Neurodegenerative diseases of the CNS

Parkinson's Disease

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Schedule: «Disease of the central nervous system»

Diseases of the CNS: Introduction, Stroke	13.11.2017
Neurodegenerative diseases of CNS: Parkinson's Disease	20.11.2017
Autoimmune diseases of the CNS: Multiple Sclerosis	27.11.2017

Handout & Lecture

Purves: Chapter 18

Diseases of the Central Nervous System

Neurodegeneration:

- Alzheimer's Disease (AD)
- Parkinson's Disease (PD)
- Amyotrophic Lateral Sclerosis (ALS)
- Huntington's Disease (HD)

Traumatic:

- Concussion
- Spinal cord injury

Neuroinfection:

- Meningitis (viral or bacterial)
- Encephalitis (viral or bacterial)

Autoimmune:

- Multiple Sclerosis (MS)
- Myasthenia gravis

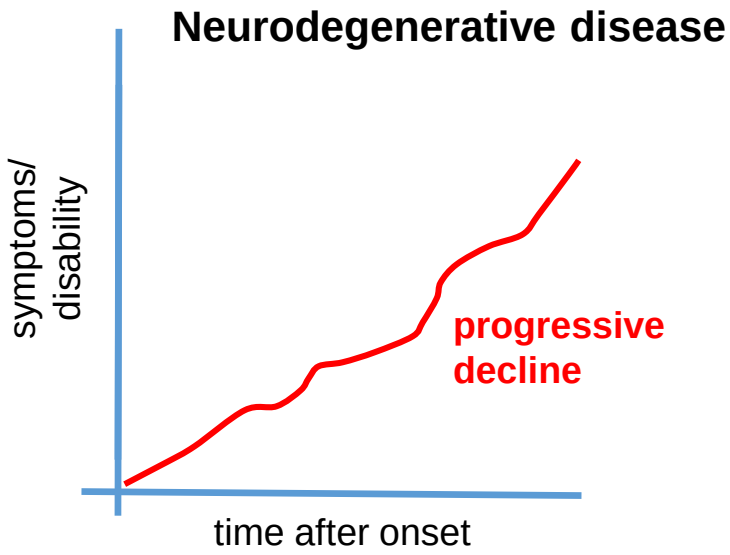
Psychiatric disorders:

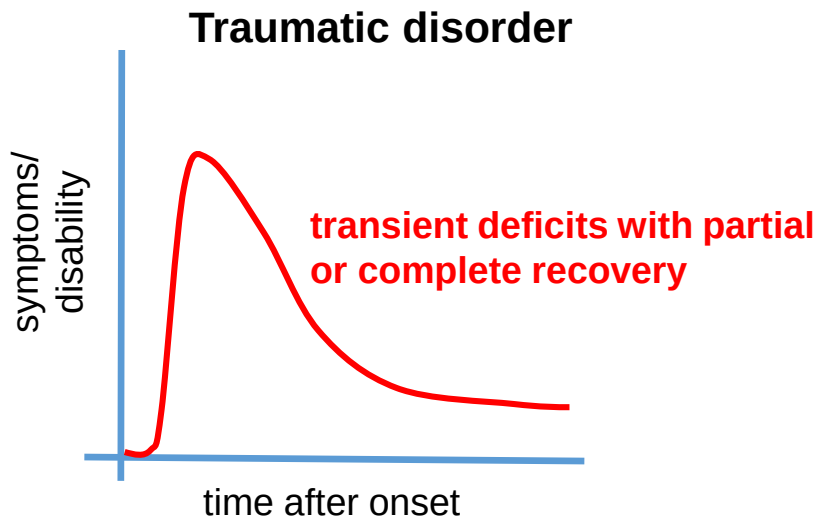
- Bipolar disorder
- Schizophrenia
- Autism

Neurodegenerative disorders

- Similar pathomechanisms among neurodegenerative diseases of CNS
- Different symptoms and deficits (dementia, motor deficits etc.)
- Age is major risk factor for neurodegenerative diseases
  (in 2030, 25% of people >65 years)
- Etiology of neurodegenerative diseases still poorly understood

Mostly symptomatic treatments. Cause of the diseases cannot be targeted yet.





Parkinson's Disease: Epidemiology

- 2nd most frequent **neurodegenerative disorder** after Alzheimer's Disease

- chronic, slowly progressive, neurodegenerative disease

- 0.3% prevalence in total US population
  - 1-2% prevalence in people >65 years of age
  - 4-5% prevalence in people >85 years of age

- Only around 10% of all PD cases occur in people <45 years of age

Wood-Kaczmar et al., 2006

- Parkinson's Disease:
  - 95% without genetic etiology (sporadic/idiopathic PD)
  - 5% with genetic origin

Parkinson's Disease: history

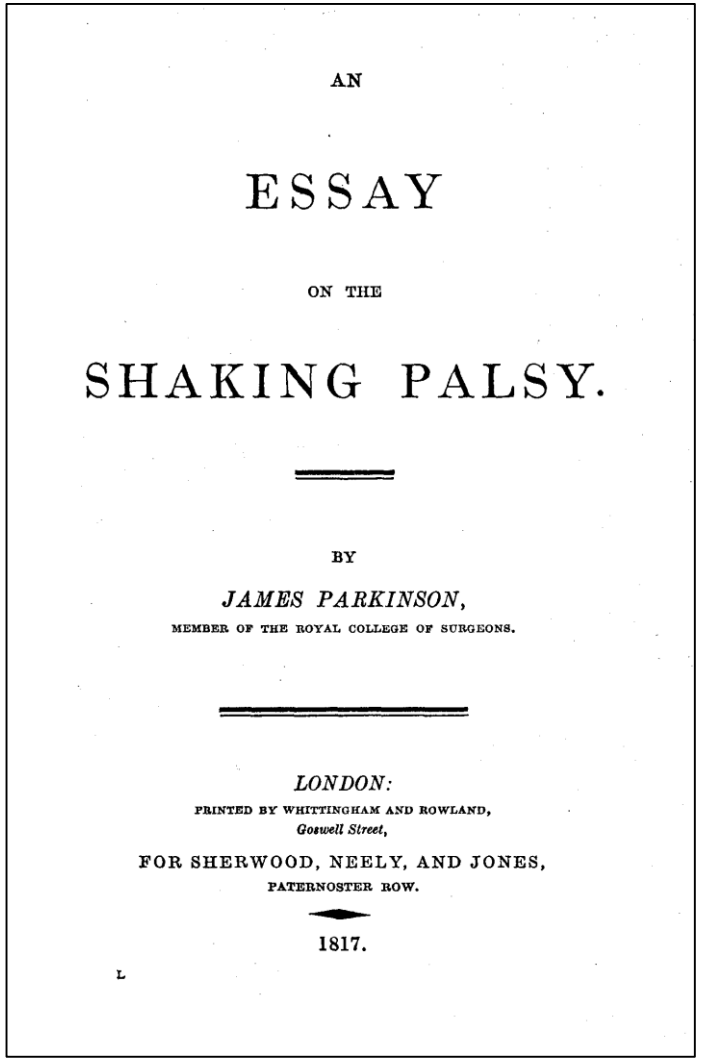
James Parkinson

"Shaking Palsy" = loss of muscle function associated with tremor *Galen, 175 AD*

"Paralysis agitans" = progressing loss of muscle function *James Parkinson, 1817*

Parkinson's Disease (Morbus Parkinson)

Jean Martin Charcot, 1877



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

Parkinson's Disease: Symptoms and course of disease

Motor features:

Parkinsonism: *(Parkinsonian Syndrome)*

- neurological syndrome that shares symptoms of PD (syndrome = association of symptoms)
- common criteria is bradykinesia and at least one of the symptoms including tremor, postural instability of rigidity,.
- ~ 80% of patients showing parkinsonisms indeed are diagnosed with PD

4 cardinal motor manifestations

1. Bradykinesia (slowness of movements and reflexes)
2. Resting tremor
3. Postural instability
4. Muscular rigidity

Parkinsonism (Parkinsonian syndrome)

Early motor symptoms:

- asymmetrical onset of deficits -> gradual spread to contralateral side
- asymmetric resting tremor (3-6 Hz)

  ->tremor at rest; decreased during voluntary movements
- Developing bradykinesia

Motor symptoms in progressed PD:

- Pronounced bradykinesia representing the *most disabling motor symptom*
- Muscular rigidity (propulsion during walking, and stiff arms without swing, cogwheel)
- Postural instability at later stages during PD: -> risk of falling
- Hypokinesia (decreased amplitude of movement) and akinesia (absence of movement)

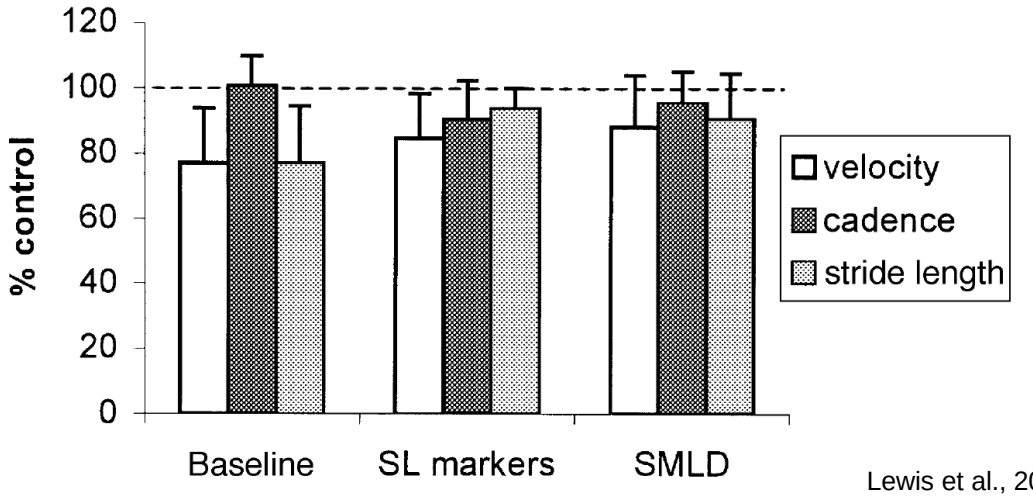
Parkinsonian Gait

- Propulsion of upper body (festination)
- Reduced arm swing

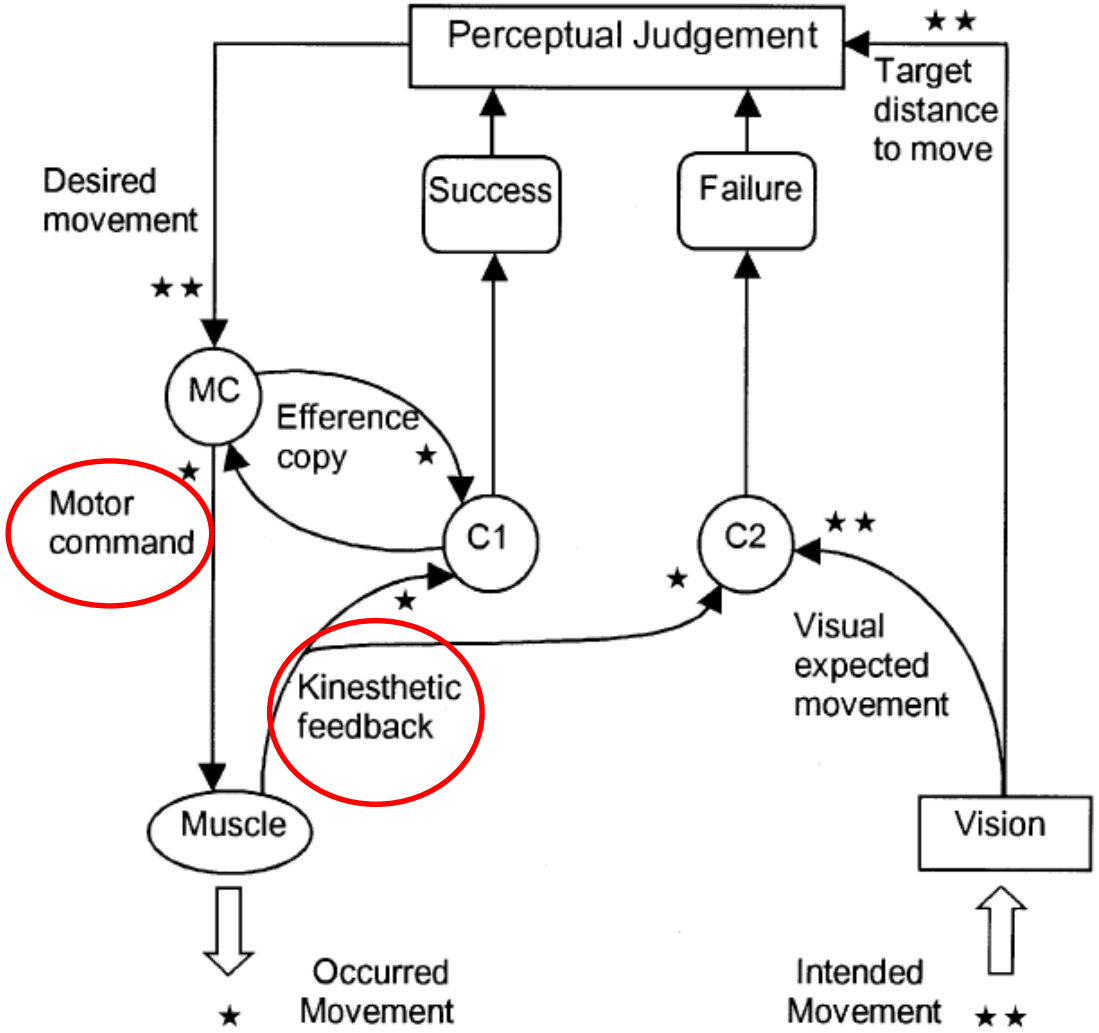
- Reduced walking speed
- Reduced step length
- Hypoextension of hip and knee joints
- Shuffling steps
- Tripping gait

Parkinsonian Gait

Visual cueing improves walking function in PD patients



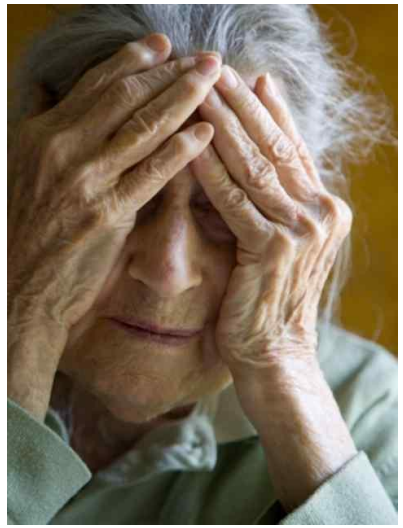
Lewis et al., 2000



Lewis et al., 2000

Parkinson’s Disease: non-motor deficits

Non-motor features:



- Usually occur at progressed stages of PD
- Most frequent non-motor consequence of PD is depression (ca. 50% of patients)
- Further non-motor deficits are dementia, psychosis
- Loss of olfactory function (70-100% of patients -> useful biomarker)
- Sleep disorders (prevalence is 60-90% at some time over the course of PD)
- Do not respond to dopaminergic treatment

Parkinson's Disease: Diagnosis

3-step approach to identify idiopathic PD (iPD):

Step 1: *Identification of Parkinsonism (Parkinsonian syndrome).*

→ **Idiopathic Parkinson's Disease:** ca. 80% of cases showing parkinsonism

Step 2: *Exclusion of other causes of Parkinsonism.*

- **Symptomatic form: (Secondary Parkinsonism)** drug-induced (e.g. Risperidone) parkinsonism, metabolic dysfunction leading to parkinsonism, post-infectious parkinsonism, post-traumatic parkinsonism, toxin-induced parkinsonism (e.g. MPTP).

- **Atypical form: (Parkinson-plus Syndromes)** Parkinsonian syndrome in the context of other neurological diseases (e.g. Alzheimer's Disease, multiple system atrophy etc.)

Step 3: *Identification of supportive features:*

1. response to application of levodopa (L-Dopa)
2. smell test to prove olfactory dysfunction often observed in PD

Parkinson's Disease: risk factors

- Only proven risk factor of PD is **age**
- **Genetic** predisposition
- Environmental hypothesis (never proven)

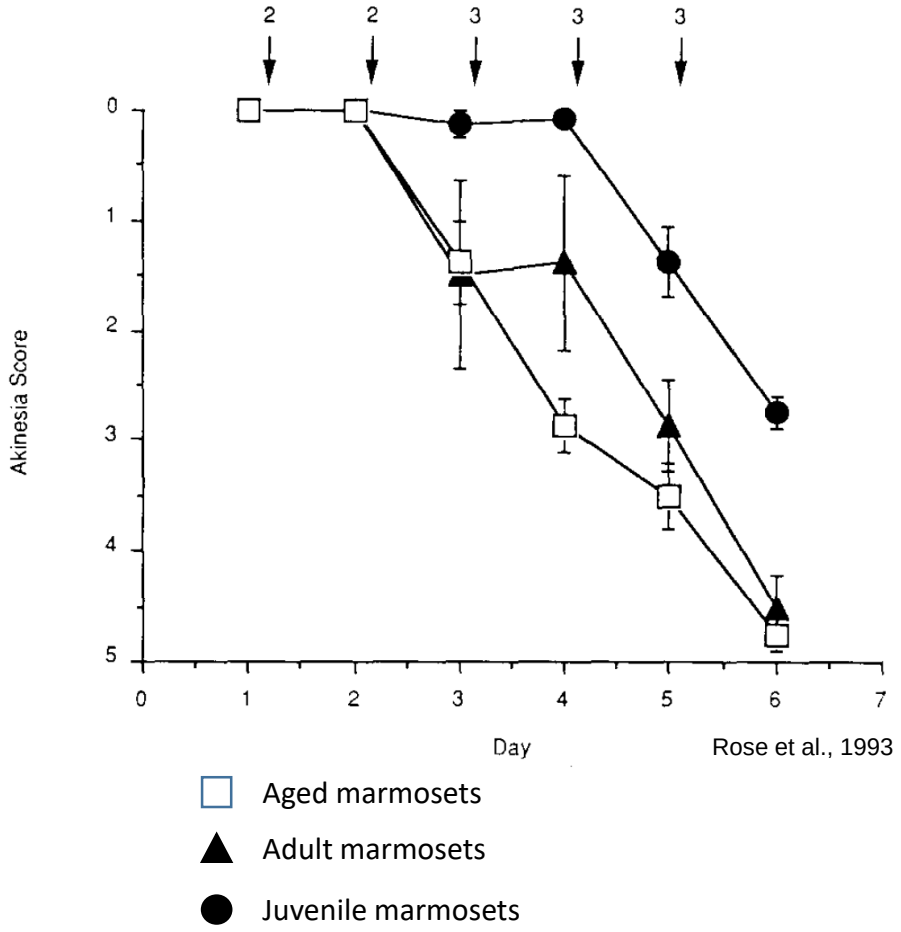
Modifiable (lifestyle) factors:

- **Rural living**
- Exposure to **pesticides and herbicides**
- **Well-water** drinking

Consumption of coffee and cigarettes seem to lower the risk for PD

Hernan et al., 2003

Marmosets of different age injected with neurotoxin leading to parkinsonism

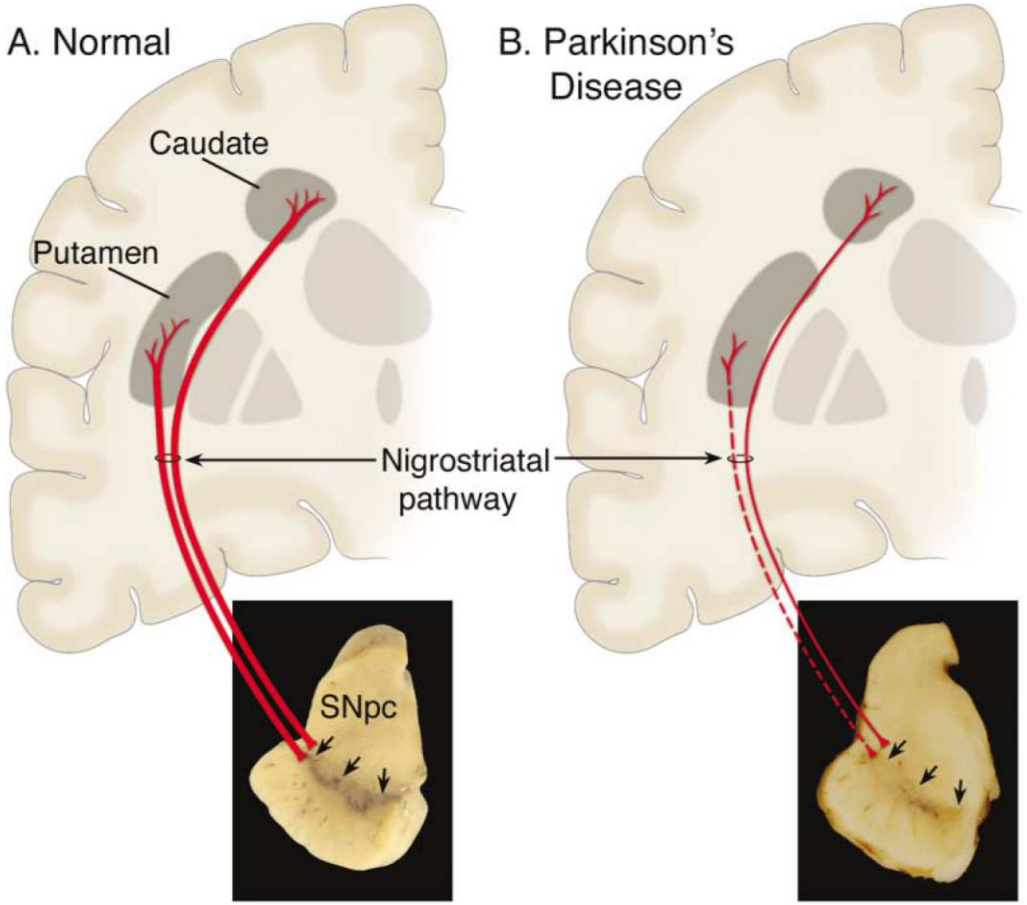


Rose et al., 1993

Parkinson's Disease: Neuropathological features

1. **Depigmentation** of melanin-rich neurons
   in Substantia Nigra pars compacta (SNpc)
   - symptoms only start after >60% of neurons in SNpc are degenerated
   - dying-back process: degeneration of nigrostriatal terminals?

2. Formation of intracytoplasmic inclusions consisting of aggregated proteins in nigrostriatal neurons (**Lewy Bodies**). Lewy Bodies are not specific for PD, but occur also in e.g. Alzheimer's disease.



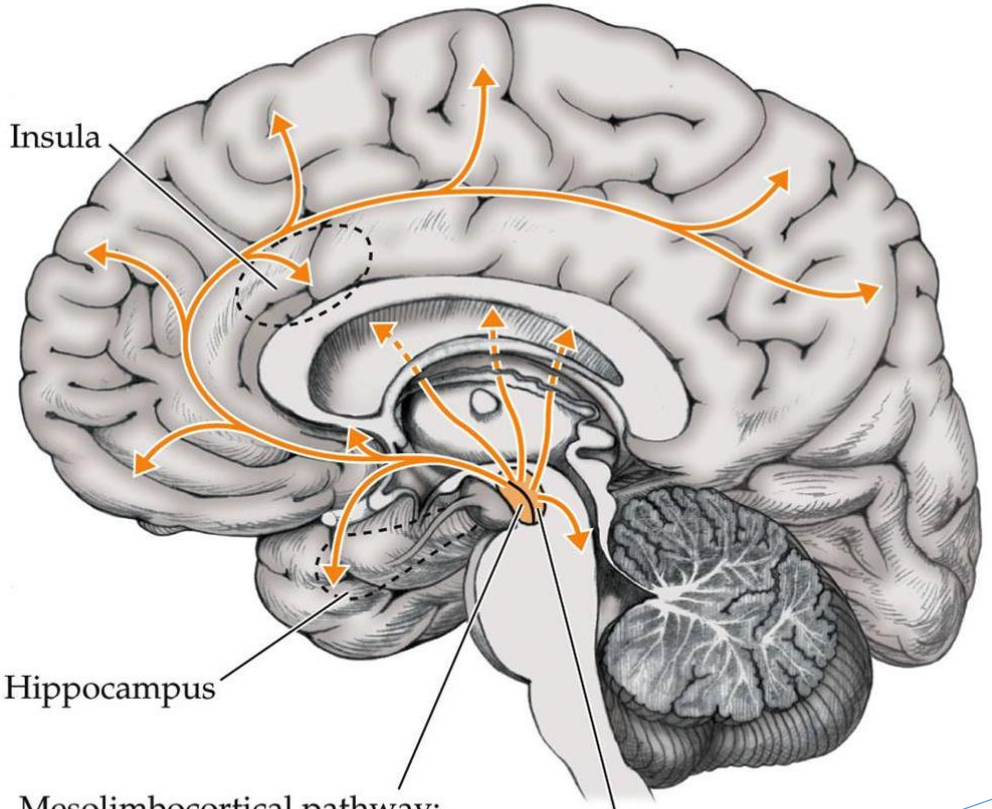
Dauer and Przedborski, 2003

Dauer and Przedborski, 2003

Parkinson's Disease: Neuropathological features

3. Moderate neurodegeneration of cells in ventral tegmental area (VTA; dopaminergic) and in the locus coeruleus (noradrenergic cells in brain stem)

Reward system, motivation, emotions, memory, Addiction, schizophrenia-like symptoms (e.g. hallucinations)



Motor control
Parkinson's disease

Biological Psychology 6e, Figure 4.3

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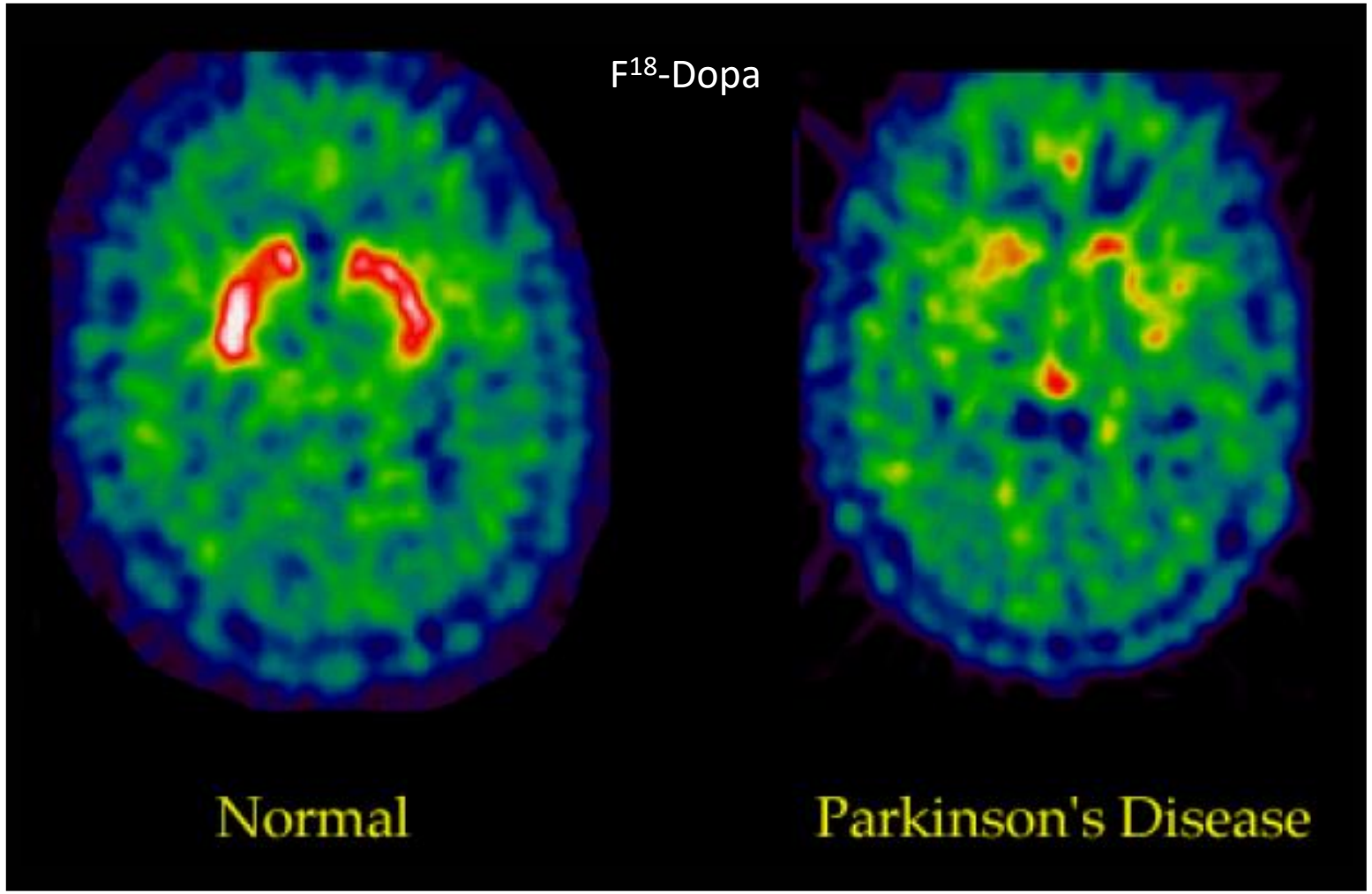
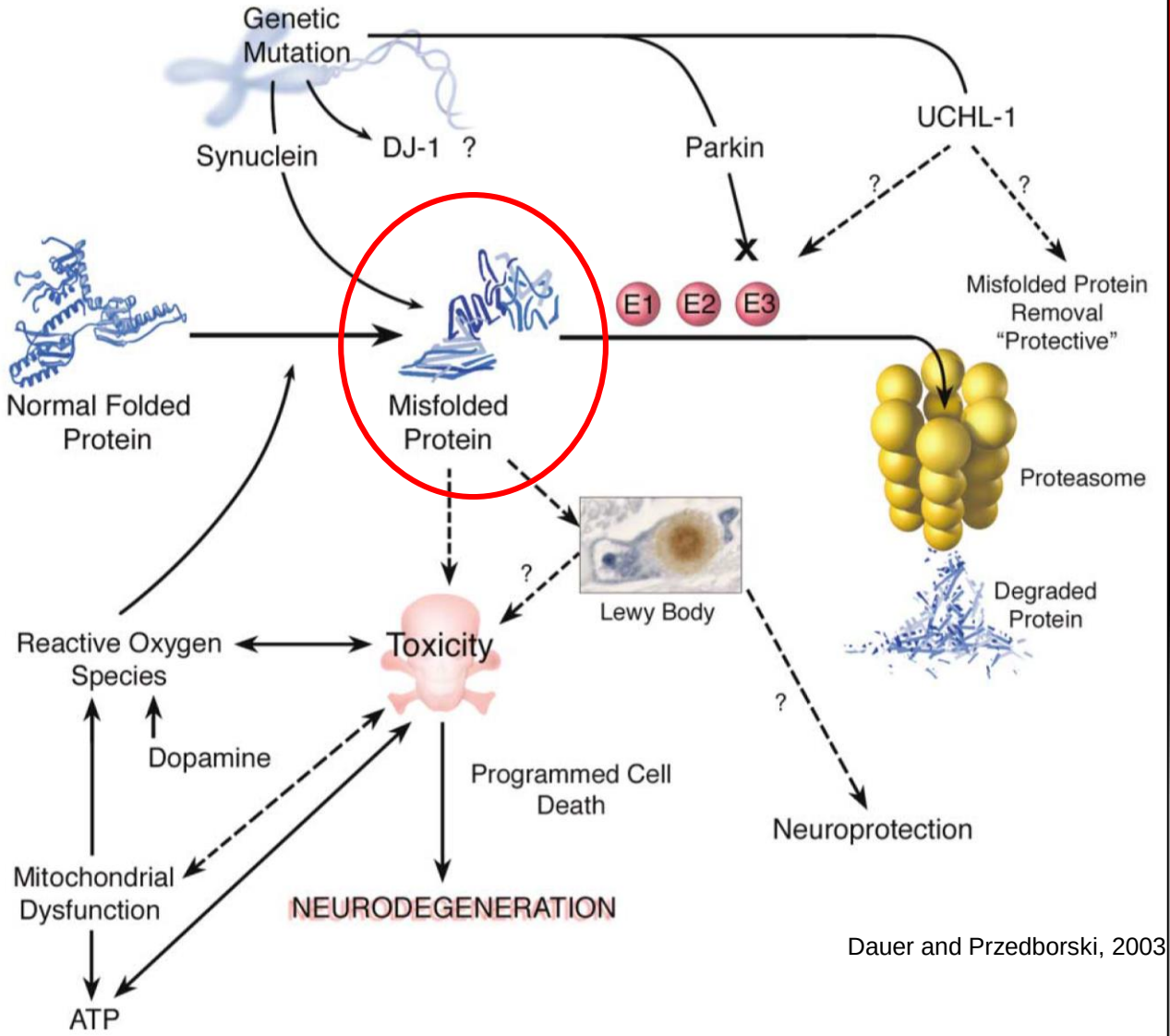
Parkinson’s Disease: Loss of Dopamine

Positron-Emission-Tomography Scan: dopaminergic metabolism



Parkinson's Disease: pathogenesis

1. Misfolding and aggregation of proteins

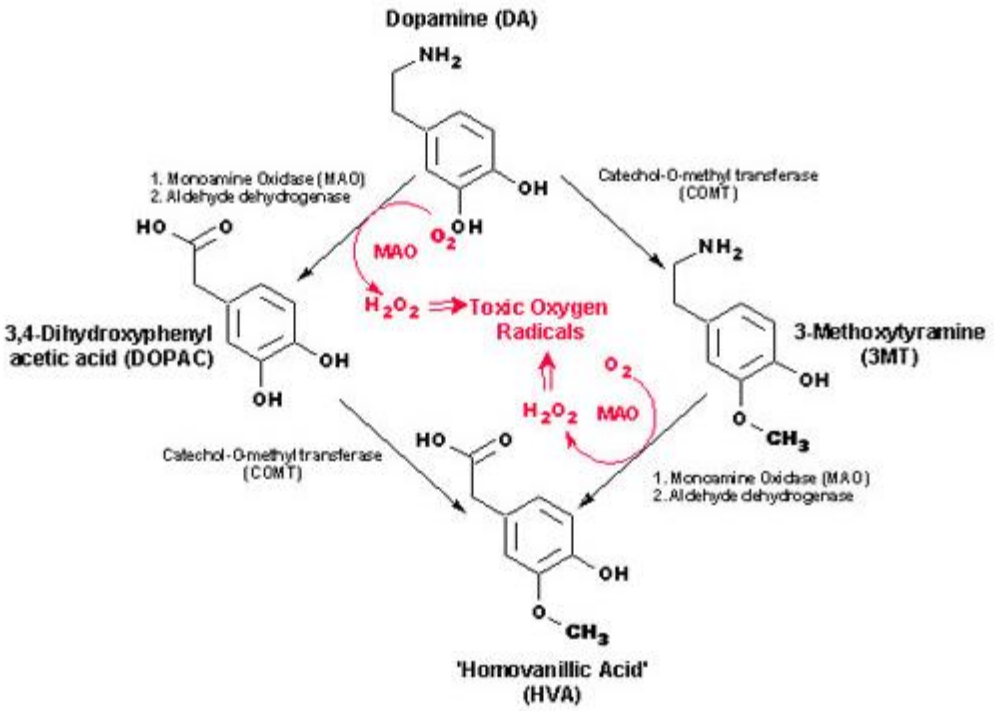


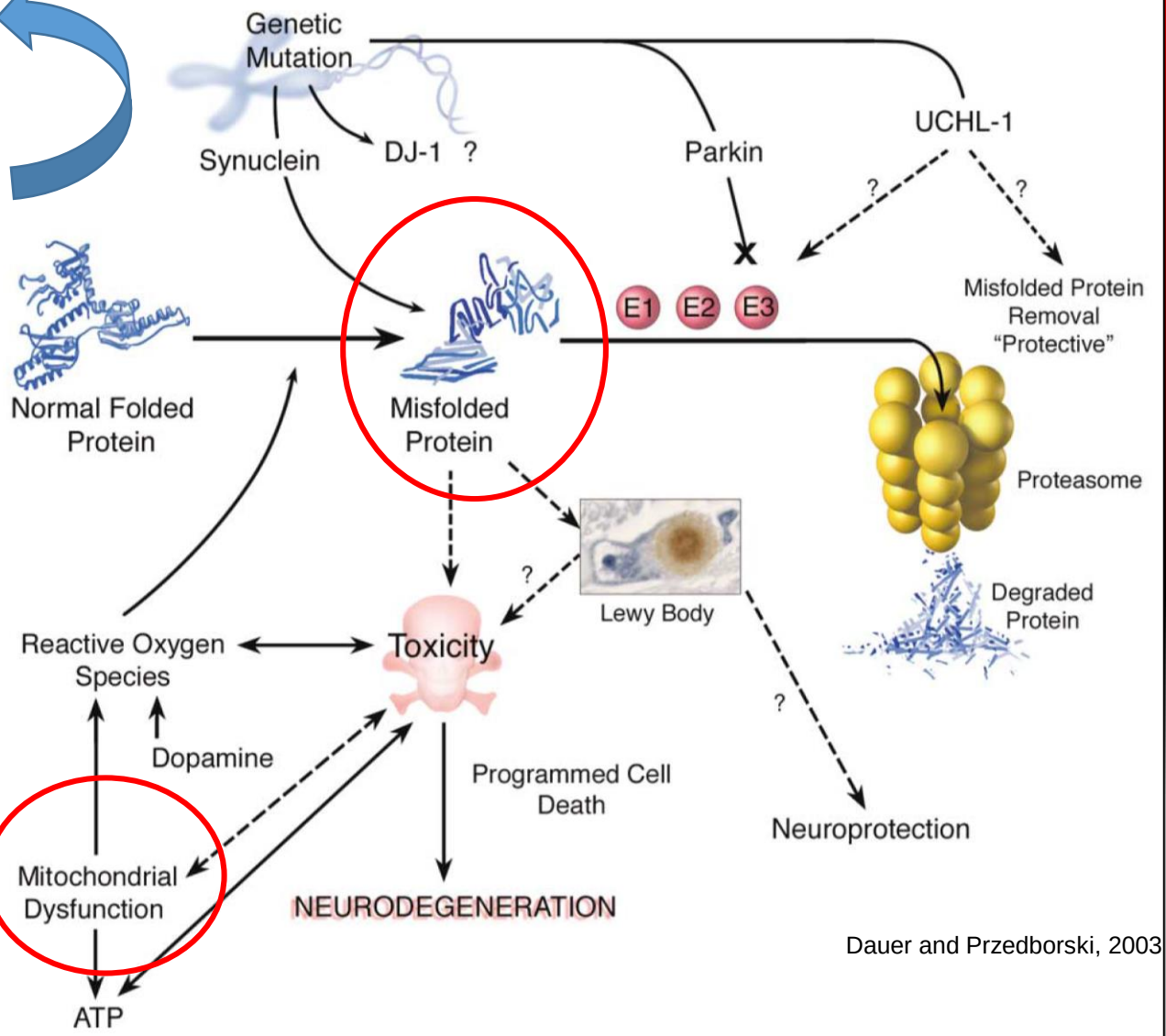
Dauer and Przedborski, 2003

Parkinson's Disease: pathogenesis

1. Misfolding and aggregation of proteins

2. Mitochondrial dysfunction leading to oxidative stress





Dauer and Przedborski, 2003

e.g. neurotoxins, genetic disorders

Parkinson's Disease: pathogenesis

1. Misfolding and aggregation of proteins

2. Mitochondrial dysfunction leading to oxidative stress

Misfolding and aggregation of proteins

PD-linked genes (PARK-genes):

α-Synuclein (autosomal dominant)

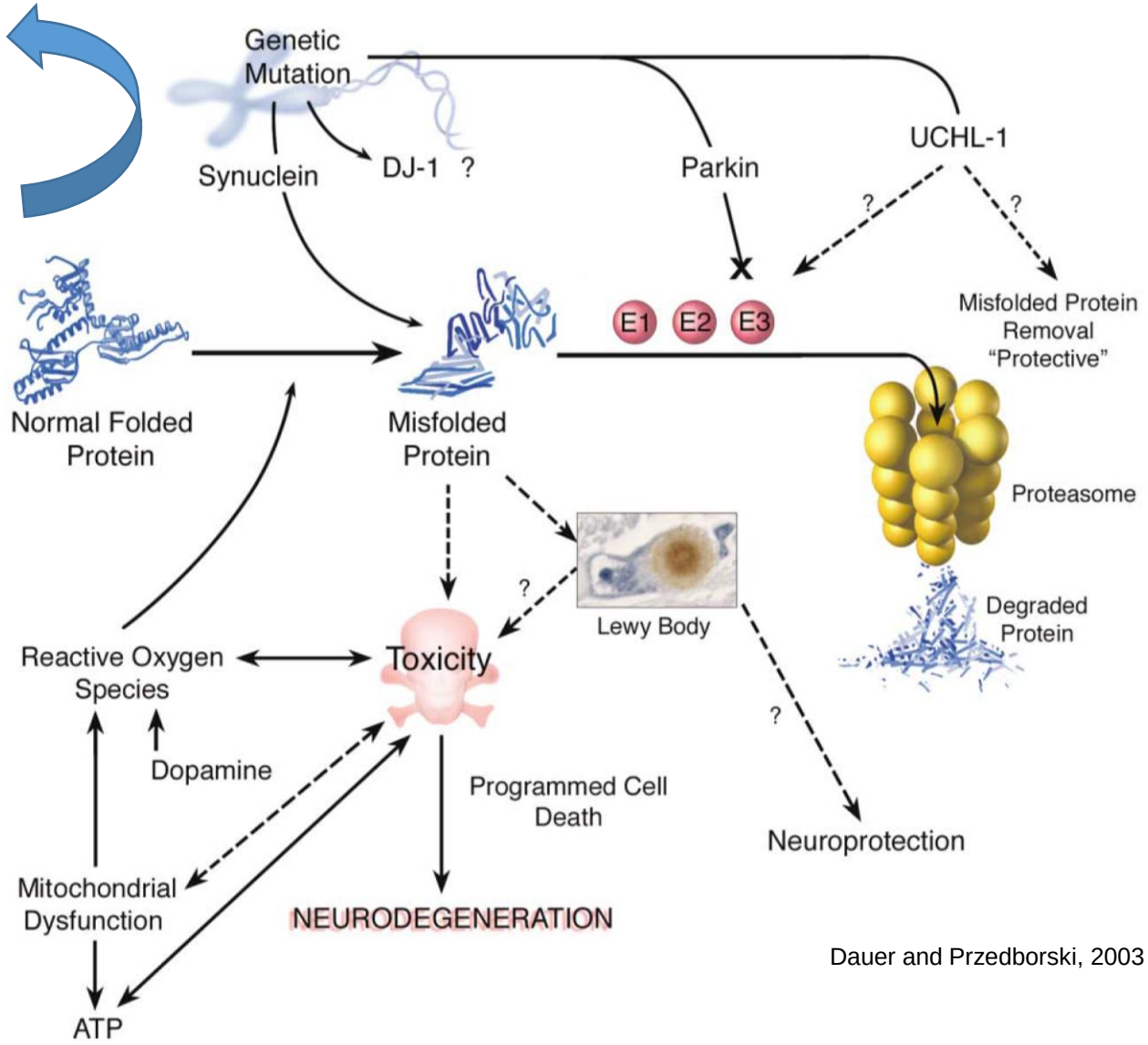
Parkin (autosomal recessive)

Ubiquitin C-terminal hydrolase L1

act on ubiquitin-proteasome pathway

PINK1 (Mitochondrial kinase)

e.g. neurotoxins, genetic disorders



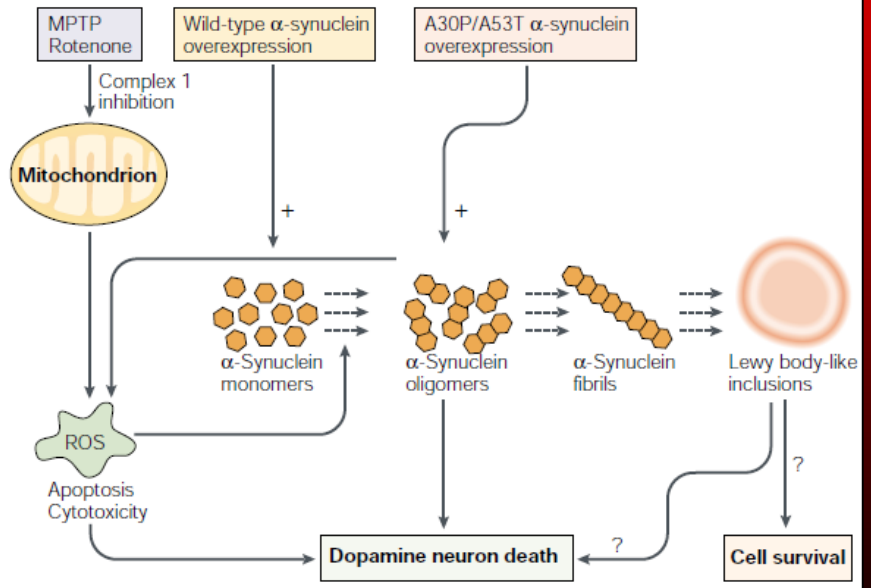
Dauer and Przedborski, 2003

Parkinson's Disease: Lewy Bodies

α –Synuclein

Physiological role:

- synaptic plasticity / NT release
- Mainly found in dopaminergic neurons



α –Synuclein:

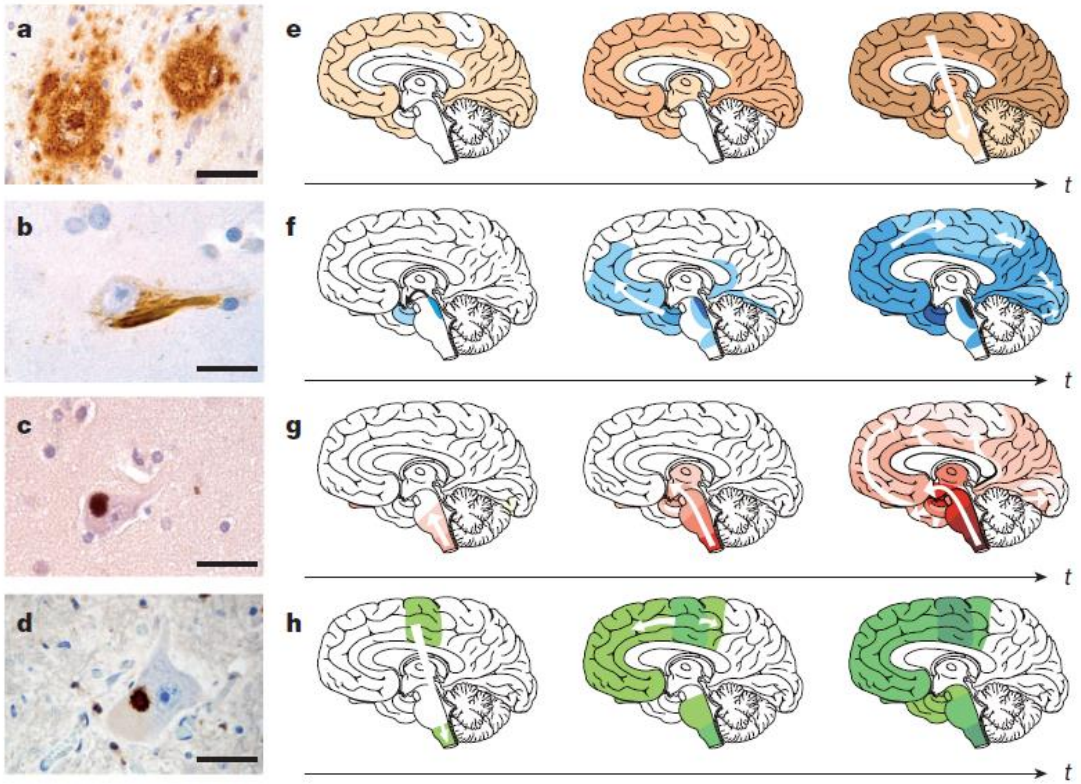
- ➢ main constituent of Lewy Bodies (LB) in PD
- ➢ is modified within LB (post-translational modifications)

(Brundin et al., 2008)

Misfolding (Amyloidation) -> fibrils -> inclusion bodies

Synucleinopathy leading to cell death of dopaminergic neurons?

Parkinson's Disease: amyloidogenic proteins

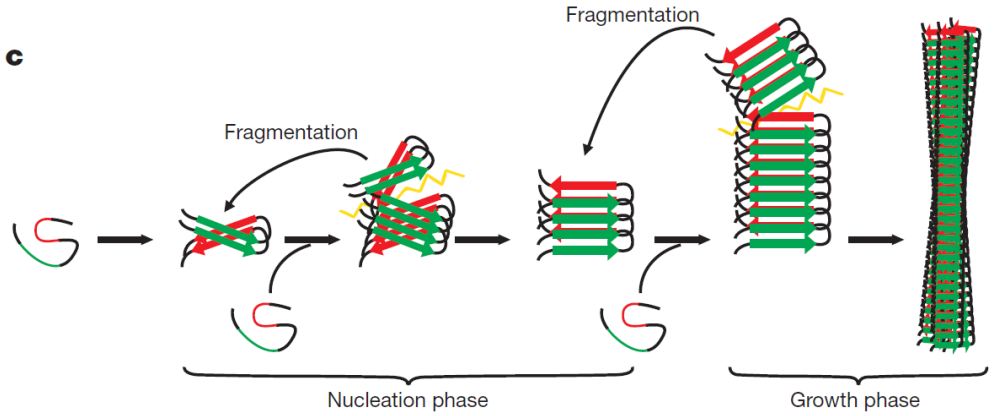


Amyloid-β deposits in AD (senile plaques)

Tau inclusions in AD (neurofibrillary tangle)

α-Synuclein inclusions in PD (Lewy body)

TDP-43 inclusion in ALS (TAR DNA-binding protein-43))

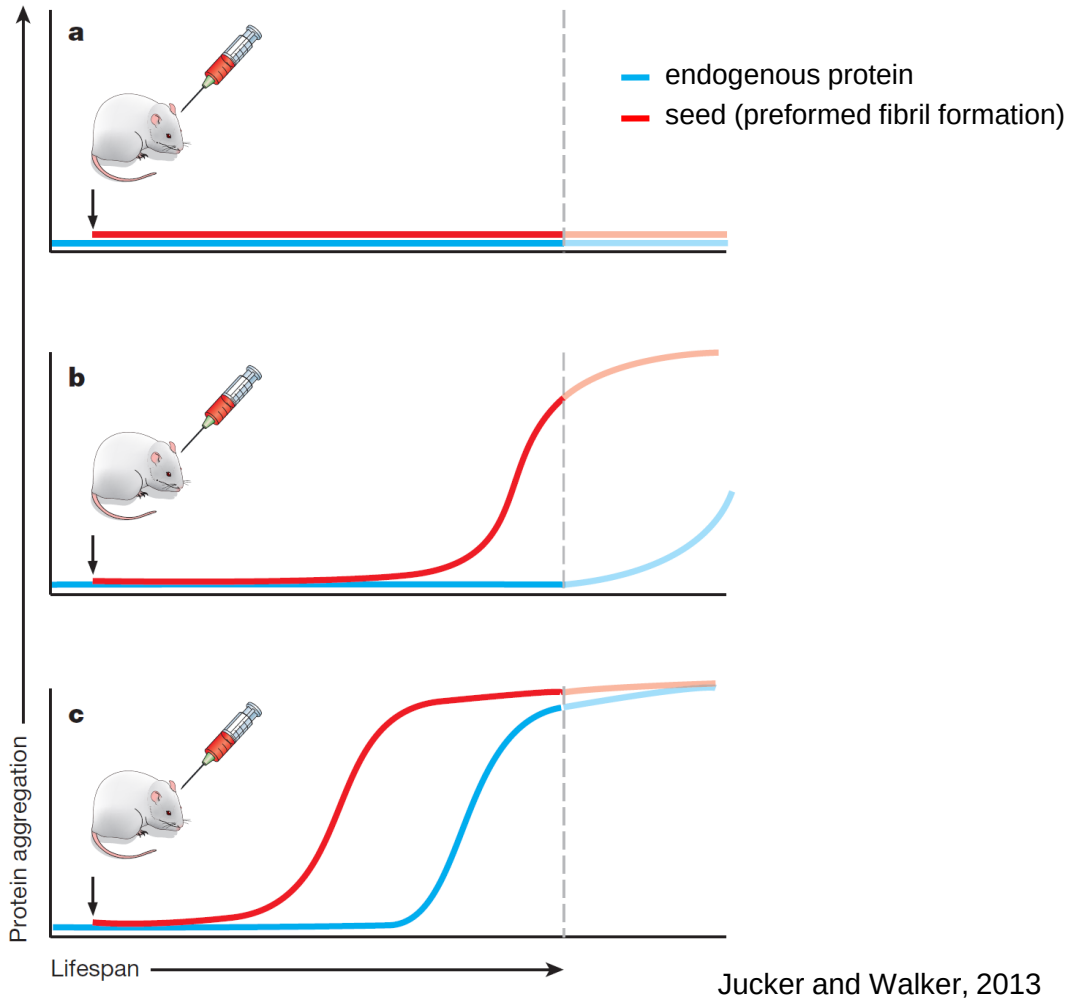


Spread along neuroanatomical pathways

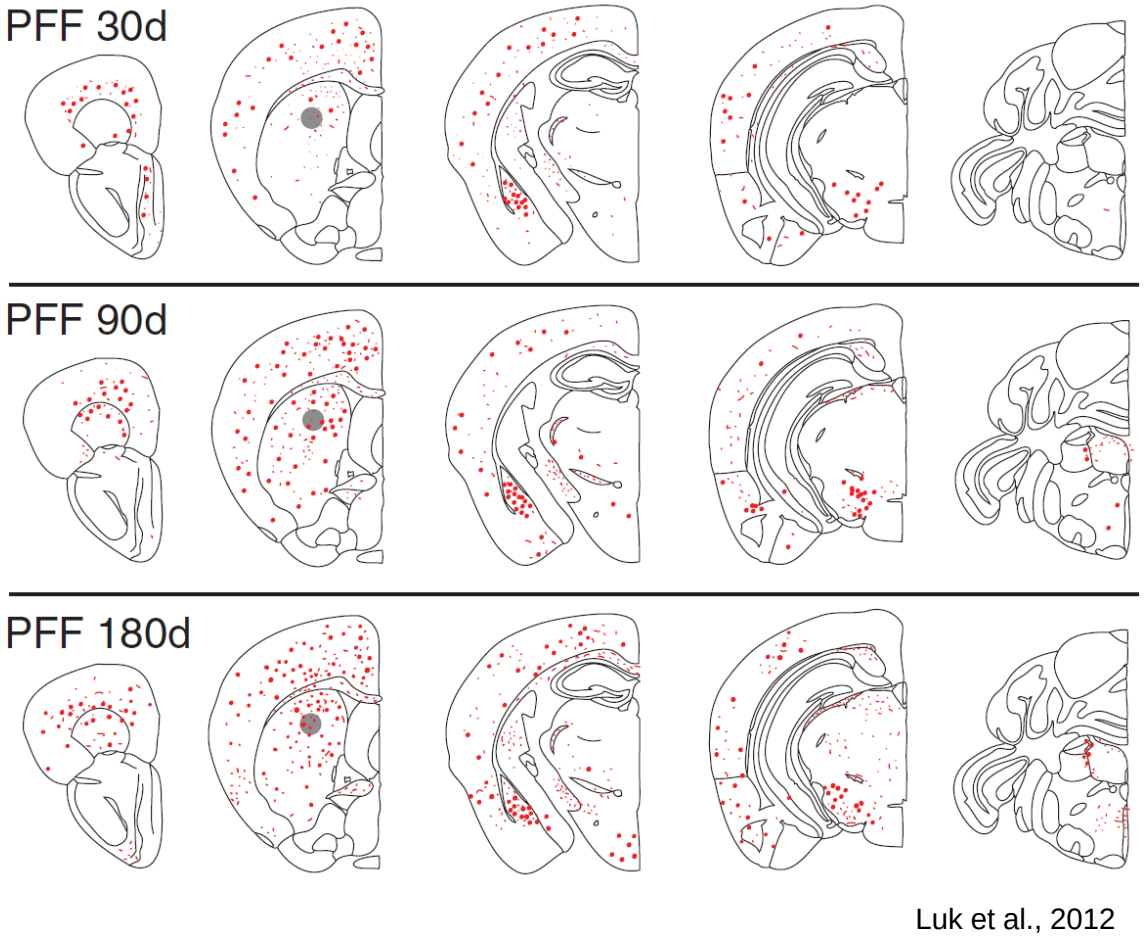
Jucker and Walker, 2013

Parkinson's Disease: pathogenesis

Experimental seeding of amyloidogenic protein aggregates:



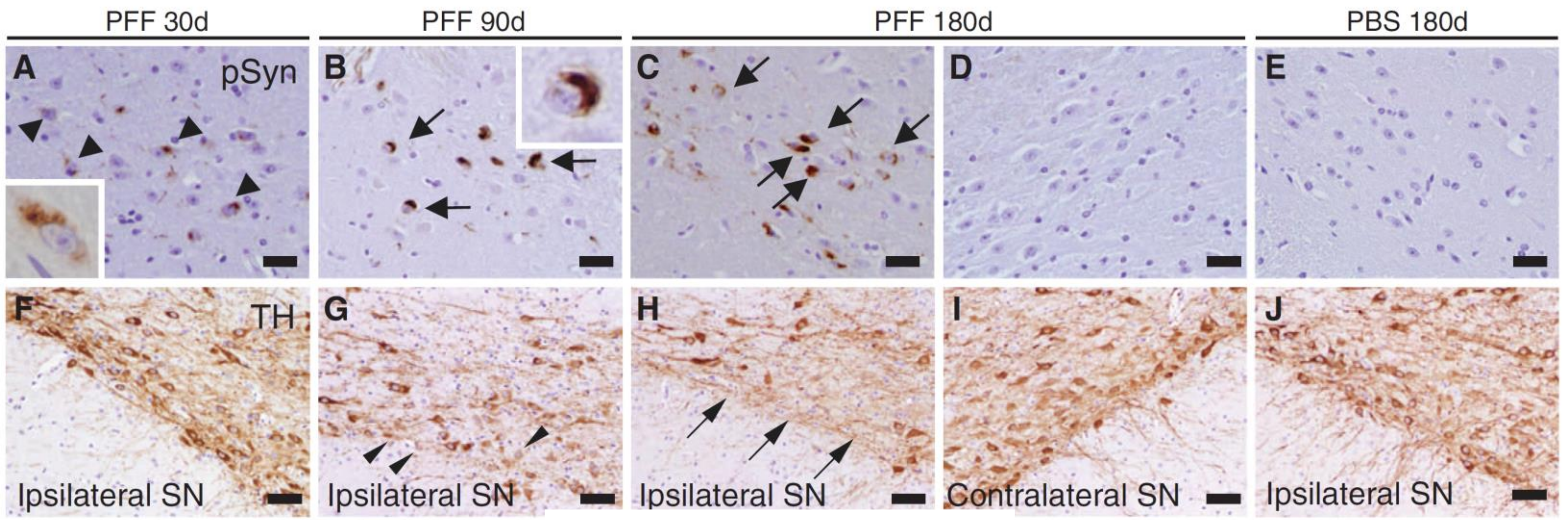
Jucker and Walker, 2013



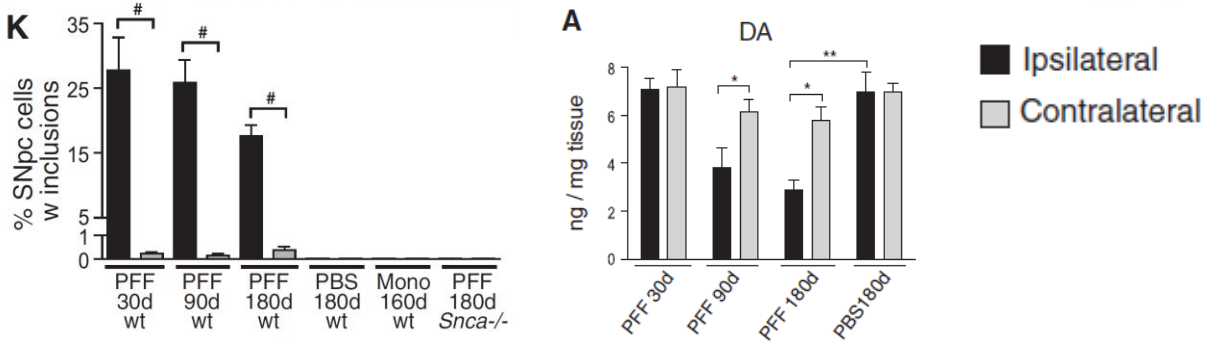
Luk et al., 2012

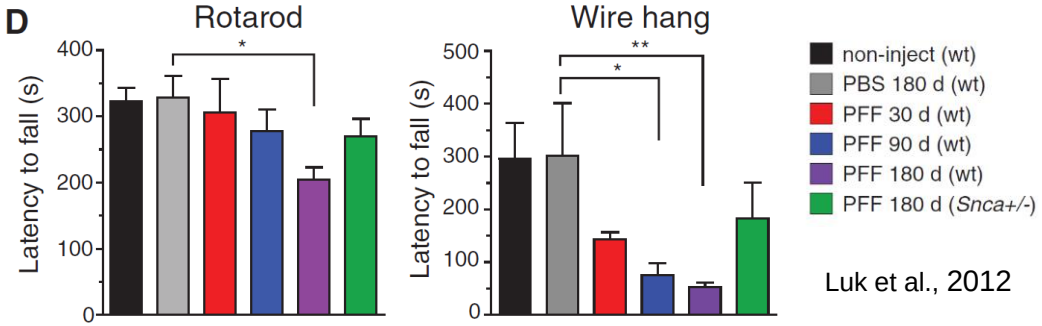
Single unilateral injection of α-Syn PFF (preformed fibrils) into striatum.

Parkinson's Disease: α - Synucleinopathy



Single unilateral injection of α-Syn PFF (preformed fibrils) into striatum. of wildtype mice





Luk et al., 2012

- Induction of neurodeg. Cascade
- Formation of Lewy bodies in DA cells
- Selective degeneration of DA cells
- Loss of function in PFF injected wt mice

Parkinson's Disease: pathogenesis and MPTP

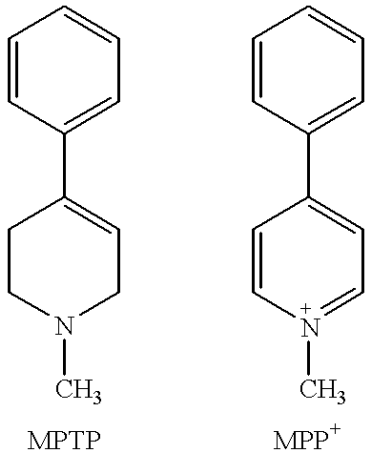
A breakthrough for PD research

The frozen addicts: *(BBC Horizon Awakening the Frozen Addicts)*

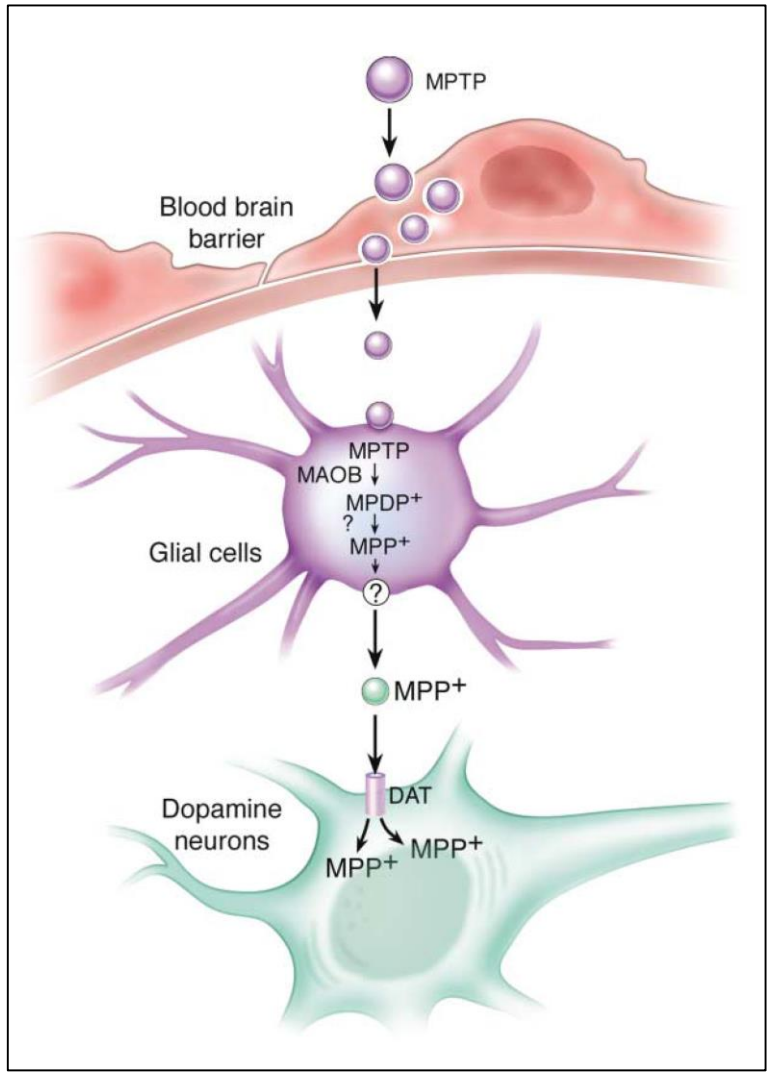
- 4 young adults with severe symptoms of PD
- all 4 consumed a new form of heroin

Chronic Parkinsonism in Humans Due to a Product of Meperidine-Analog Synthesis

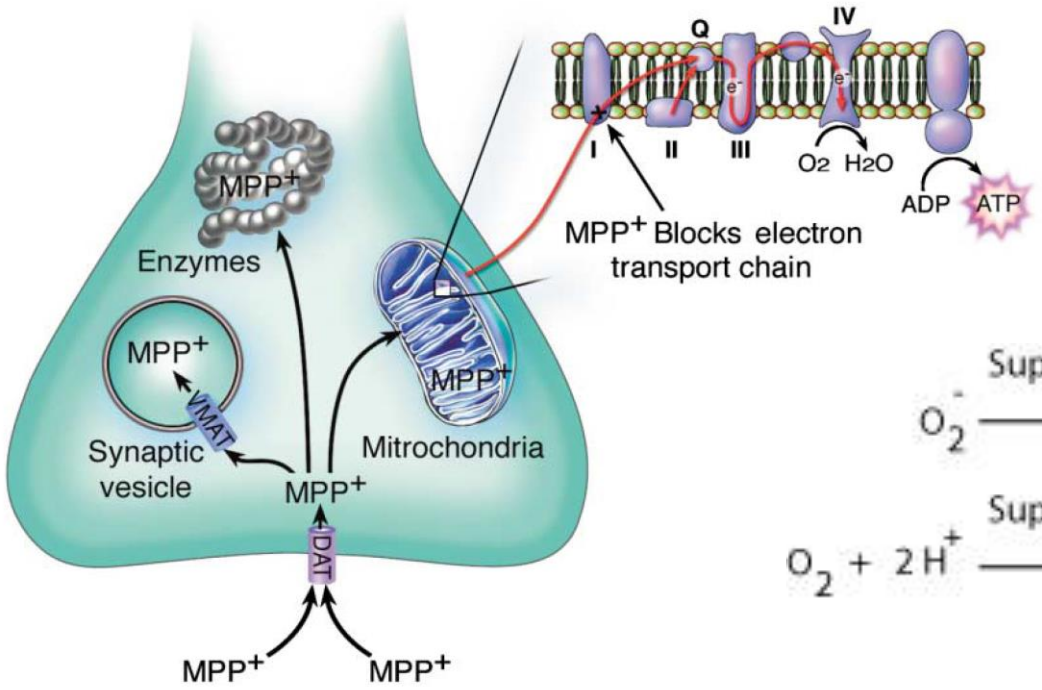
Science, 1983

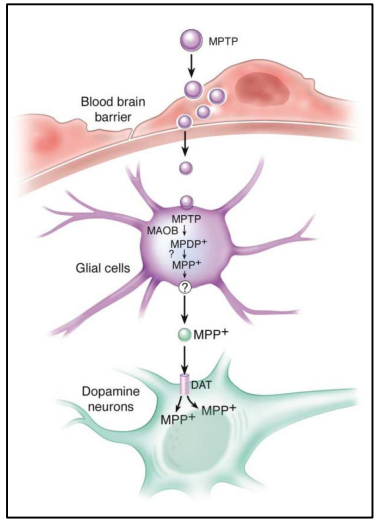


MPTP (1-Methyl-4-phenyl-1,2,3,6,-tetrahydropyridine)



Parkinson's Disease: pathogenesis and MPTP





$$O_2^- \xrightarrow{\text{Superoxide Dismutase}} O_2$$

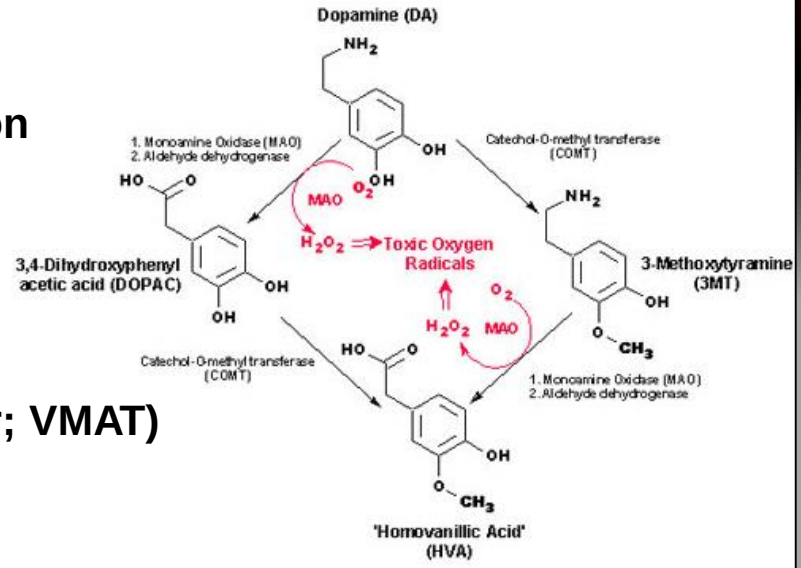
$$O_2 + 2H^+ \xrightarrow{\text{Superoxide Dismutase}} H_2O_2$$

1. Inhibition of respiratory chain (complex I) during oxidative phosphorylation

-> bioenergetic failure (low ATP, high oxidative and nitrative stress)

-> Dopamine leaks from vesicles into cytosol -> ROS

Mice overexpressing superoxide dismutase1 (SOD1) are resistant to MPTP



2. Sequestration of MPP+ into vesicles (by vesicular monoamine transporter; VMAT)

-> ratio VMAT to DAT

3. Interactions with negatively charged molecules in cytosol

Parkinson's Disease: MPTP as gold standard for animal research of PD

MPTP in different monkeys led to Parkinson's-like syndrome including bradykinesia, paucity of movements, rigidity AND tremor, postural instability.

MPTP-induced symptoms improve when L-DOPA is applied; oversupply of L-DOPA leads to dyskinesia (e.g. chorea)

MPTP leads to greater degeneration of neurons in putamen than of dopaminergic cell terminals in caudate

MPTP leads to greater cell loss in SNpc than in VTA.

MPTP leads to greater damage in melanin-rich dopaminergic cells

MPTP leads to similar protein inclusions as seen with Lewy Bodies in human PD

} mimics human PD

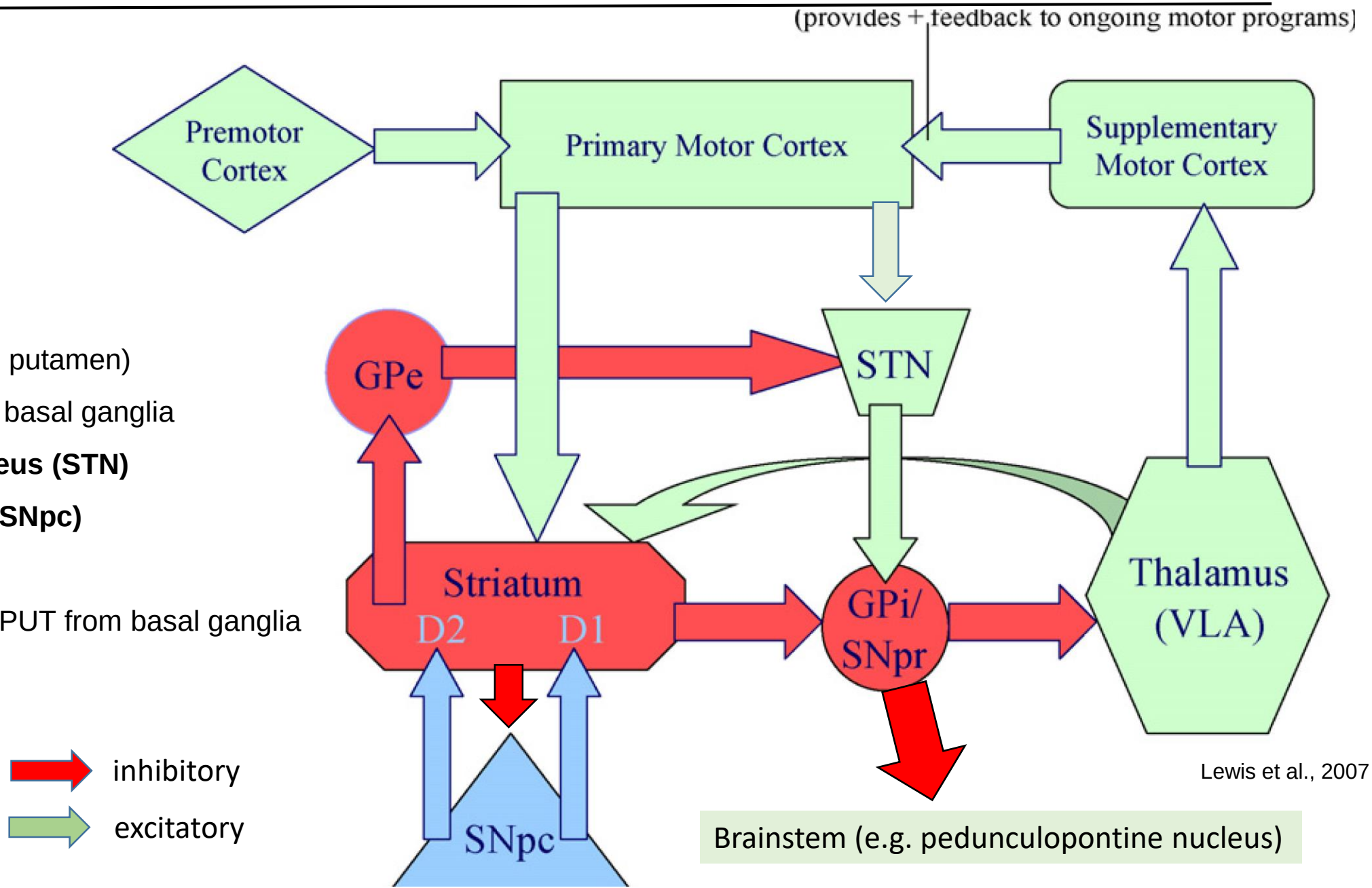
Gold standard for behavioral, pharmacological and pathological model

Parkinson's Disease: Basal Ganglia Network

- **Striatum** (caudate, putamen)

  -> INPUT center of basal ganglia
- **Subthalamic nucleus (STN)**
- **Substantia nigra (SNpc)**
- **Globus pallidus**

  GPi: MAJOR OUTPUT from basal ganglia



Lewis et al., 2007

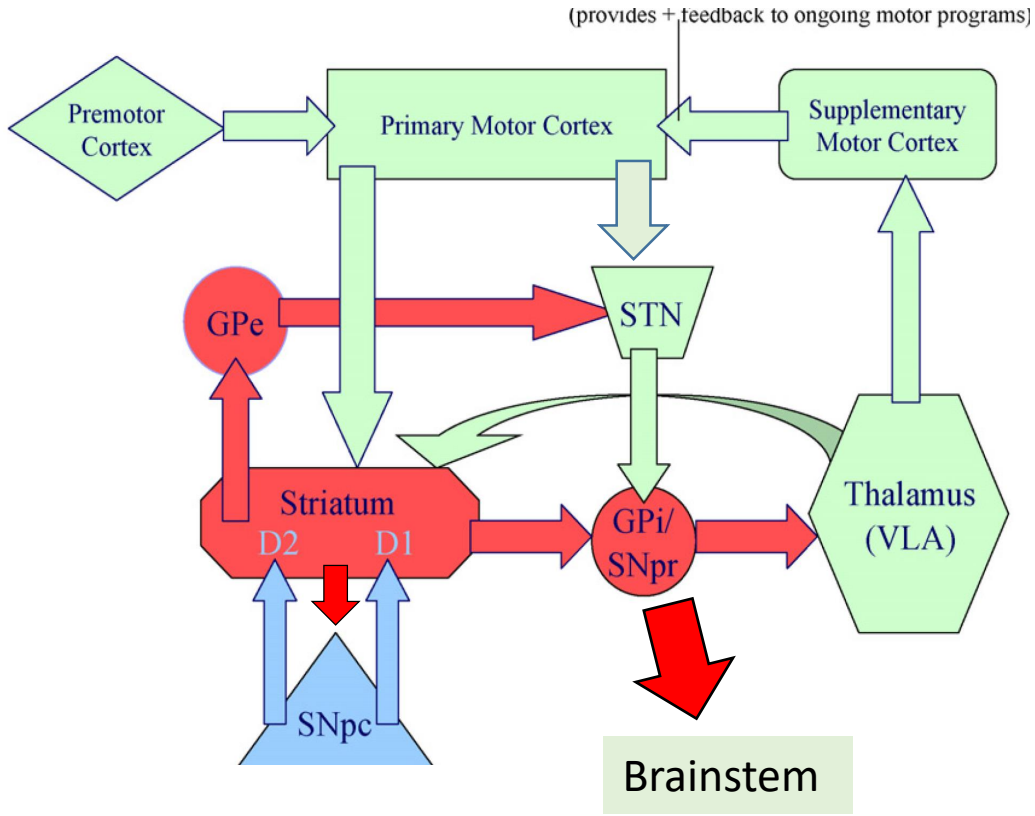
Parkinson's Disease: Basal Ganglia Network

Striatum (caudate and putamen)

- Major input relay of basal ganglia
- Input nearly from all cortical areas and from dopaminergic SNpc fibers

- Striatum sends direct inhibitory output to GPi
  - Direct striatopallidal pathway

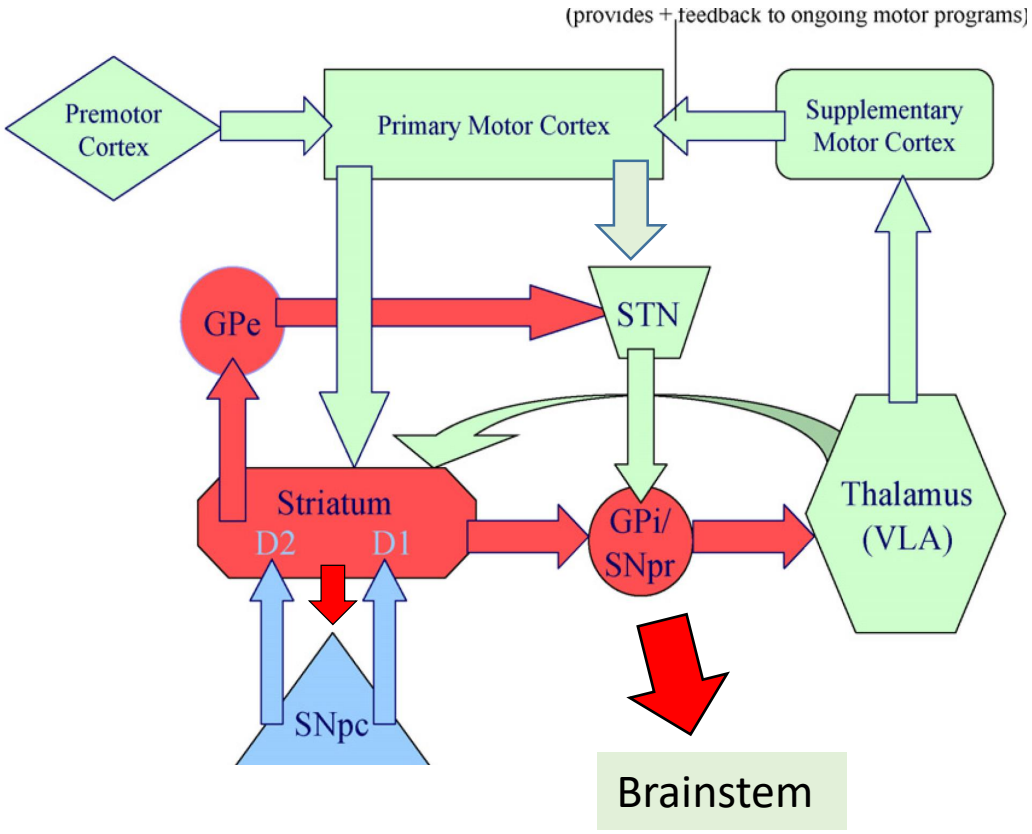
- Striatum sends indirect inhibitory output to GPe
  - Indirect striatopallidal pathway



Parkinson's Disease: Basal Ganglia Network

Subthalamic nucleus (STN)

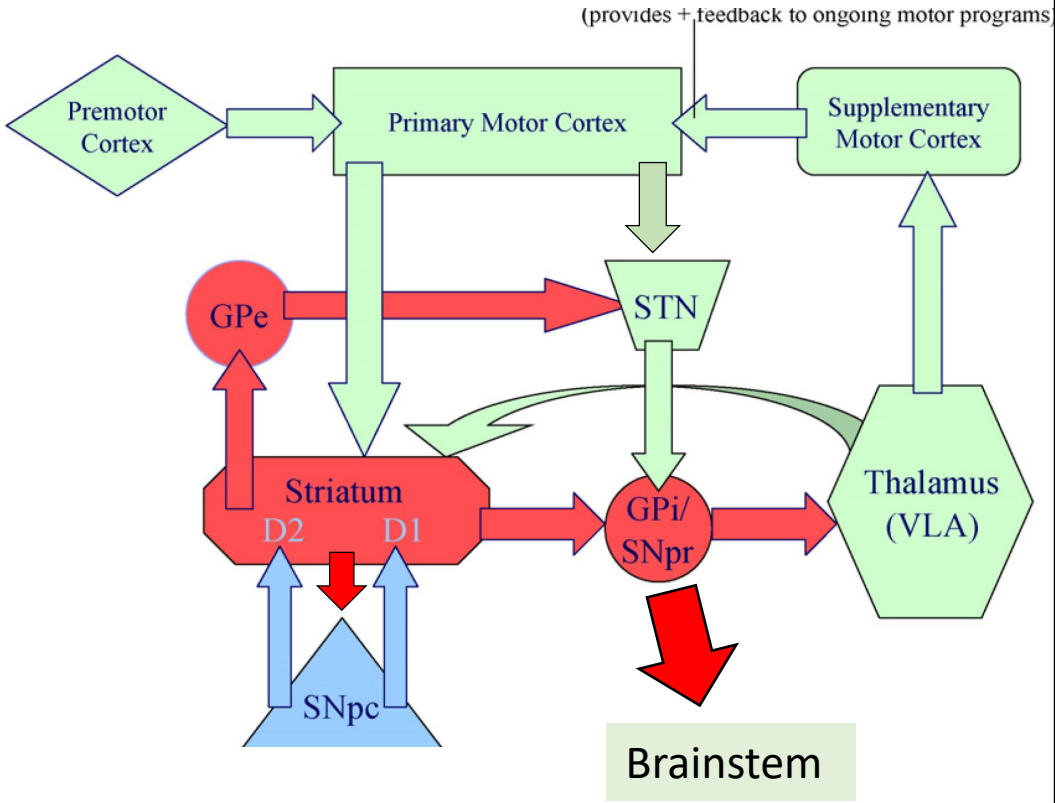
- The STN receives excitatory input from the frontal cortex and inhibitory input from the GPe
- Excitatory output to GPi

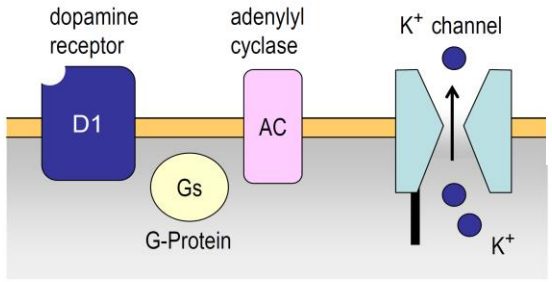


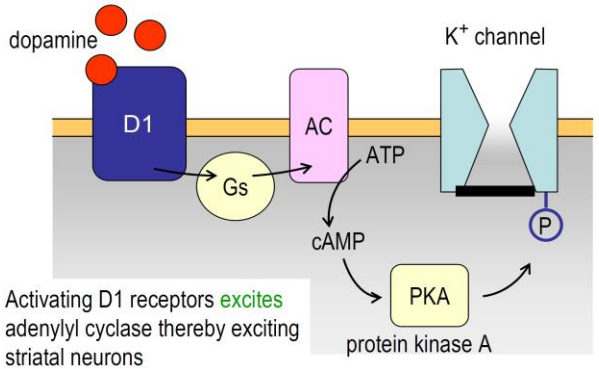
Parkinson's Disease: Basal Ganglia Network

Substantia Nigra pars compacta (SNpc)

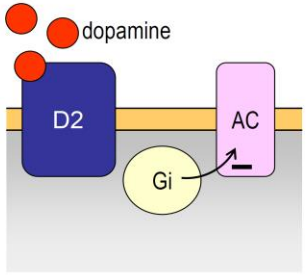
- Sends dopaminergic input to striatum and receives gabaergic input from striatum (reciprocal connections)
- D1 receptor family expressed on striatal neurons projecting to the direct striatopallidal pathway
- D2 receptor family expressed on striatal cells projecting to indirect striatopallidal pathway







Activating D1 receptors excites adenylyl cyclase thereby exciting striatal neurons



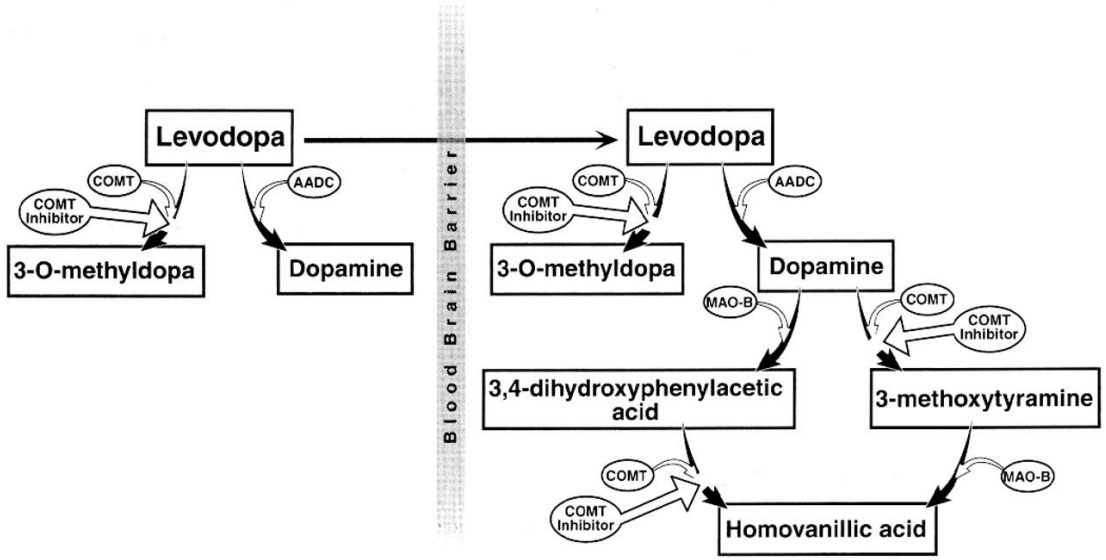
Activating D2 eceptors inhibits adenylyl cyclase thereby inhibiting striatal neurons

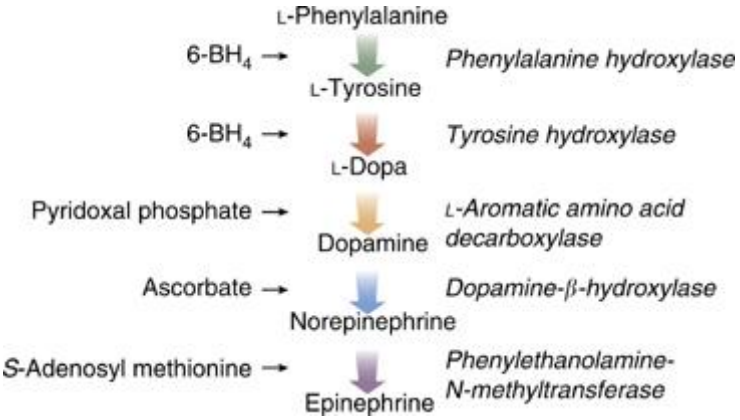
Parkinson's Disease: Treatments

Levodopa, L-DOPA

Arvid Carlsson

Arvid Carlsson discovered dopamine in 1958 and measured peak values in the basal ganglia system



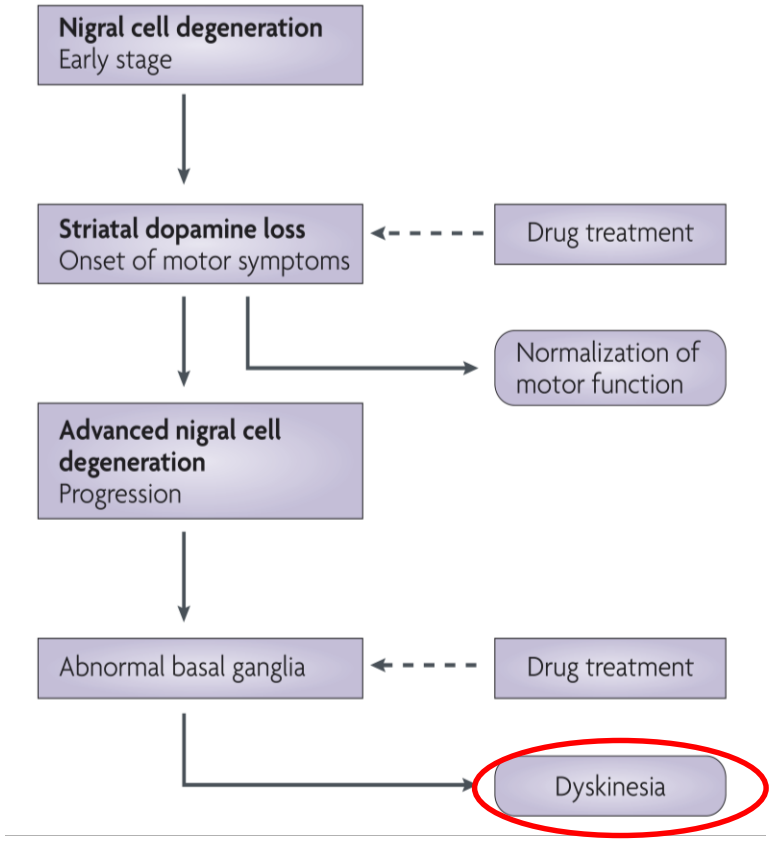


- before the development of dopaminergic treatments, PD led to severe disability within < 10 years
- Effect of dopaminergic treatment on long-term outcome of PD is unknown
- PD is not lethal: life expectancy is approx. 10 years shorter with PD
- Death in late progressed PD is caused by secondary complications (pneumonia, thrombosis etc.).

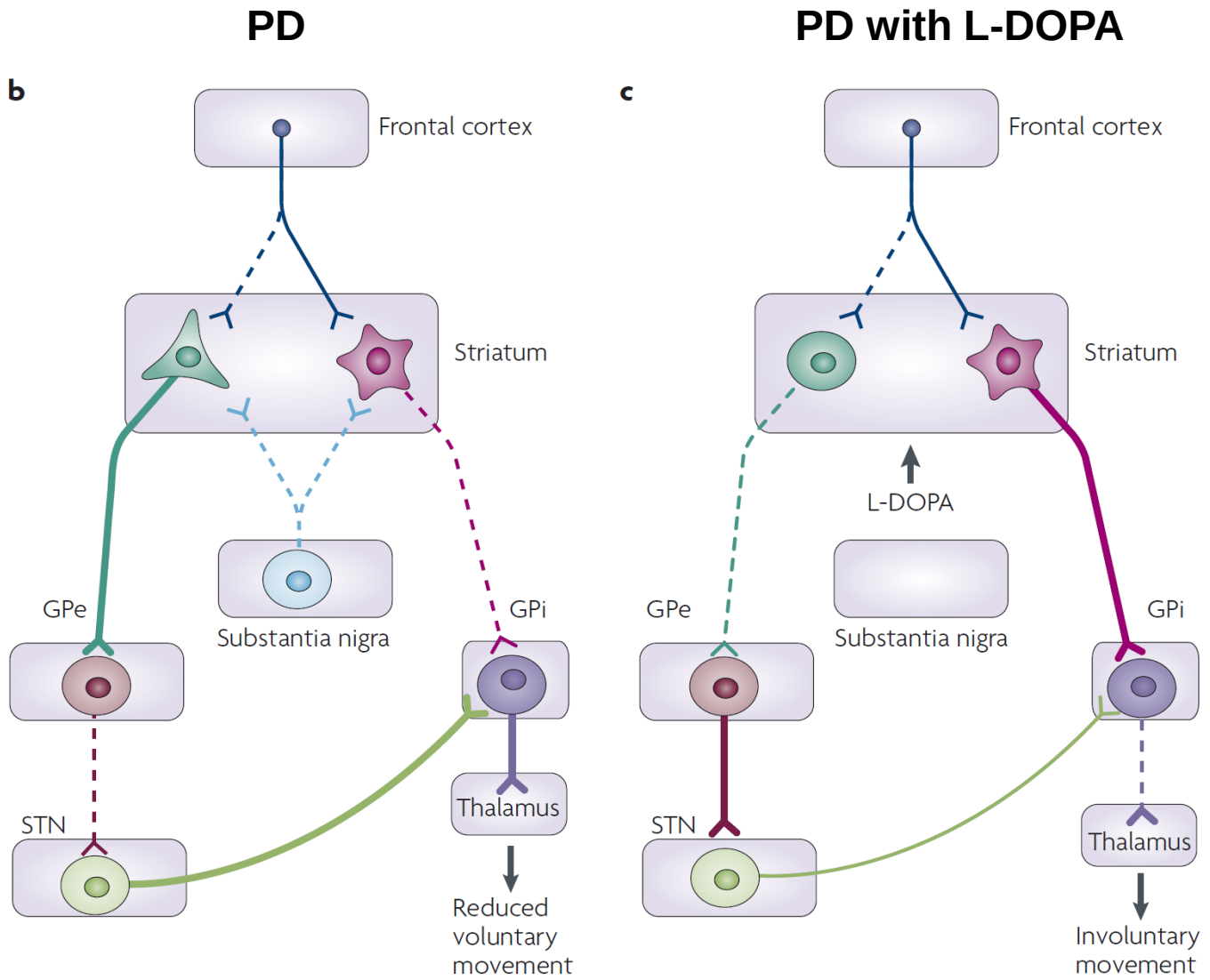
Parkinson's Disease: L-DOPA

L-DOPA is often transiently efficient and can induce severe **dyskinesia** when chronically applied

Dyskinesia: involuntary movements



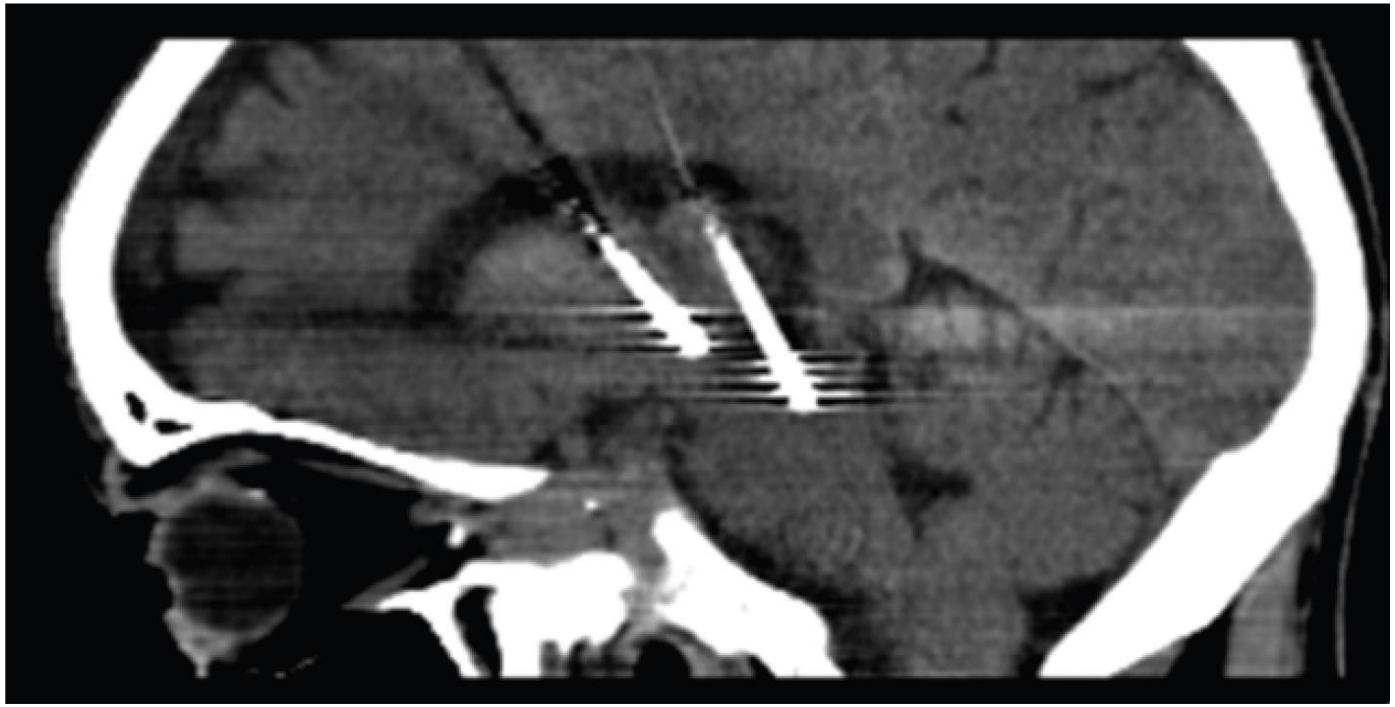
Jenner, 2008

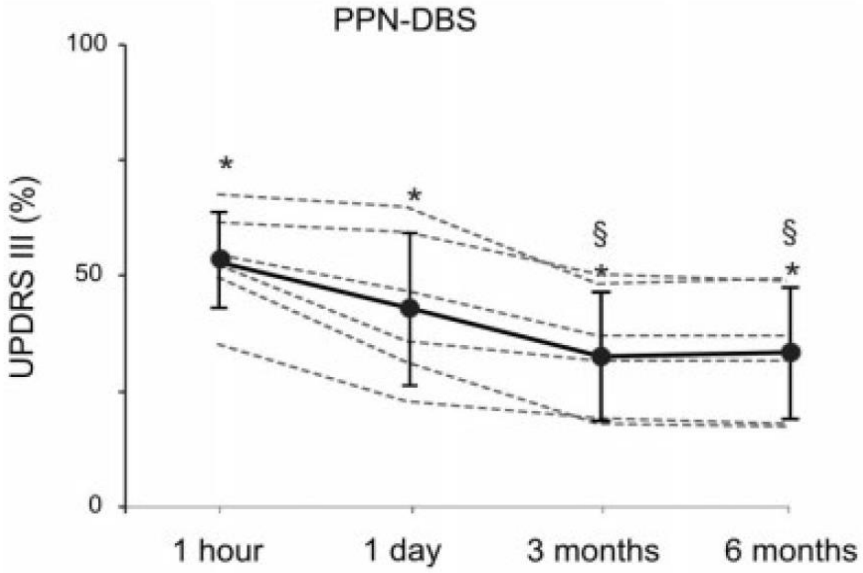


Parkinson's Disease: Deep Brain Stimulation (DBS)

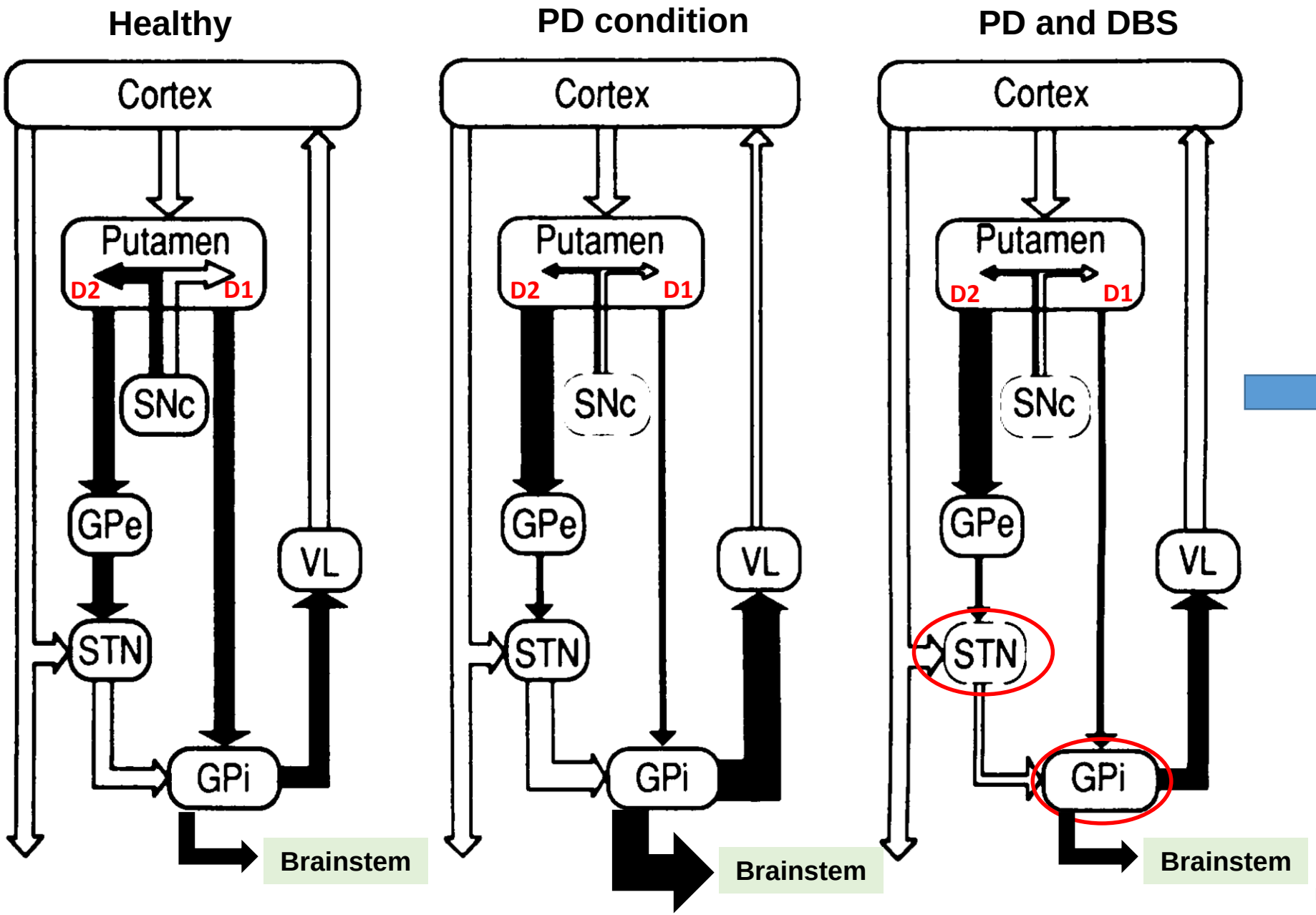
Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease

Alessandro Stefani,[1,2] Andres M. Lozano,[6] Antonella Peppe,[2] Paolo Stanzione,[1,2] Salvatore Galati,[1] Domenicantonio Tropepi,[1] Mariangela Pierantozzi,[1] Livia Brusa,[4] Eugenio Scarnati[3] and Paolo Mazzone[5]





Parkinson's Disease: Deep Brain Stimulation (DBS)

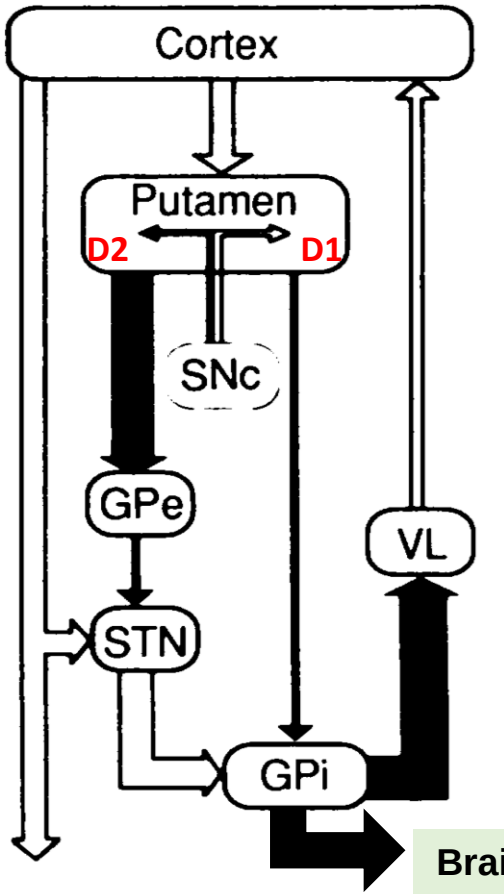


Bergman et al., 1990

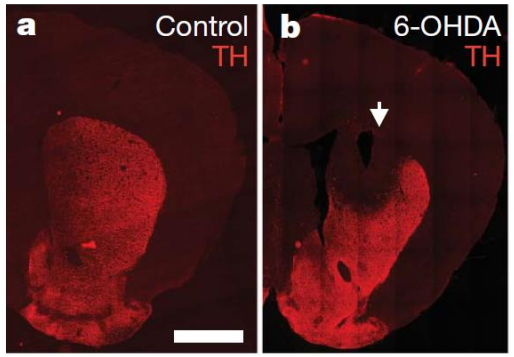
Parkinson's Disease: animal research using optogenetics

Stimulation and inhibition of **subthalamic nucleus (STN):**

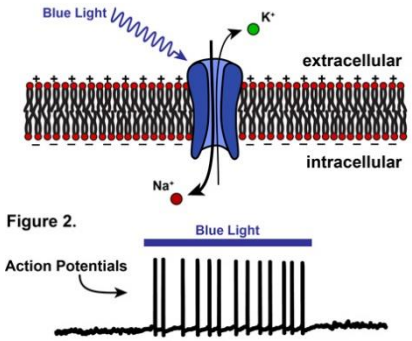
PD condition

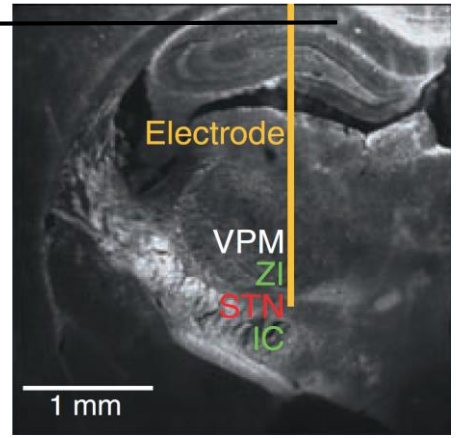


unilateral 6-OHDA injection



channelrhodopsin-2

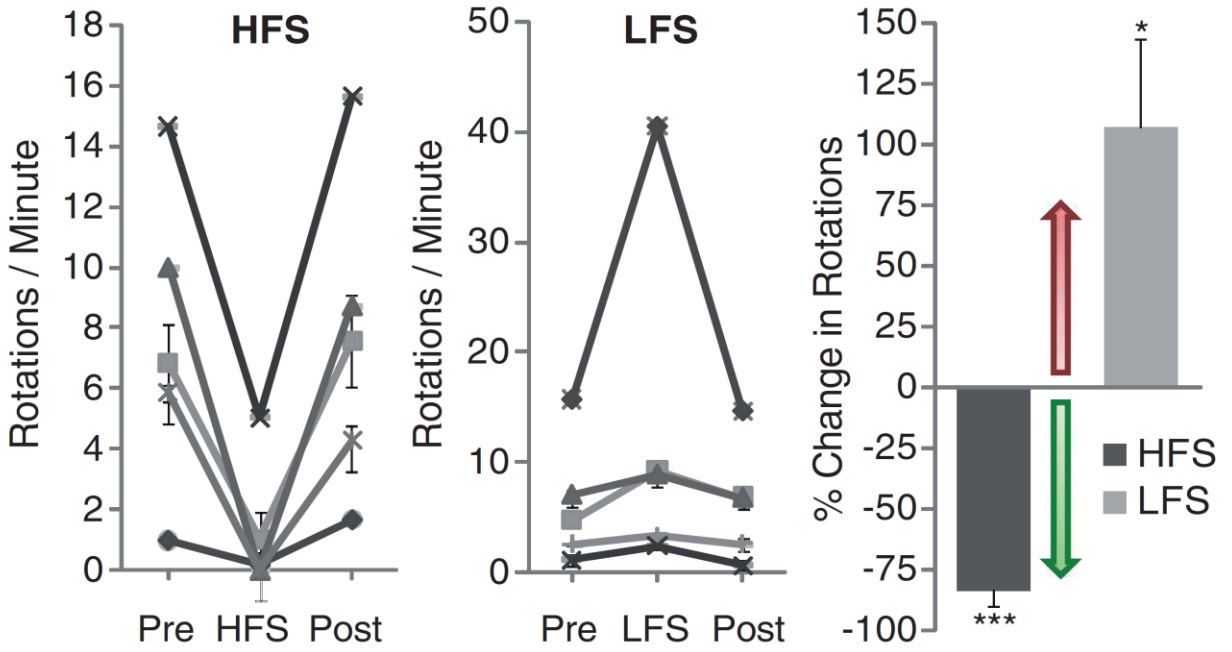




HFS: inactivation

LFS: activation

Thy1::ChR2 STN Behavior

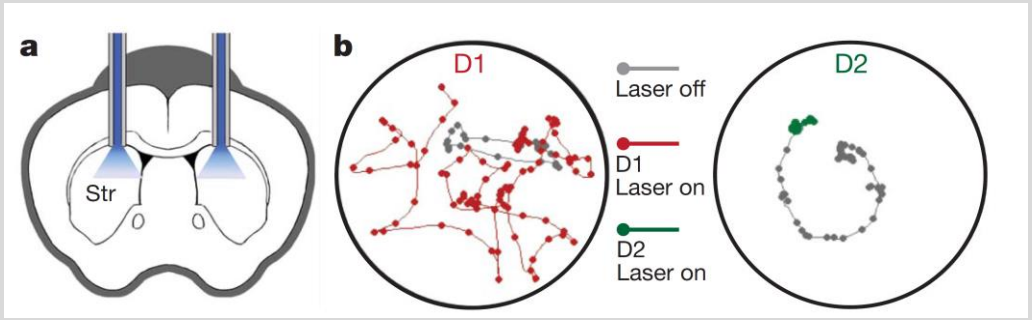


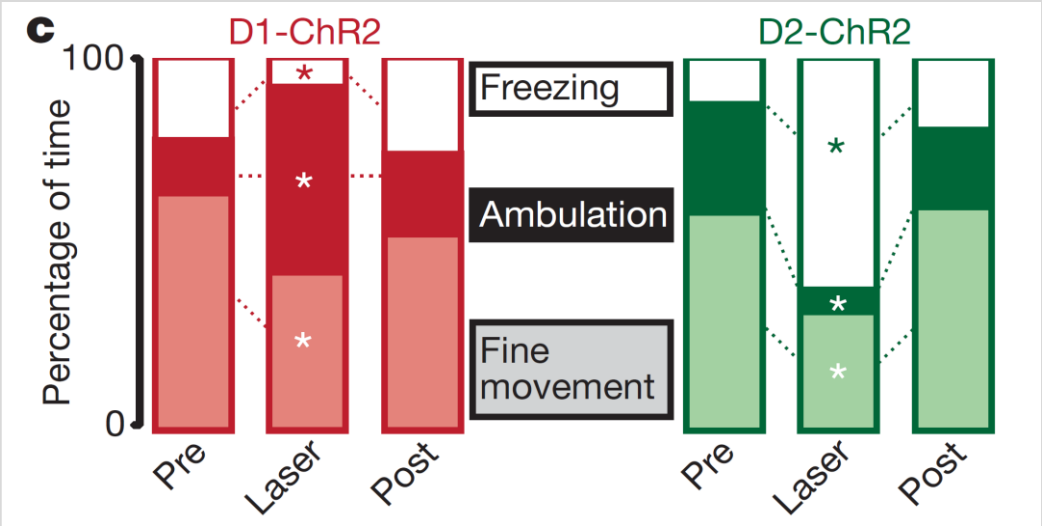
Gradinaru et al., 2009

Parkinson's Disease: optogenetics

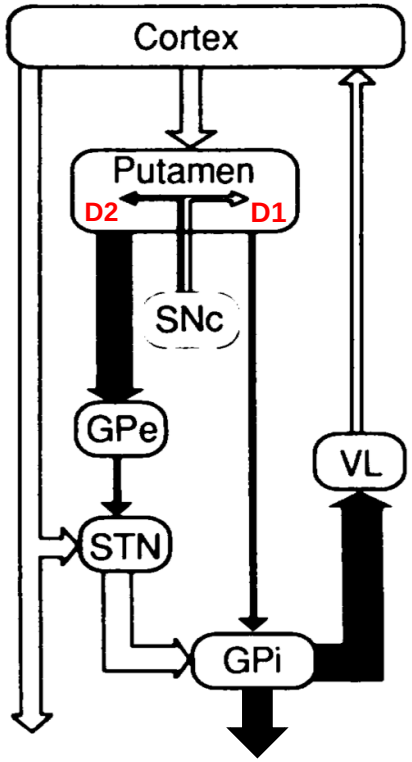
Stimulation of D1- (direct pathway) and D2-postivive (indirect pathway) striatal neurons

Healthy condition



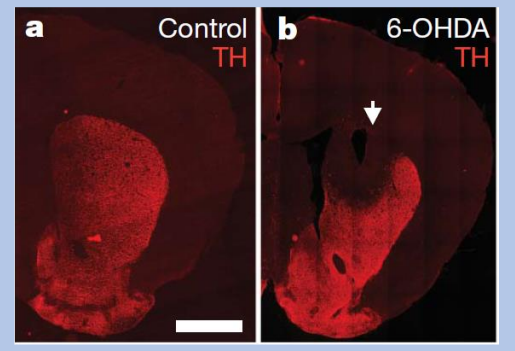


PD condition

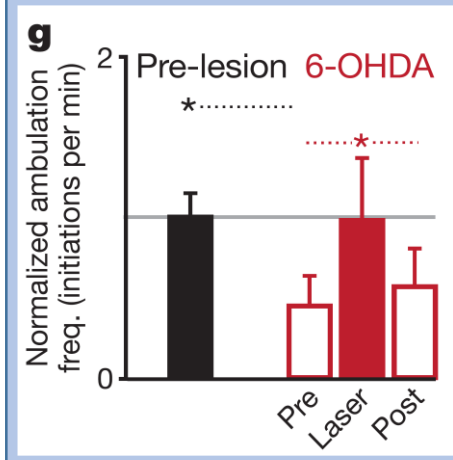


Brainstem

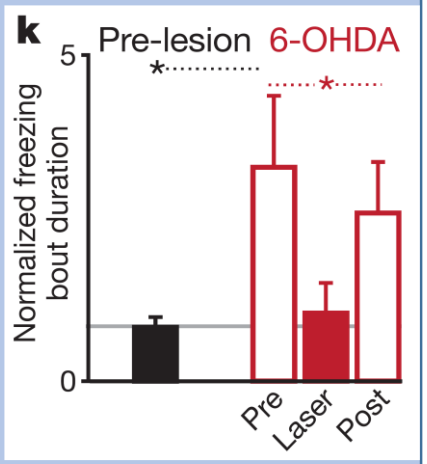
PD model



D1-ChR2



D1-ChR2



Kravitz et al., 2010

Parkinson's Disease: future PD treatments?

So far, no treatment can change the natural course of the disease once it has started

Adenosine A2a Receptor Agonists

Transcranial magnetic stimulation

mGluR5 modulators

Cell replacement

Gene therapies