabid in 1980s (Grenoble)
- Discovery of DBS efficacy was made when performing thalamotomy using thermocouple electrodes
- Various stimulation frequencies were tested with the electrode to verify placement
- High frequencies (>100 Hz) were found to alleviate tremor

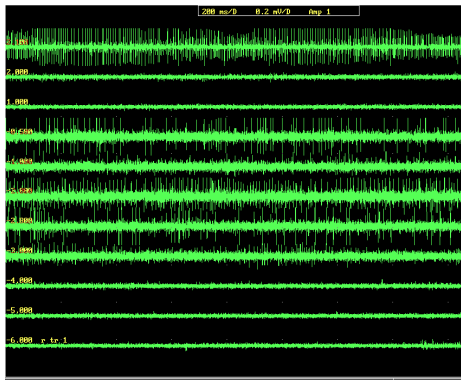
Okun MS et al., N Engl J Med 367;16 2012

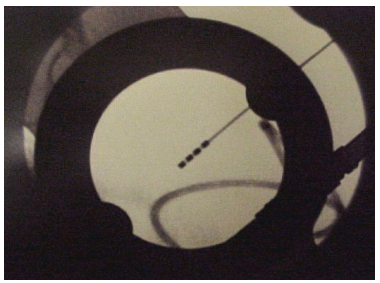
Basal ganglia: deep brain stimulation

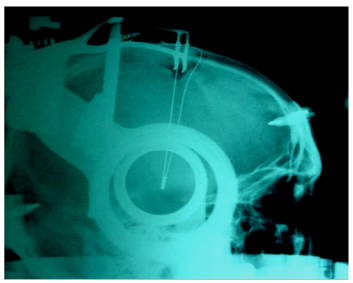
Stereotaxic implantation of the electrodes

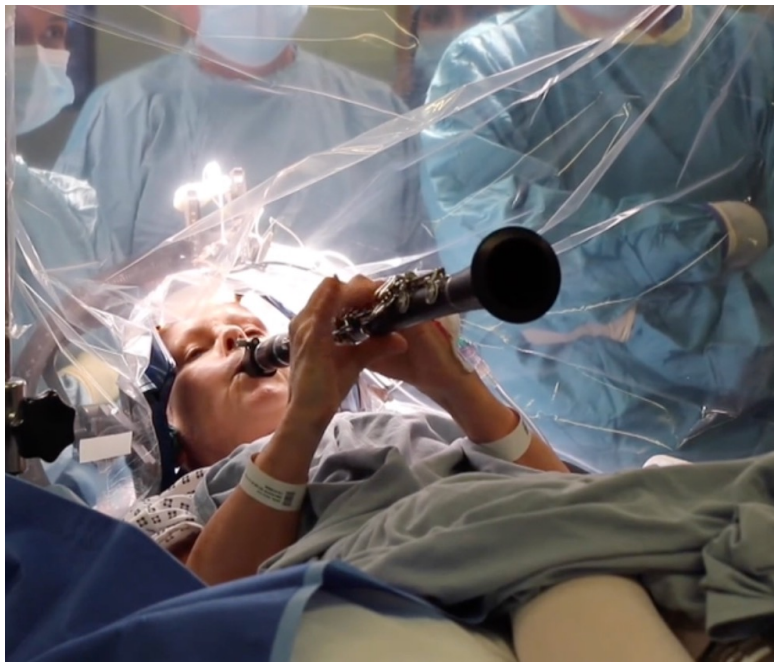
- Adjustable, reversible.
- High frequency, pulsatile electrical stimulation.
- Placement: by MRI or Computerized Tomography.
  physiologically by coordinated firing and tremor monitoring.











Basal ganglia: deep brain stimulation

Deep Brain Stimulation: clinical benefits

- Improvement in “OFF” state, some improvement in “ON” state
- Reduction in l-DOPA
- With disease progression, worsening of motor function is not prevented
- No demonstration of a disease-modifying effect

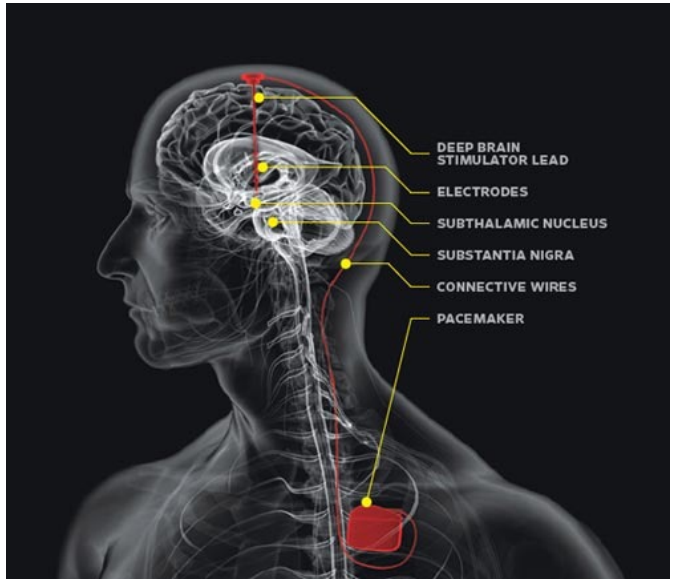
- **FDA approval:**

  for essential tremor in 1997

  for Parkinson’s disease in 2002

  for dystonia in 2003

- **>160,000 PD patients** treated worldwide



Basal ganglia: deep brain stimulation

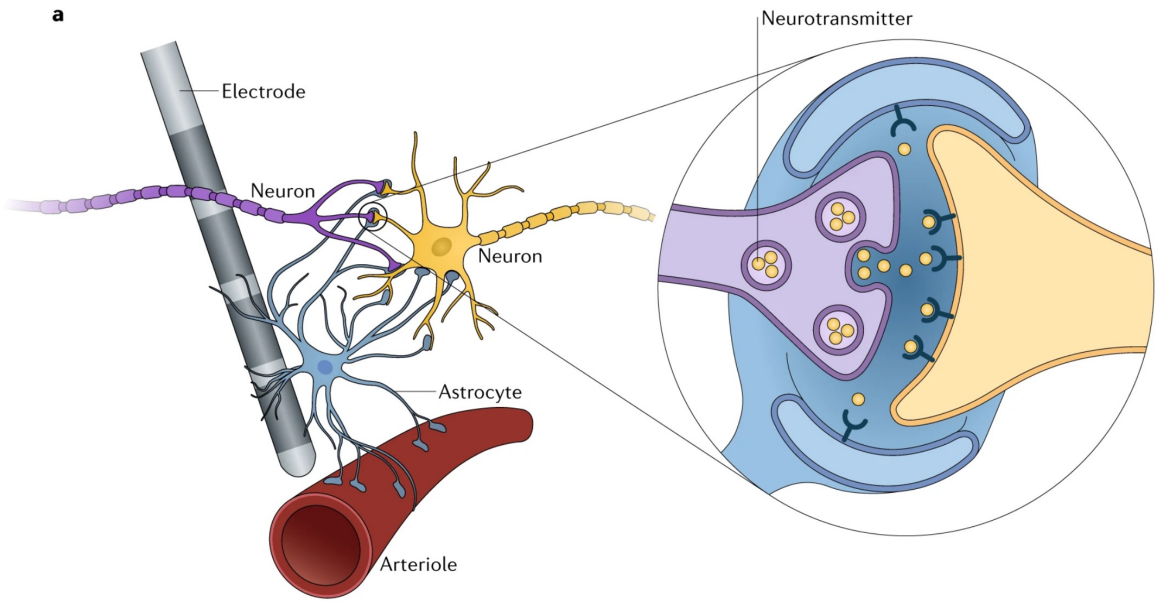
Deep Brain Stimulation (DBS)

Basal ganglia: deep brain stimulation

Mechanisms:

- DBS mechanisms remain in part unknown ⇒ “jamming”

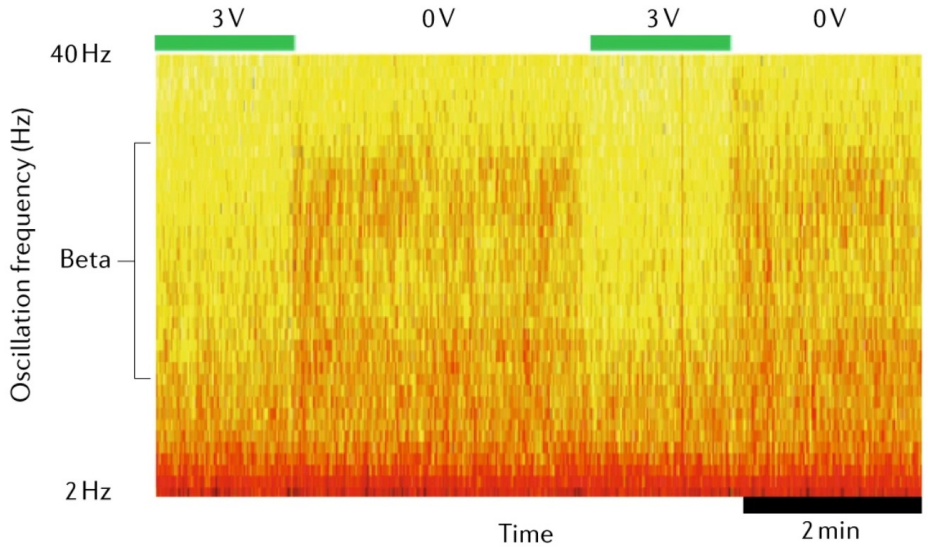
- Neurotransmitters are released in response to stimulation.
- Axon terminals exhaust their readily releasable pool of neurotransmitters and postsynaptic receptors become depressed under high-frequency activity.
- Calcium waves and subsequent release of gliotransmitters.
- Arteriole dilation and increased regional blood flow.



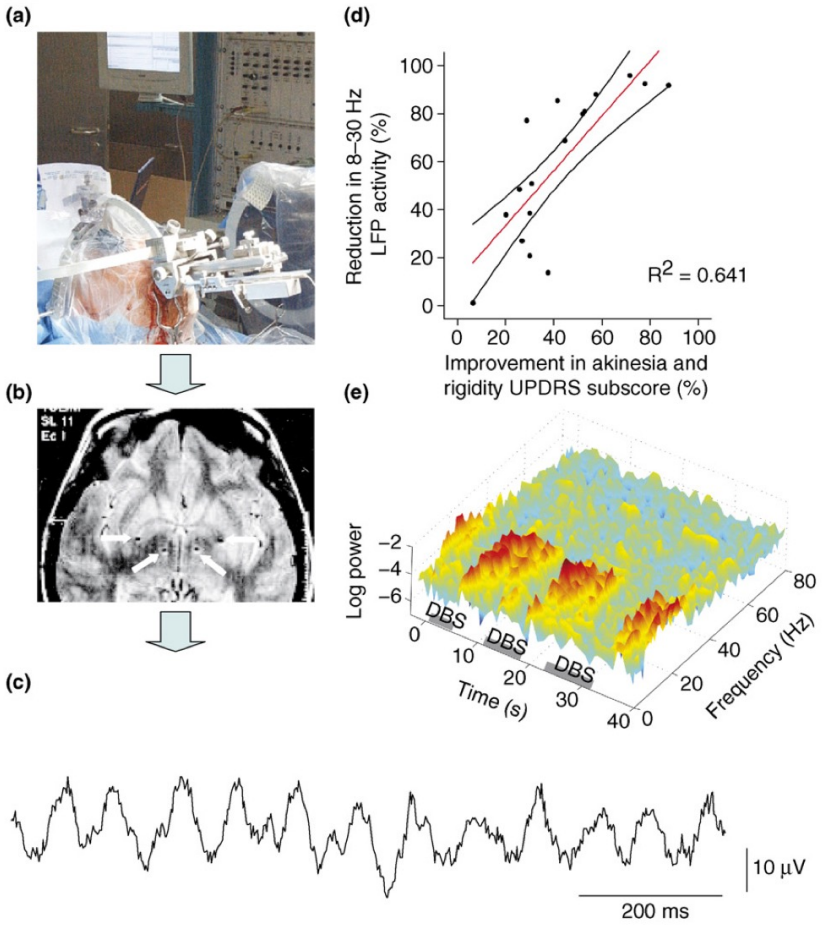
- *Nature Reviews Neurology volume 15, pages 148–160 (2019)*

DBS relieves pathological synchrony in the basal ganglia

- DBS-induced changes in local field potentials within the subthalamic nucleus.
- Activity in the beta band is rapidly reduced with DBS.
- Correlates with reduced akinesia and rigidity.



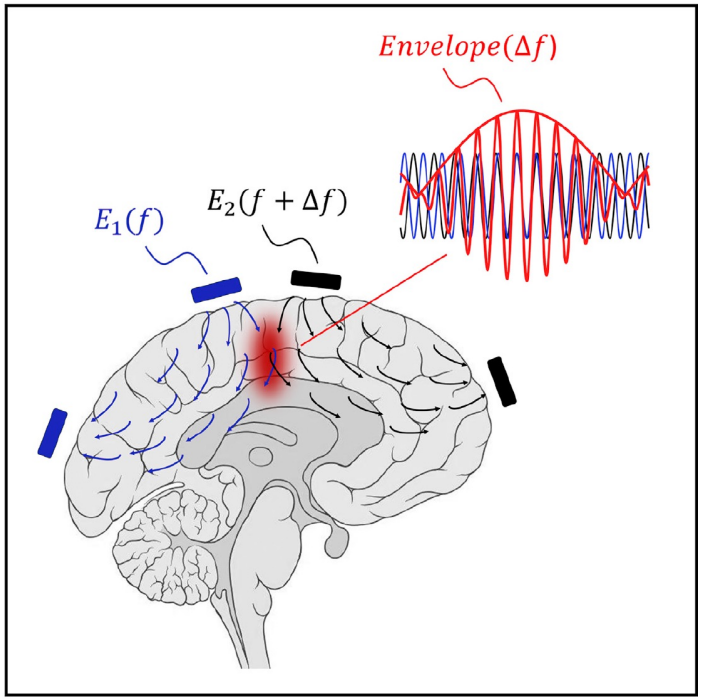
DBS blocks 15 Hz oscillations in PD patient

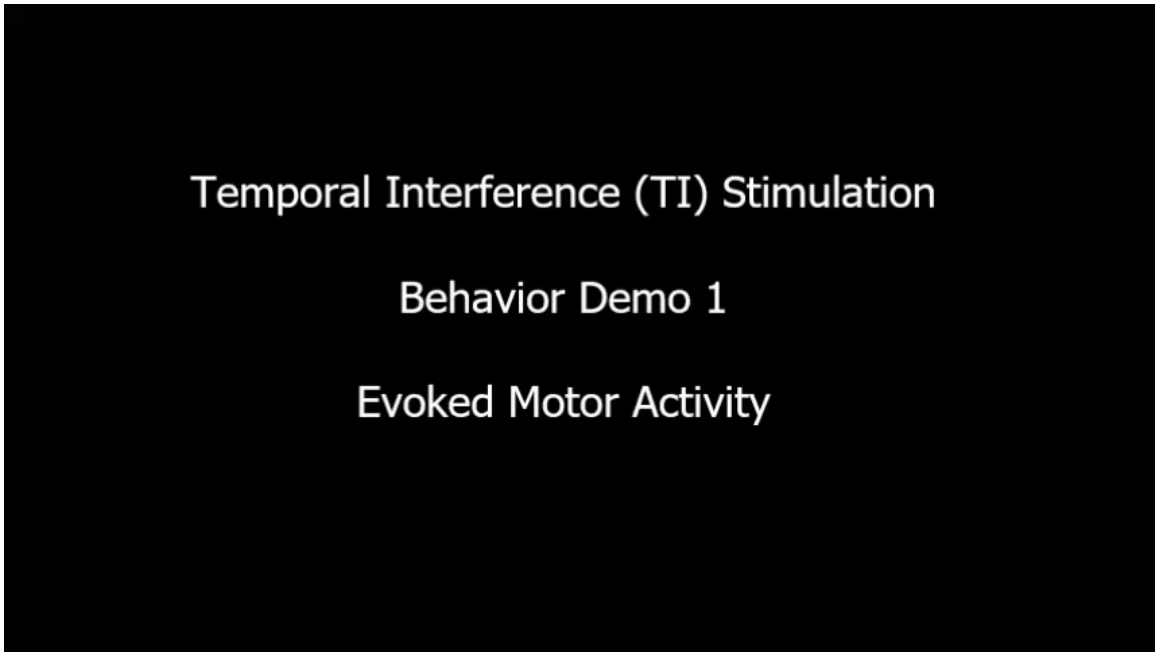


- *Nature Reviews Neurology volume 15, pages 148–160 (2019)*

Non-invasive deep brain stimulation: temporal interference stimulation

Non-invasive focal modulation of evoked neural activity





Cell

Article

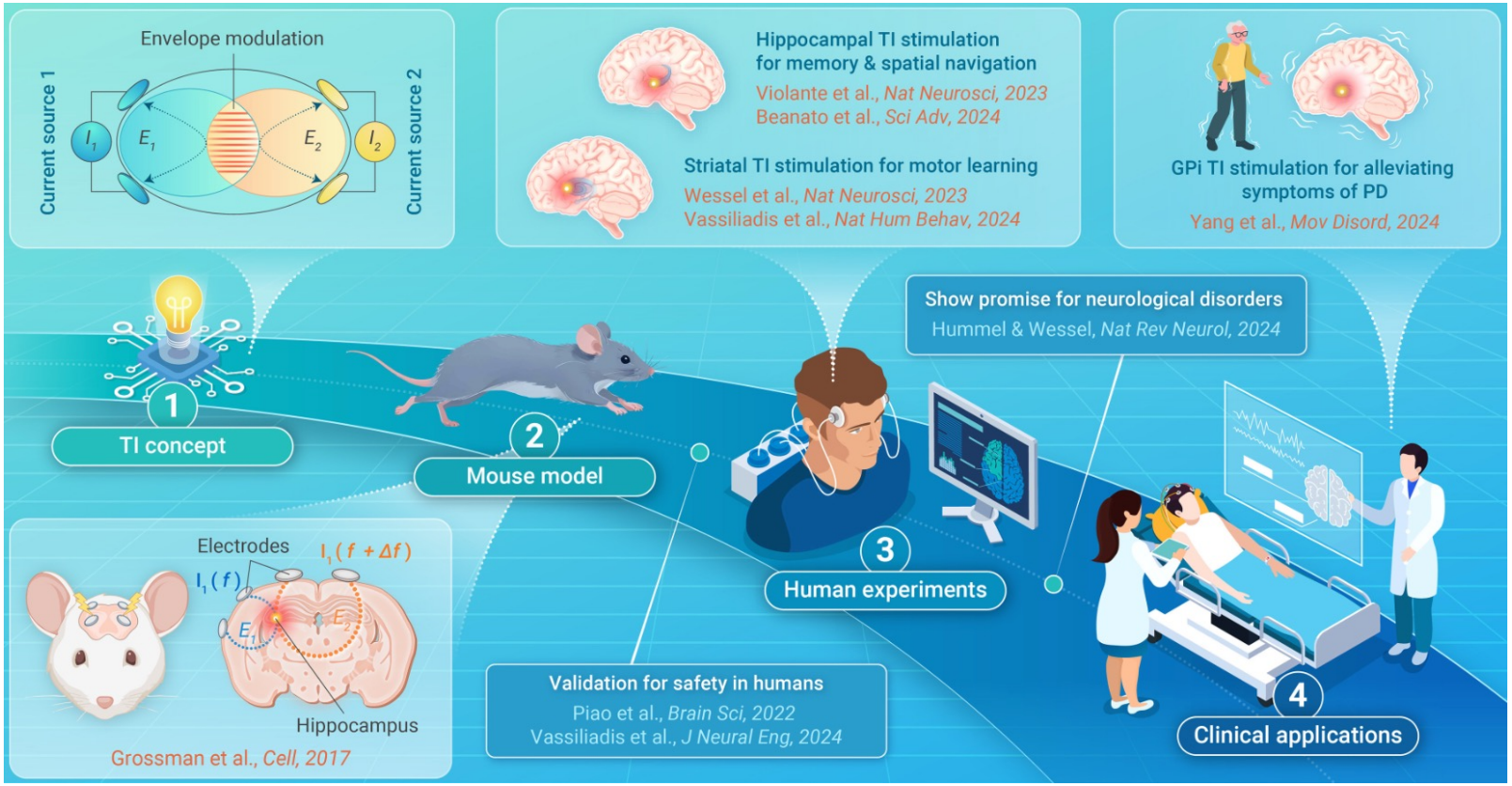
Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields

Authors

Nir Grossman, David Bono, Nina Dedic, ..., Li-Huei Tsai, Alvaro Pascual-Leone, Edward S. Boyden

Non-invasive deep brain stimulation: temporal interference stimulation

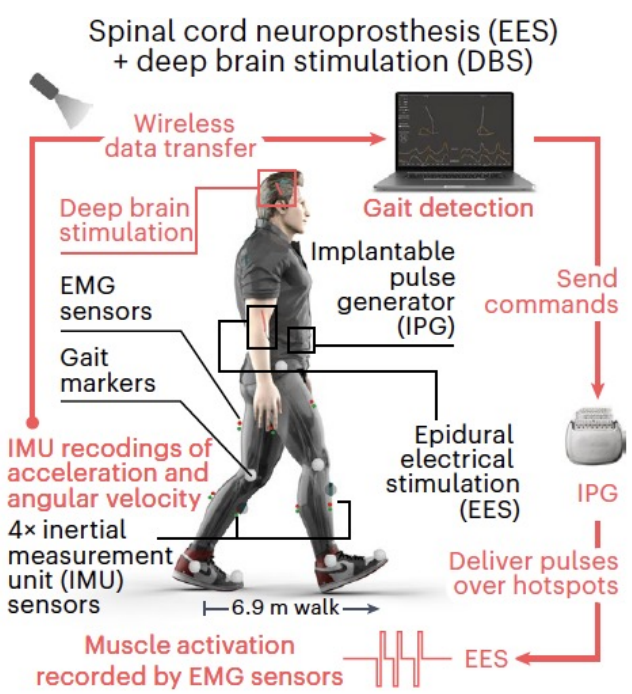
Non-invasive focal modulation of evoked neural activity

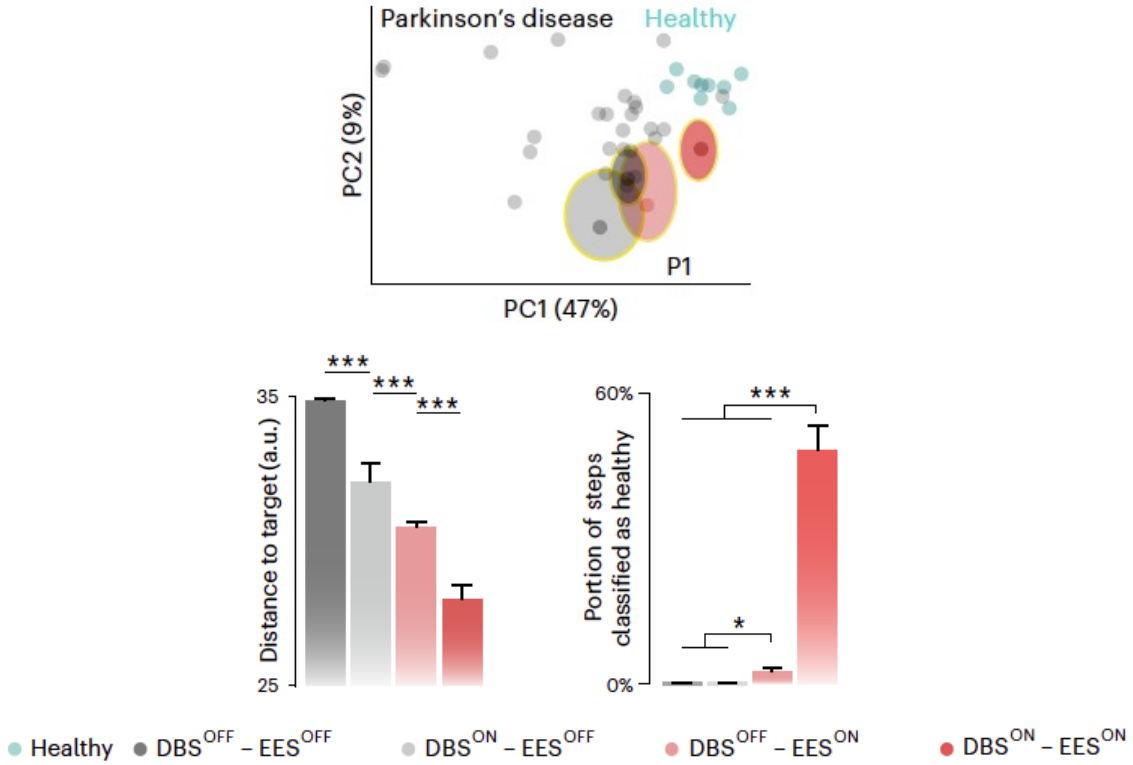


- *DOI: 10.1016/j.xinn.2025.100803*

A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease

- neuroprosthesis operating in closed loop.
- targets the dorsal root entry zones innervating lumbosacral segments to reproduce the natural spatiotemporal activation of the spinal cord during walking.





Lecture plan

1. Basal ganglia circuitry

2. Nigrostriatal degeneration and symptomatic treatments
   - Motor symptoms → dopamine replacement
   - Deep brain stimulation

3. Neuronal degeneration / Lewy body pathology
   - Selective vulnerability of neuronal subtypes
   - Spreading of the α-synuclein pathology

4. PD etiology: organelle quality control
   - Recessive forms: parkin, PINK1 and mitochondrial turnover

Parkinson's disease pathology: causes of selective neuronal vulnerability

Ventral midbrain dopamine neurons:

NB: the degeneration of dopamine neurons is the cause of the most important motor symptoms.
Other types of neurons are also affected in Parkinson's disease.

Neurotransmitter

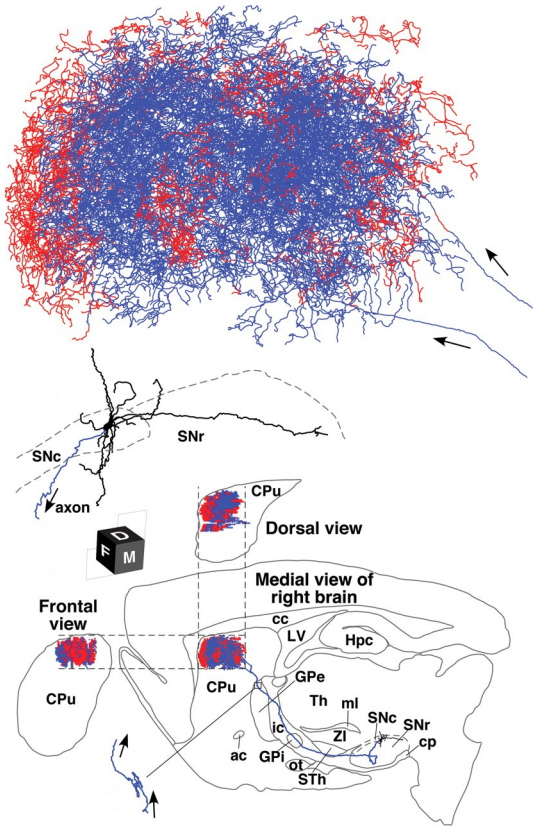
- Presence of **DOPAMINE** is a stress factor.
- Accumulation of DA degradation products in neuromelanin ⇒ risk factor?
- DA metabolism produces ROS ⇒ sequestration into vesicles is crucial.

Structure

- Long, unmyelinated axons, high energy demand
- Neuron function depends largely on axonal transport
- >1'000'000 presynaptic terminals/neuron in humans
- Massive dendritic arborization, cell body <<1% total cell volume

Activity

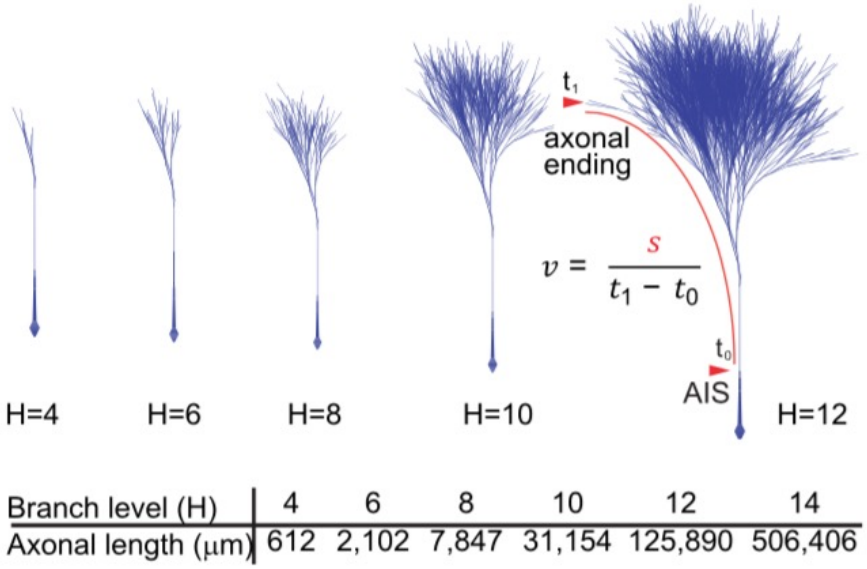
- Autonomously active, slow pacemaking firing activity (2-4Hz).
- Ca_v 1.3 channels: calcium-related stress.



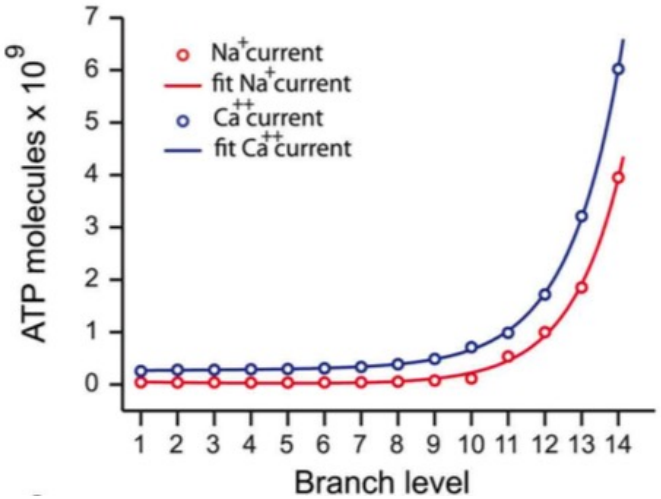
Chan CS et al., TINS 32(5), 2009
Matsuda W et al., J. Neurosci 29(2), 2009

Parkinson's disease pathology: selective neuronal vulnerability

ATP demand increases exponentially with increasing levels of axonal branching



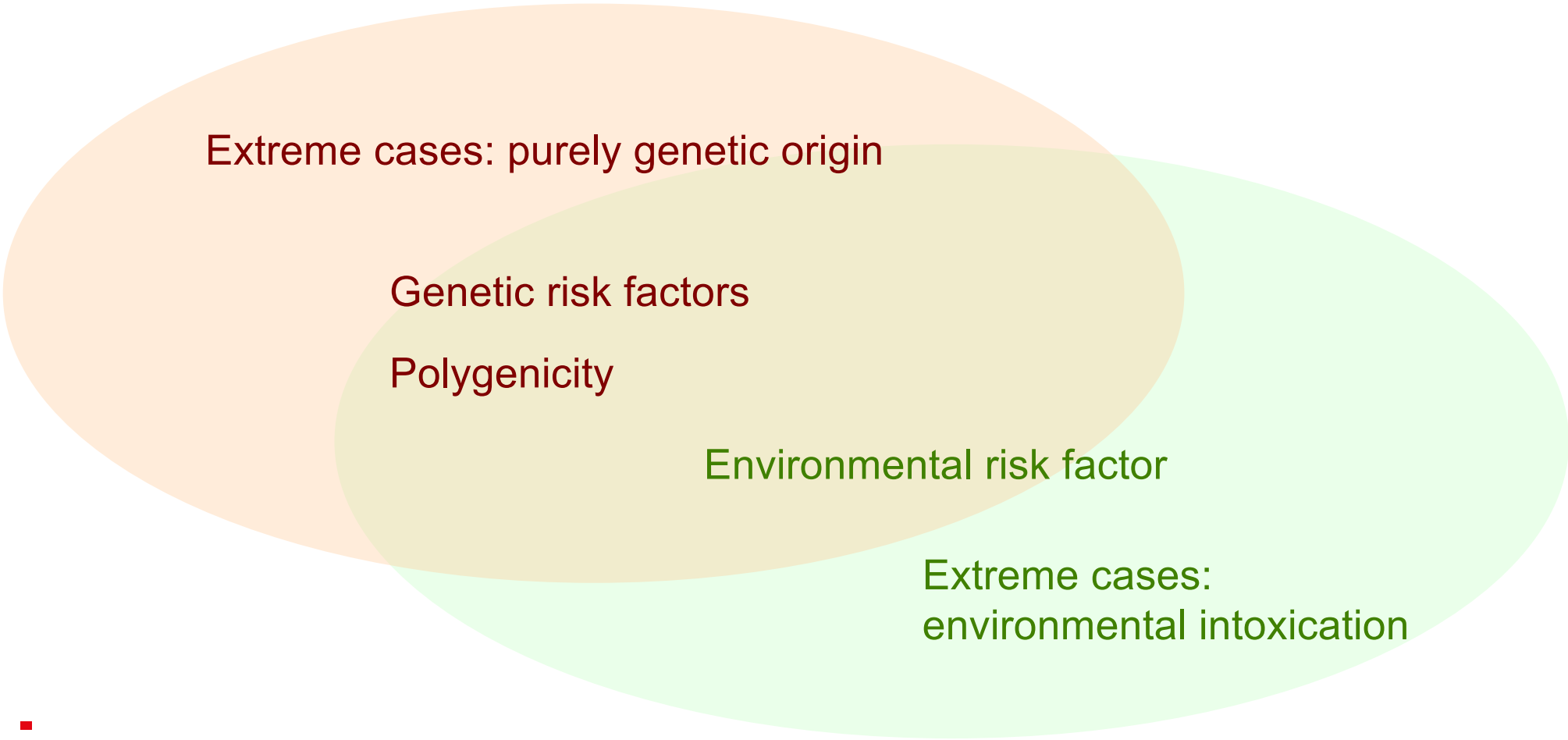
Branch level (H)	4	6	8	10	12	14
Axonal length (μm)	612	2,102	7,847	31,154	125,890	506,406



- Pissadaki E.K. & Bolam P, Front Comput Neurosci. 2013; 7: 13

Parkinson's disease : genetic and environmental causes

Parkinson's disease: complex etiology !



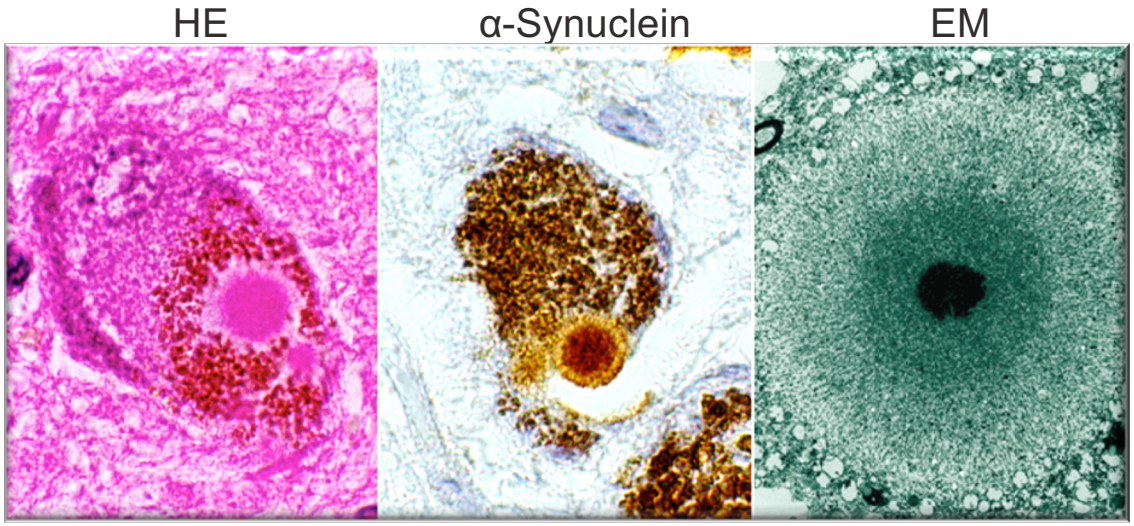
Parkinson's disease etiology : familial forms

Locus	Protein	Mode of inheritance	Atypical PD features	Lewy bodies	Frequency
PARK1/4	**α-synuclein (SNCA)**	**AD**	**Early onset, rapid progression**	**+**	**<1%**
PARK8	LRRK2	AD	-	+	1-7% of PD patients
PARK5	UCH-L1	AD	?	?	rare
PARK17	VPS35	AD	?	?	0.13% of PD patients
PARK2	Parkin	AR	Early onset, dyskinesias, slow progression	(-)	10-25% of early-onset PD
PARK6	PINK1	AR	Early onset, slow progression	(+)	1-8% of early-onset PD
PARK9	ATP13A2	AR	Juvenile onset, dementia	?	rare
PARK7	DJ-1	AR	Early onset, slow progression, psychiatric symptoms	?	1-2% of early-onset PD
PARK14	PLA2G6	AR	Early onset, dystonia	?	rare

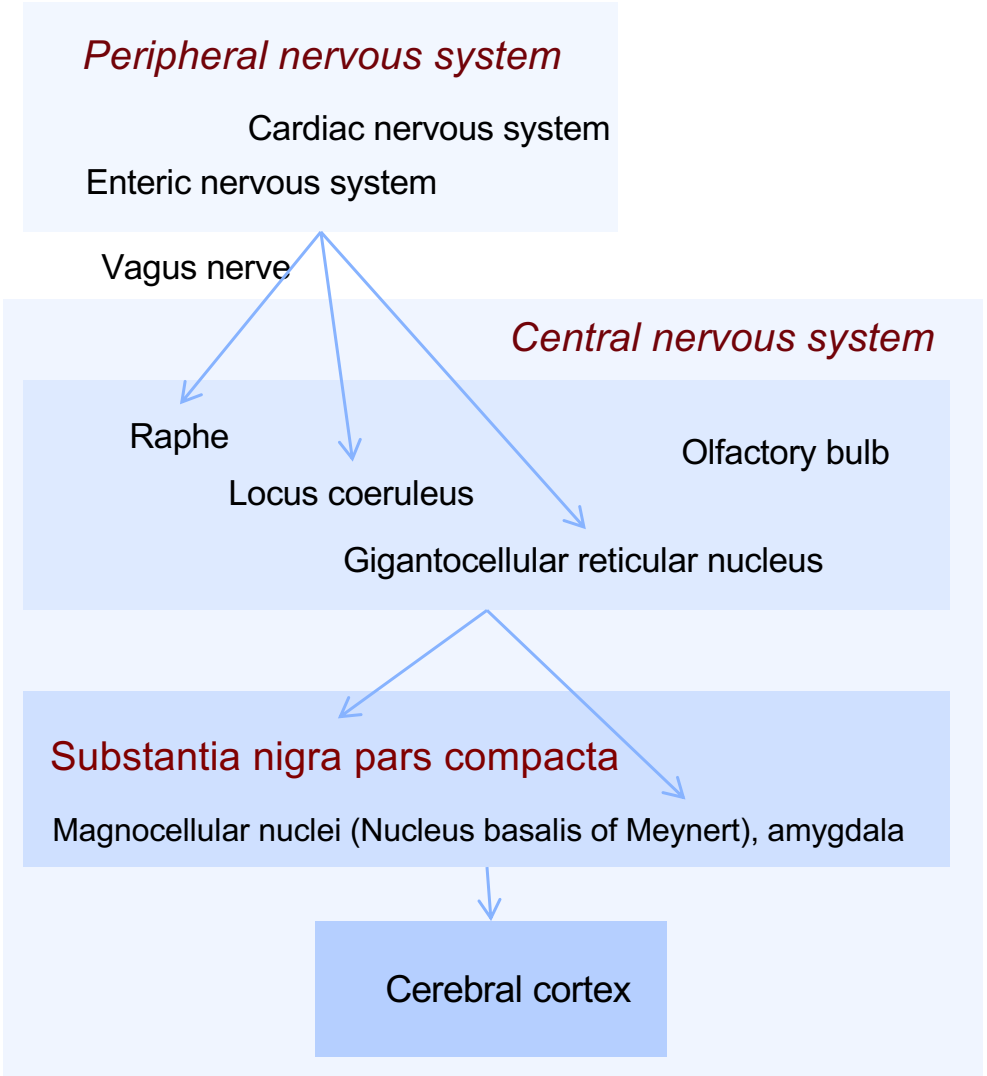
Parkinson's disease pathology: Lewy bodies

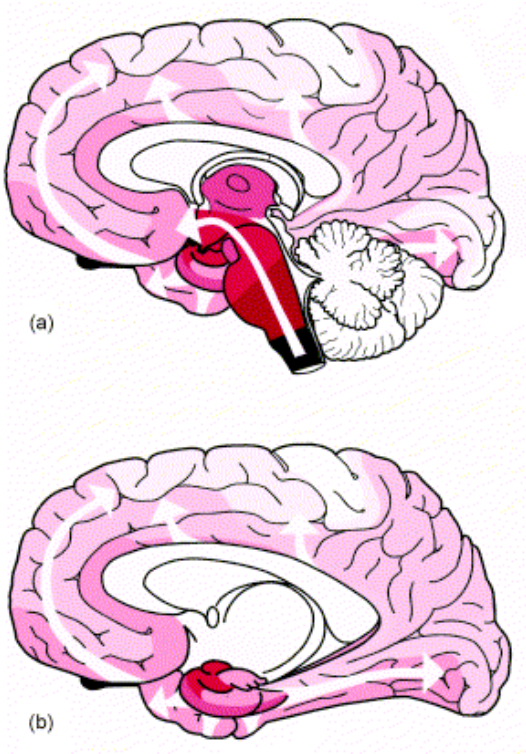
Pathological hallmark: **Lewy body** aggregates

- First described in 1912 by Friedrich Lewy
- Hallmark of synucleinopathies
- Aggregates, composed mainly of proteins, and some lipids
- The protein **alpha-synuclein** is the main constituent
- Cytoplasmic
- Mostly neuronal
- In the cell soma (Lewy bodies)
- In the neurites (Lewy neurites)



Widespread and progressive Lewy body pathology in Parkinson's disease

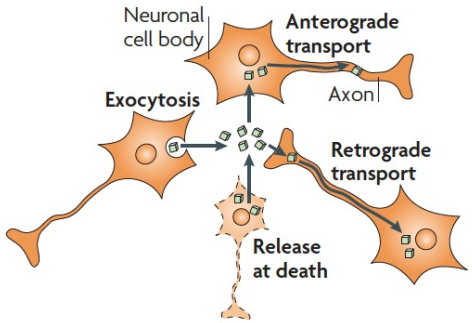




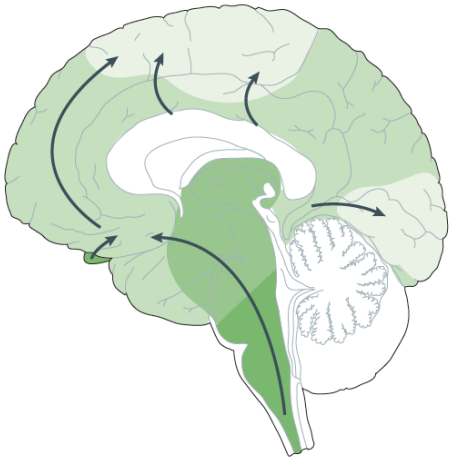
Braak H. et al.,
Neurobiology of Aging 2003, 24: 197-211

Neurodegeneration: spreading pathologies

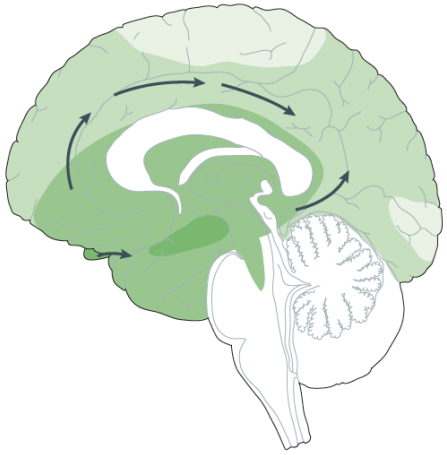
Propagation patterns of neurodegenerative proteopathies



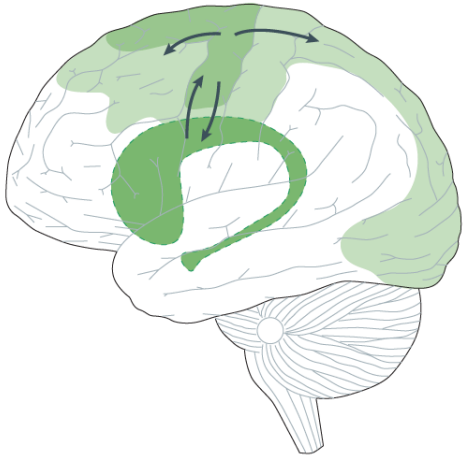
Parkinson's disease (α-synuclein)



Alzheimer's disease (tau)



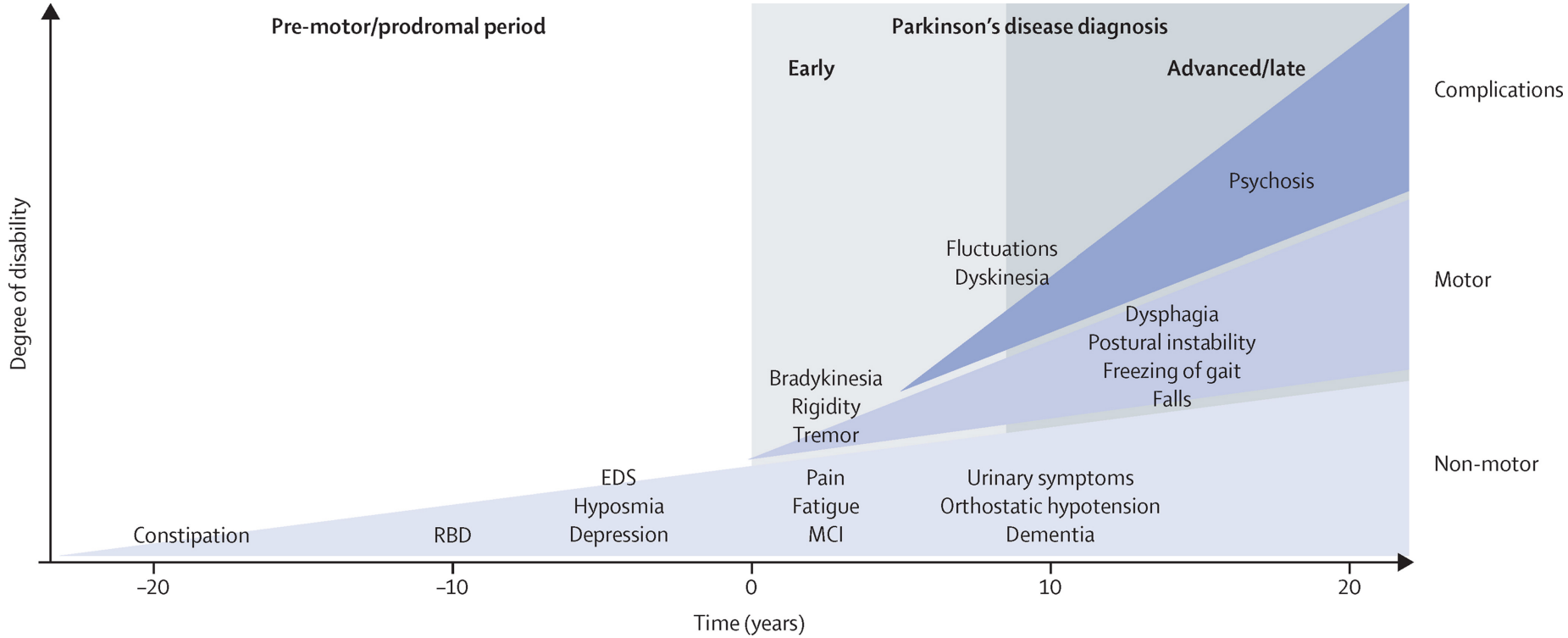
Huntington's disease (huntingtin)



Lewy body pathology in Parkinson's disease: correlation with early symptoms

Evolution of Parkinson's disease

(many symptoms poorly respond to dopamine treatment)



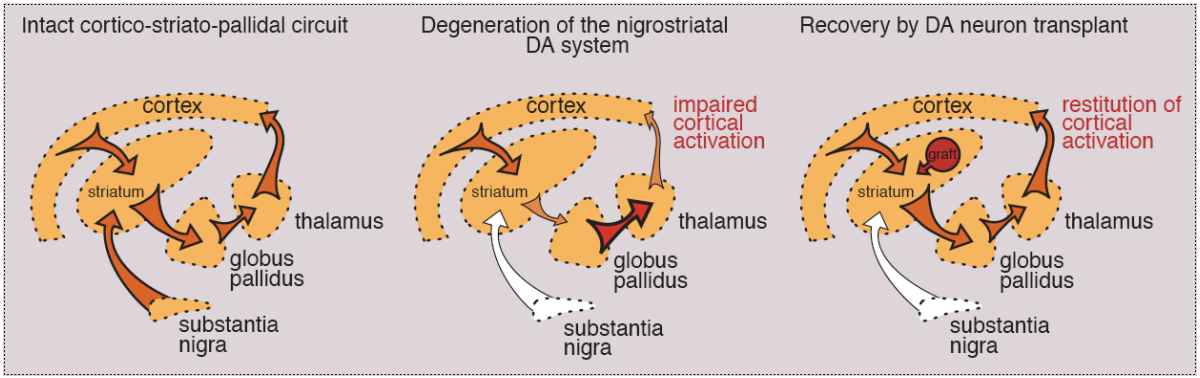
Kalia LV et al, the Lancet 2015

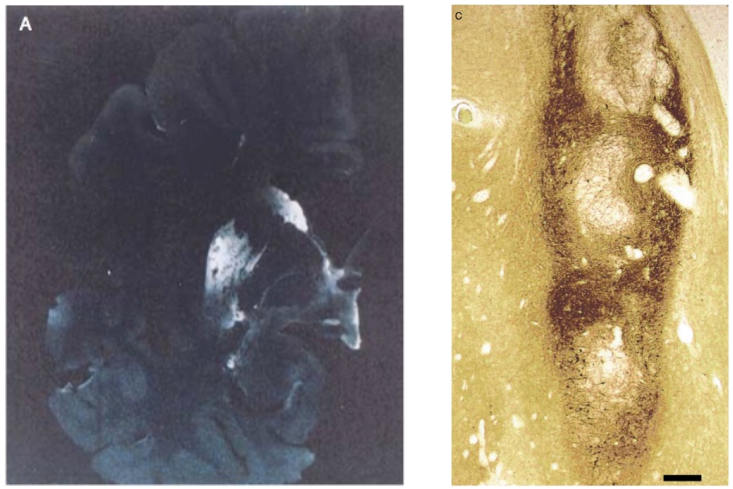
RBD: REM (rapid eye movement) Sleep Behavior Disorder
EDS: Excessive daytime sleepiness

PD pathology: evidence for spreading

Cell therapy: implantation in the striatum of fetal dopamine neurons

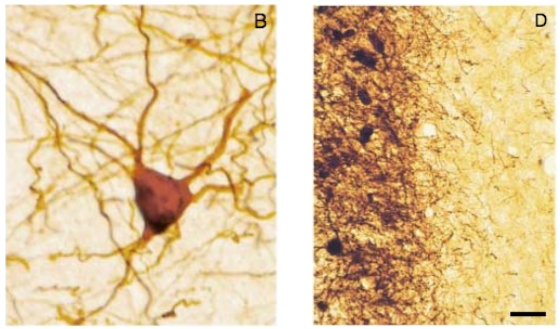
Cell therapy
for dopamine replacement
in the striatum (ectopic
implantation)





Survival / engraftment

Fetal graft (7 embryos, 6½-9 wks)
18 months post transplantation
Tyrosine hydroxylase staining



Connectivity with host striatum

Kordower et al., NEJM 332 (1995), Björklund & Lindvall, Nature Neuroscience 3 (2000)

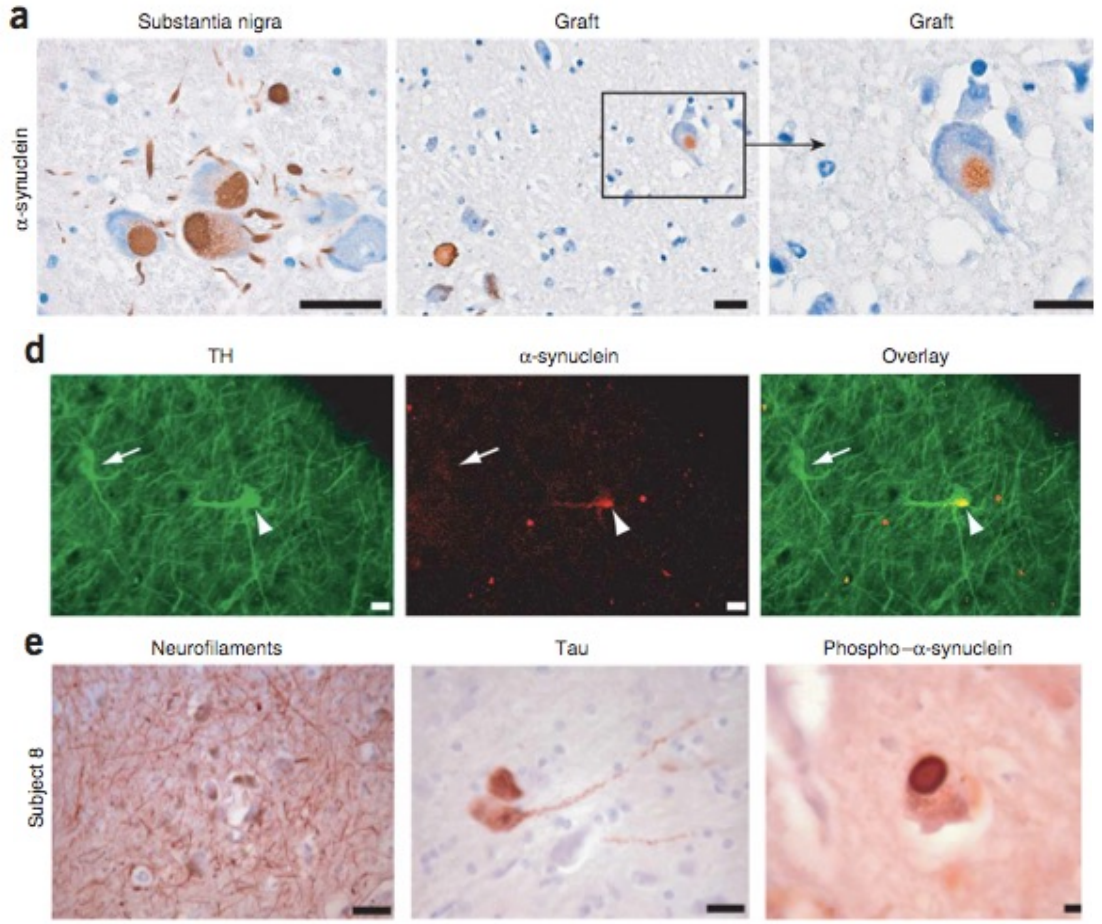
PD pathology: evidence for spreading

Post-mortem analysis of long-term grafted patients: 11-16 yrs post surgery

Lewy-body pathology in some grafted neurons !

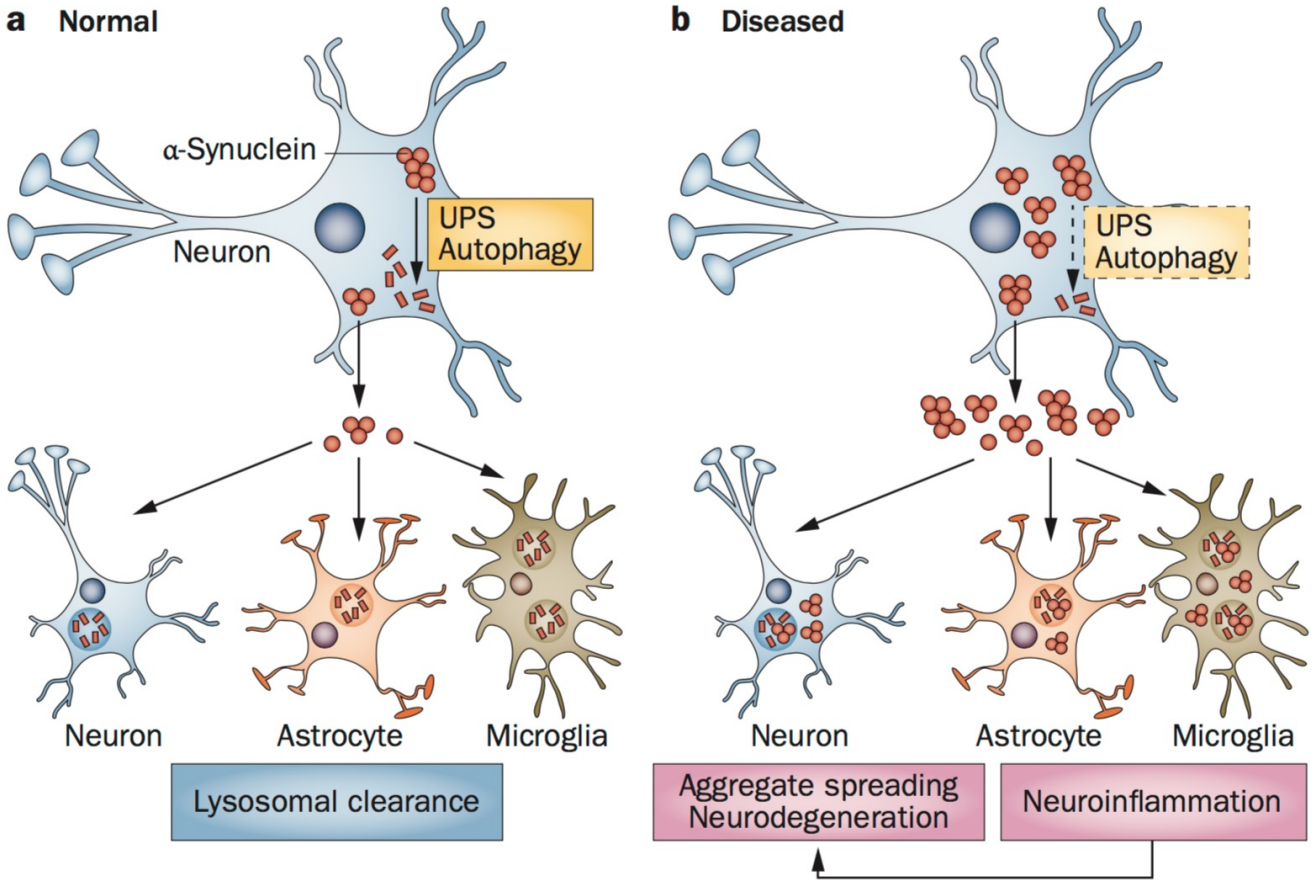
« Prion-like » disease transmission ?

Graft exposed to a noxious microenvironment (microglia, lack of trophic support) ??



Li et al., Nature Medicine 2008
Kordower et al., Nature Medicine 2008
Mendez et al., Nature Medicine 2008

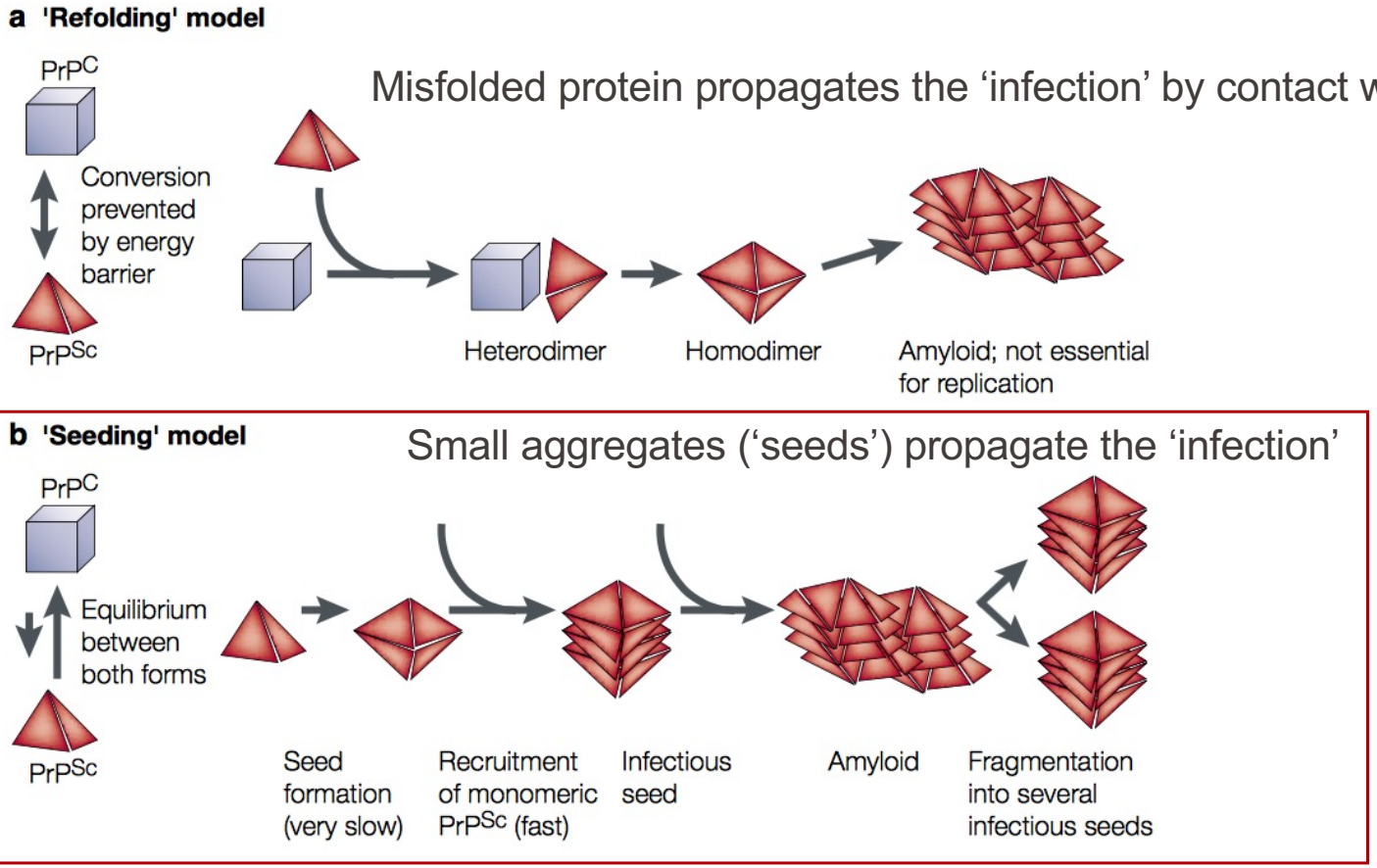
PD pathology: evidence for spreading



- *Lee HJ et al, Nat Rev Neurol 2014*

Spreading of PD pathology: a prion-like mechanism ?

Infectious proteins: proposed models

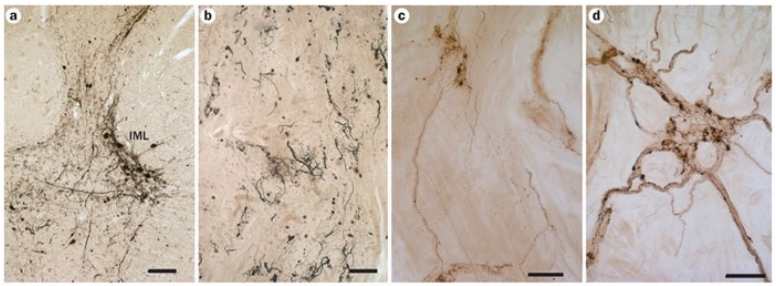


Most likely model for Parkinson's disease and α-synuclein

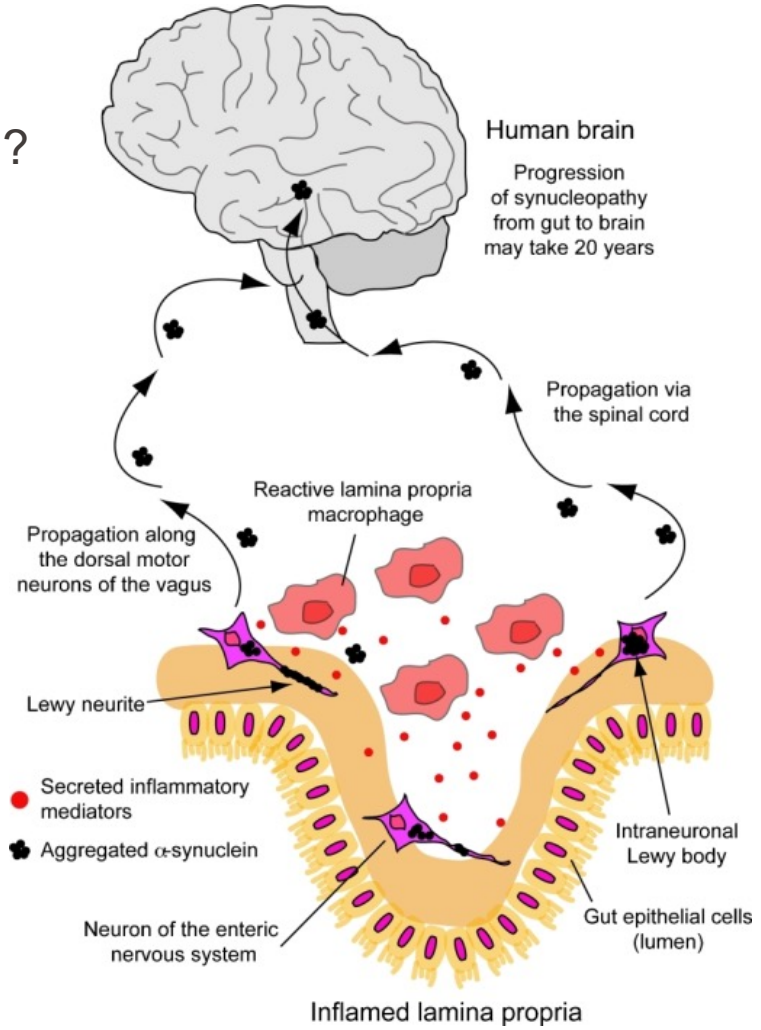
- *Aguzzi A et al, Nat Rev Mol Cell Biol 2, 118-126 (2001) | doi:10.1038/35052063*

PD pathology: evidence for spreading

Is there a propagation of the α-synuclein pathology from the periphery towards the brain ?

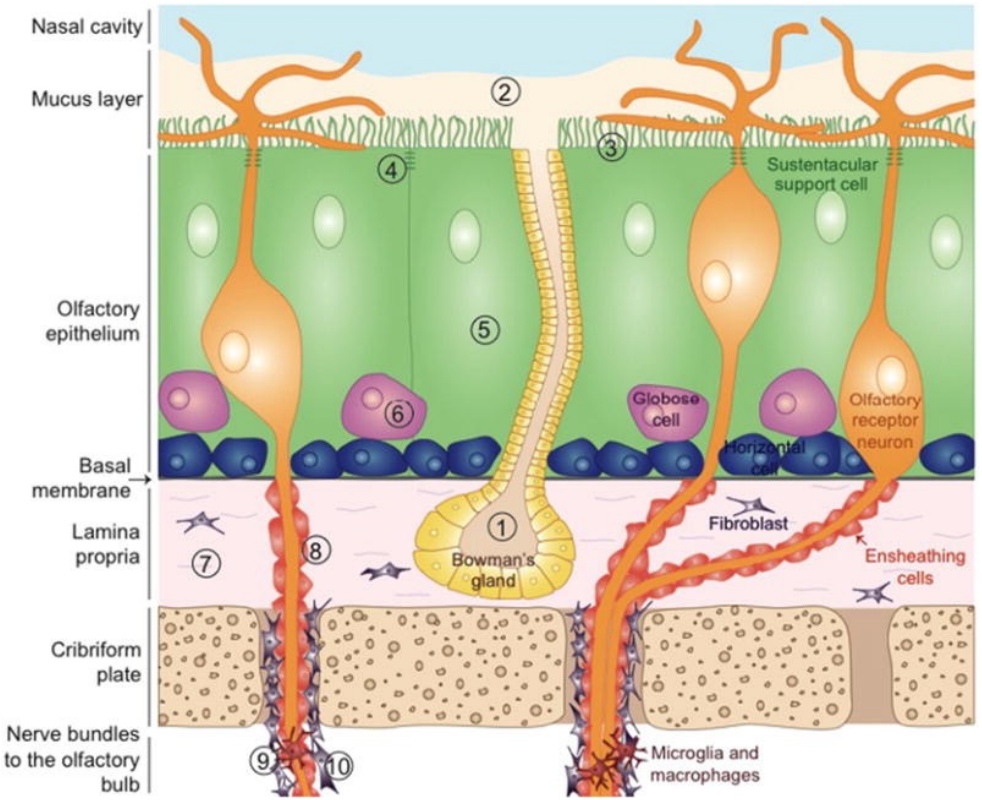


Synuclein-immunoreactive Lewy pathology in the PD spinal cord,
coeliac ganglion and gastrointestinal tract

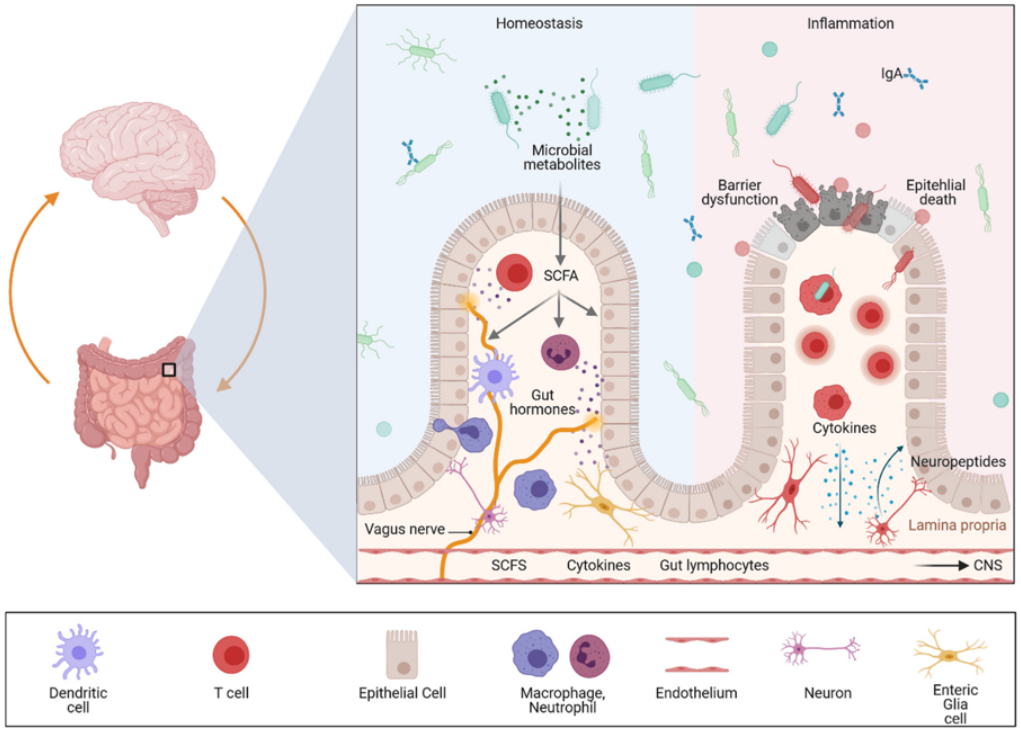


Are the olfactory epithelium and the gut epithelium starting points for spreading of the α-synuclein pathology to the central nervous system ?

Olfactory epithelium



Gut epithelium



Parkinson's disease: question 6

Alpha-synuclein pathology propagates across defined pathways in the CNS. What are the implications of this observation ?

Select all the correct statements:

A. Similar to prion, α-synuclein misfolding is an infectious mechanism

B. This shows that the protein may be accessible to therapeutic intervention outside cells

C. This mechanism may be either pathological or physiological

D. This mechanism has no therapeutic implication