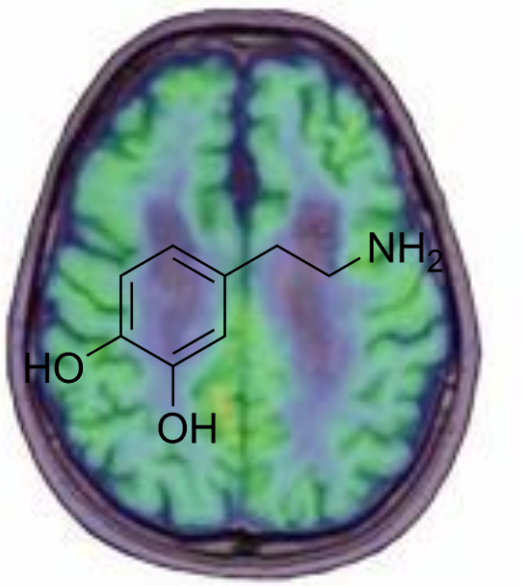
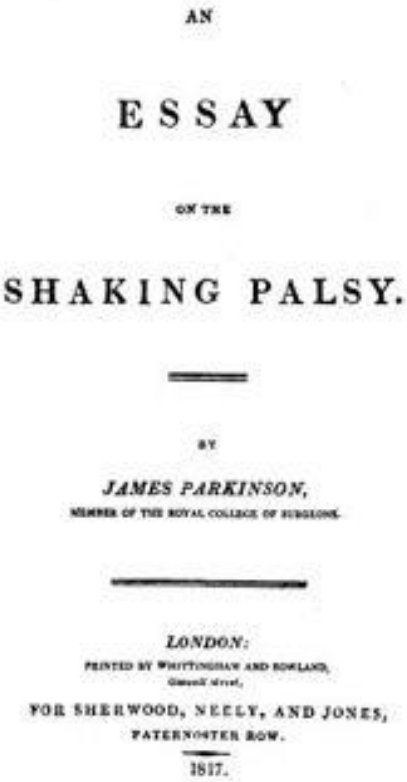
The Biology of Parkinson's Disease and its treatments



Paola Sacchetti, Ph.D.
Assistant Professor
Director MS Neuroscience
Department of Biology
University of Hartford, CT
psacchett@hartford.edu
(860)768-5926



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

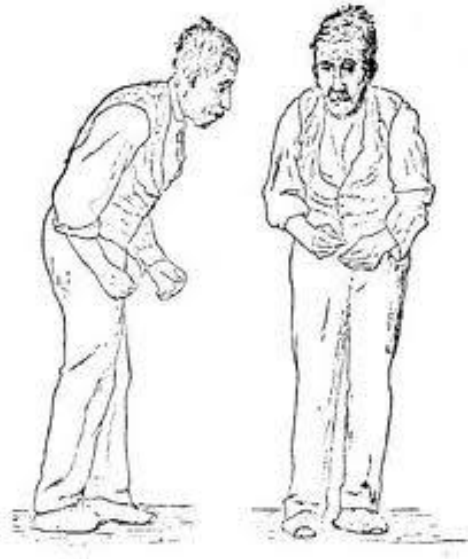
LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,
FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.
1817.

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 intellects*** *being* ***uninjured***.

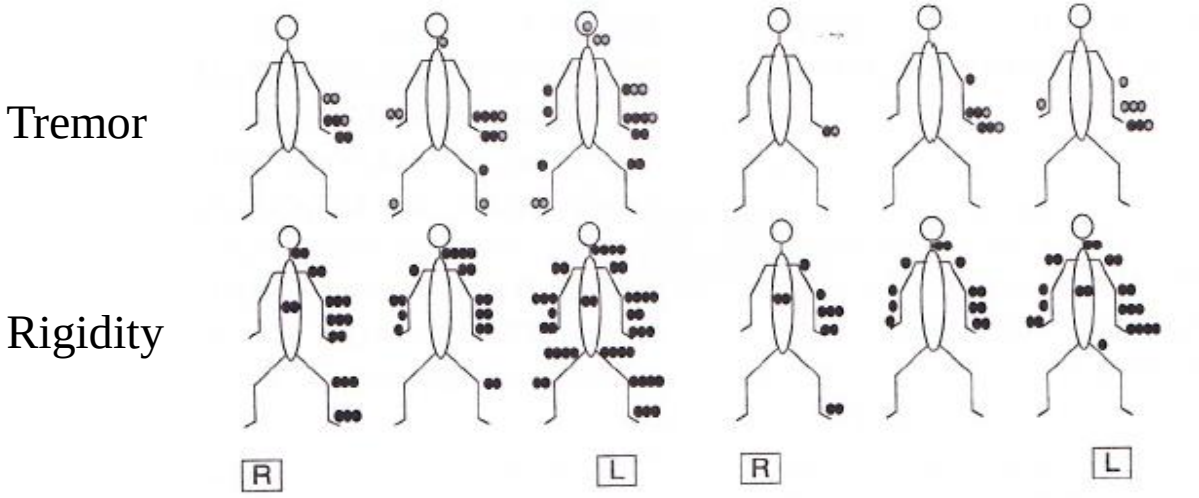
"So slight and nearly imperceptible are the inroads of this malady, and so extremely slow its progress ... that the patient cannot recall the onset. The first symptoms perceived are, a slight sense of weakness with a Proneness to trembling ... most commonly in one of the hands and arms.“ *James Parkinson, 1817*

It was Nov. 13, 1990. He writes:
“I woke up to find the message in my left hand. It had me trembling. It wasn’t a fax, telegram, memo or the usual sort of missive bringing disturbing news. In fact, my hand held nothing at all.
The trembling was the message.“ *Michael J. Fox, 2002 “Lucky Man.“*

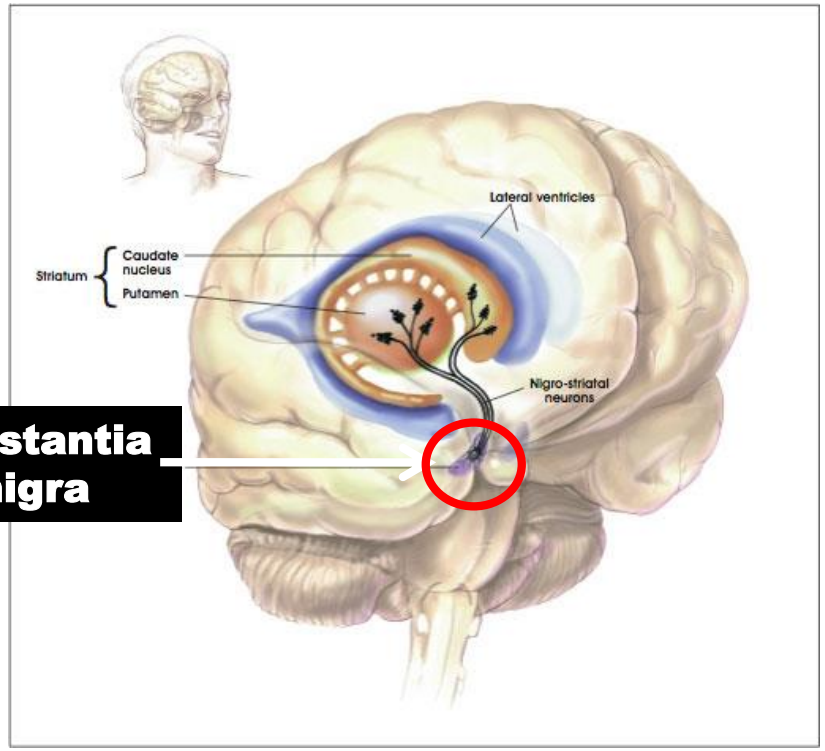
Cardinal symptoms:

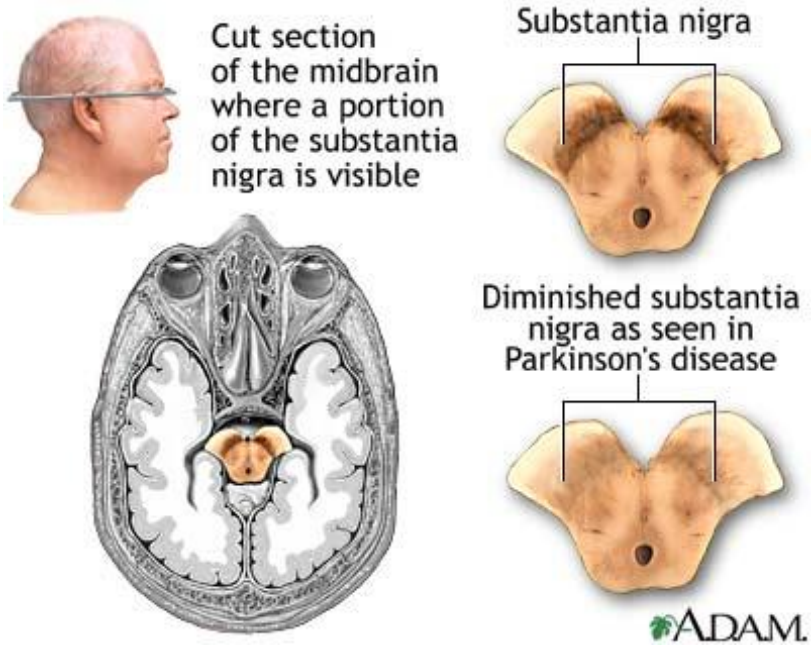


- Tremor – *J.M. Charcot (1825-1893)*
- Bradikinesia (slowness of movement execution) - *Armand Trousseau (1801-1867)*
- Akinesia (inability to initiate movements)
- Postural instability
- Rigidity

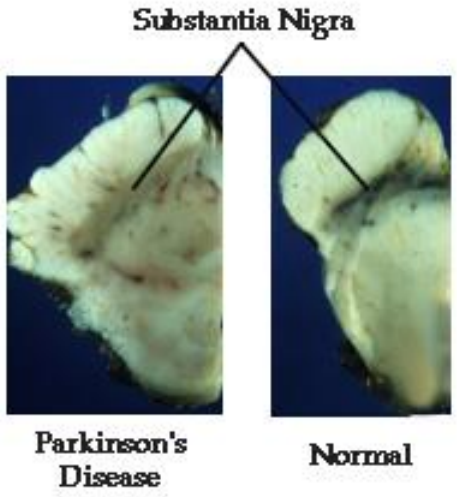


What explains the motor deficits?

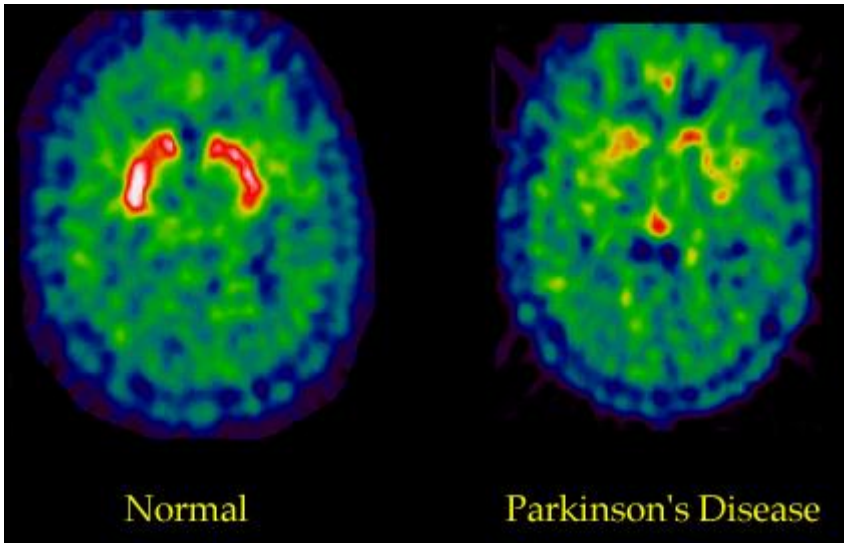




Degeneration of the *Substantia Nigra* (SN) and *Ventral Tegmental Area* (VTA) and projections to the *Corpus Striatum (nigrostriatal pathway)* for movement control



Evaluation of dopamine function loss in PD patients



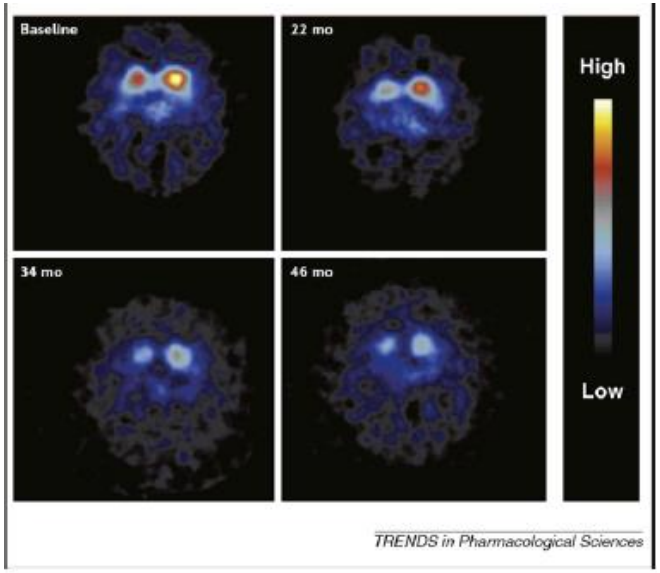
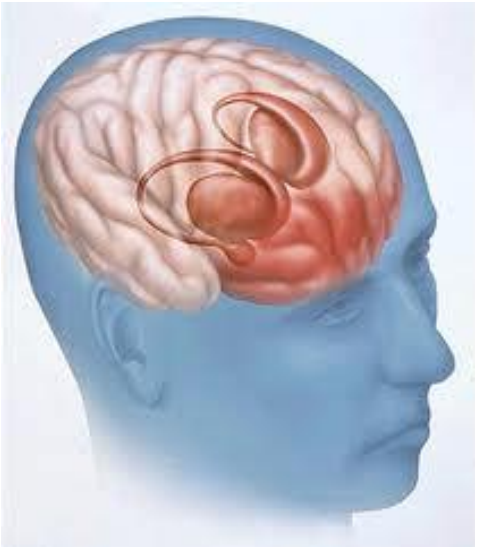


Figure 2. Progressive loss of dopamine transporter binding in a patient from diagnosis (baseline) to 46 months [59].

Today's definition of Parkinson's disease:

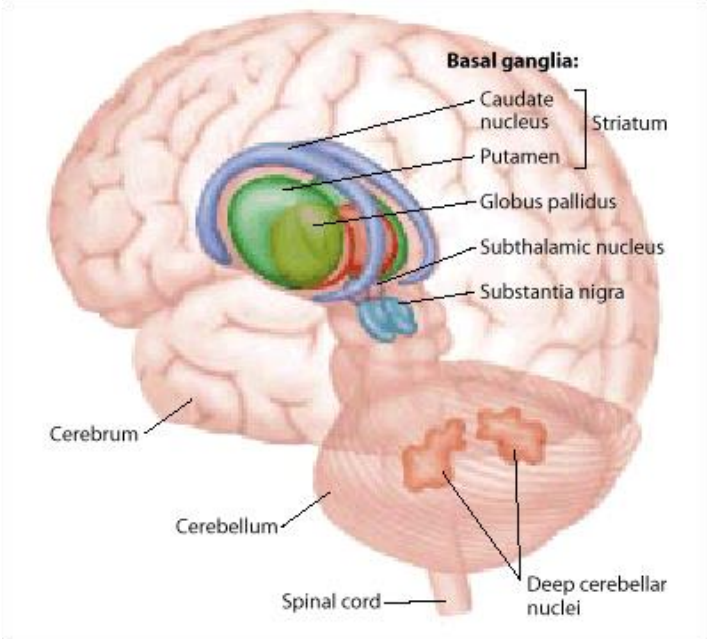
a chronic progressive neurological disease chiefly of later life that is linked to decreased dopamine production in the *Substantia nigra* and is marked especially by tremor of resting muscles, rigidity, slowness of movement, impaired balance, and a shuffling gait.

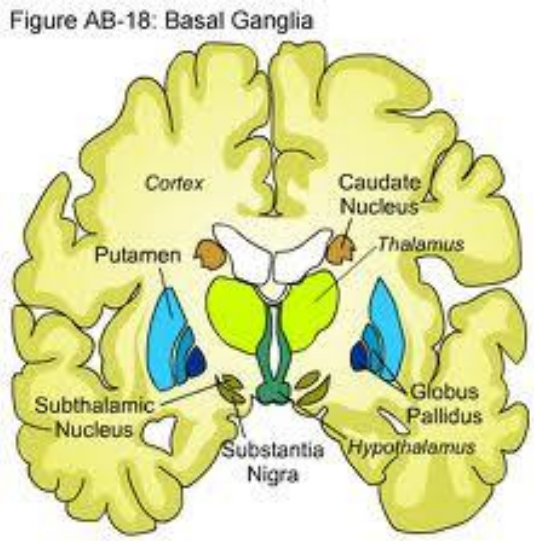
The Basal Ganglia



- Subcortical structures

- Several nuclei interconnected



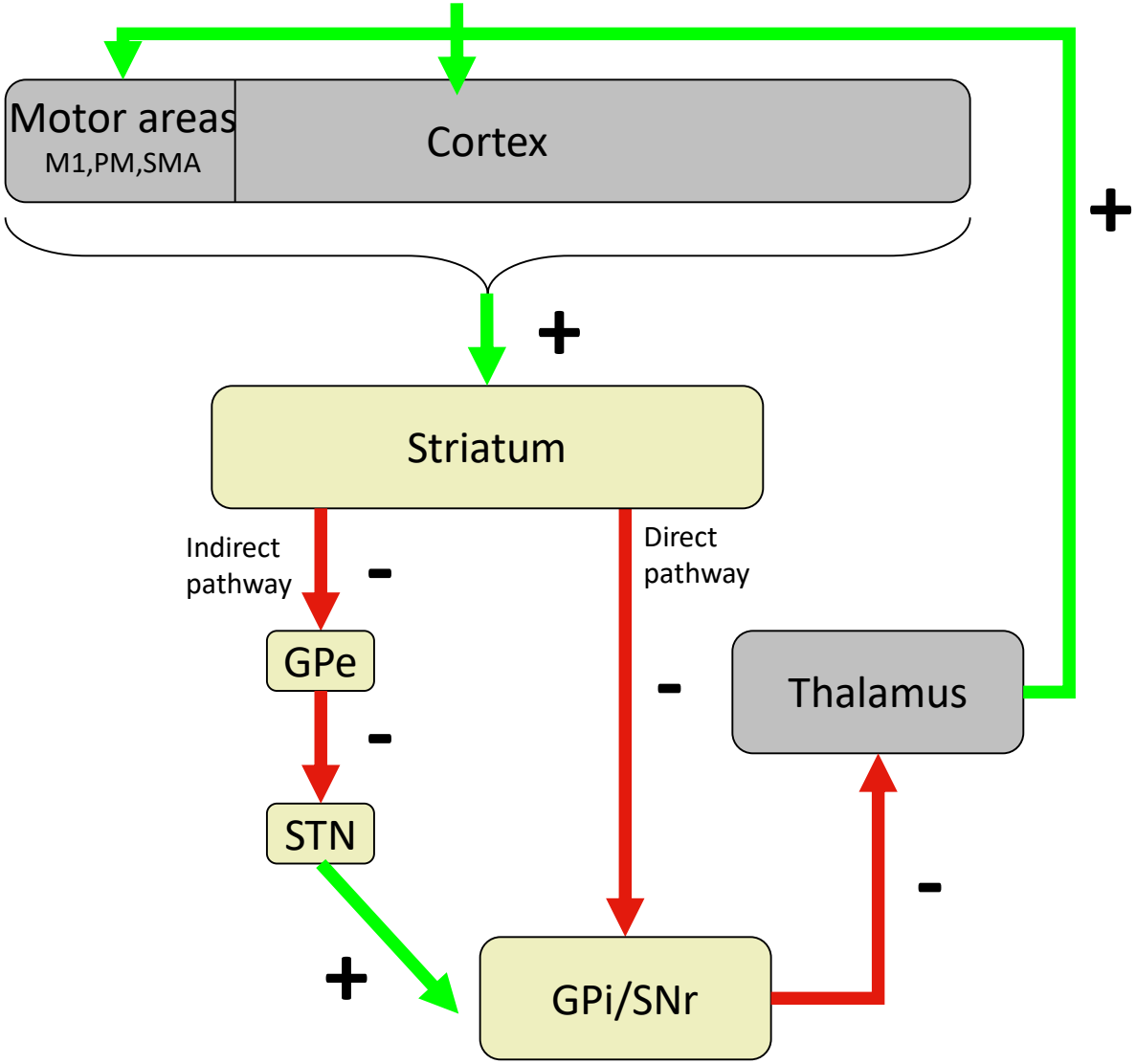


[Basal ganglia anatomy narrated]

Basal Ganglia Functions

- Motor planning, sequencing, learning, maintenance
- Initiation of willing movements
- Inhibit undesired movement and permit desired ones
- Important for movement selection process/decision to move toward…

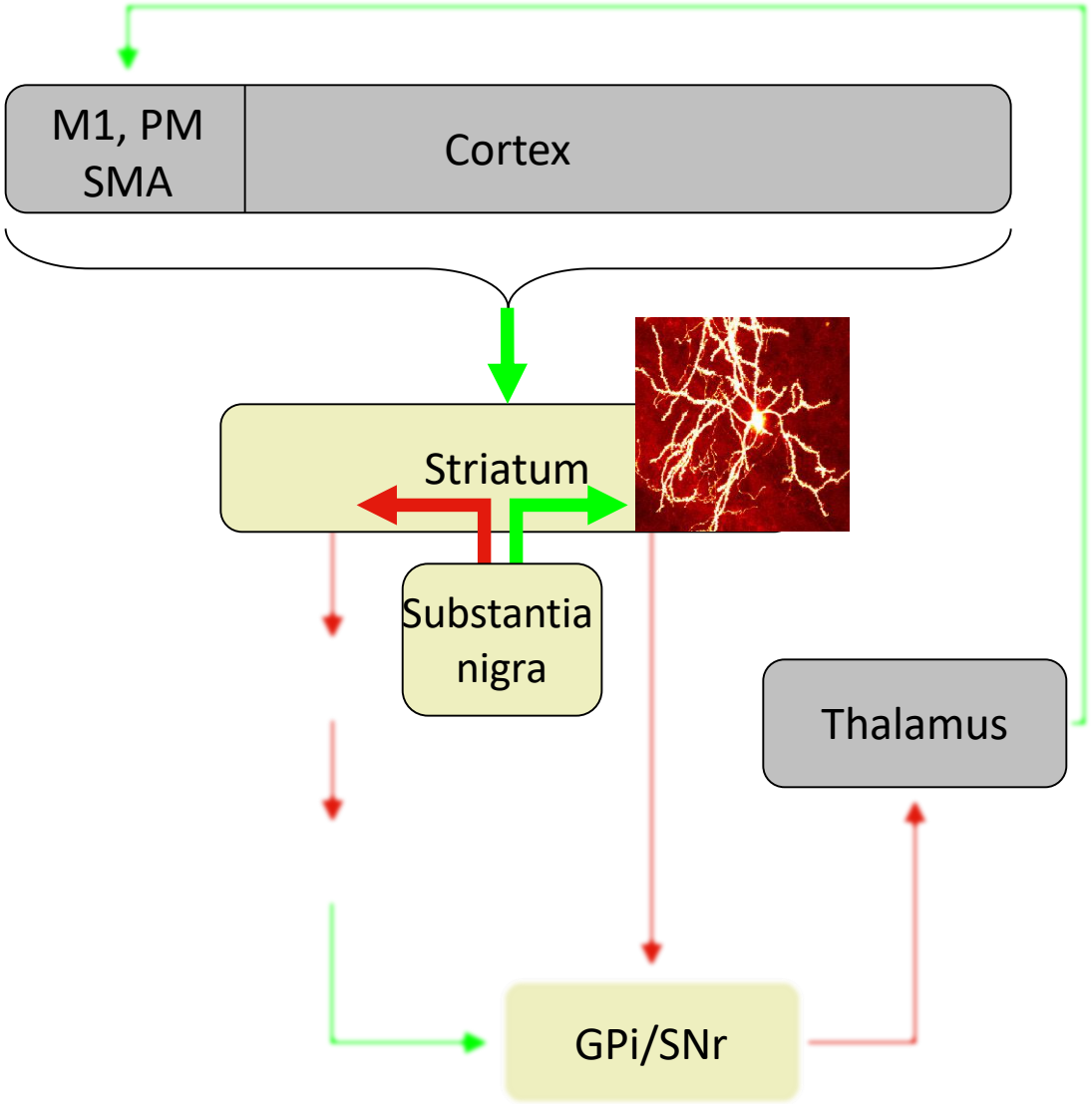
Motor Cortex-Basal Ganglia Circuit



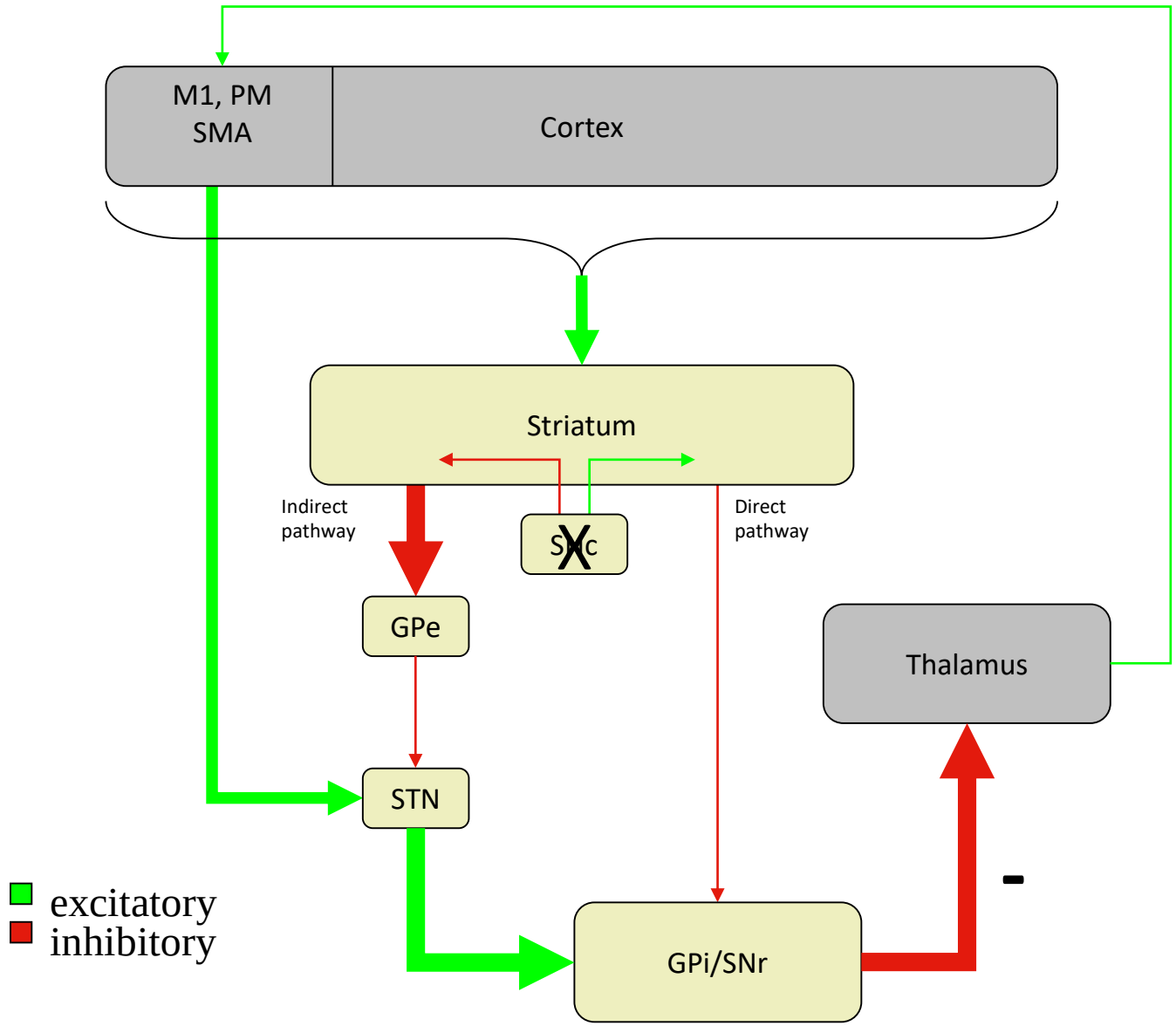
+ glutamate

- GABA

Where does DA come into play?



Effects of loss of Dopamine from the SN on movement control

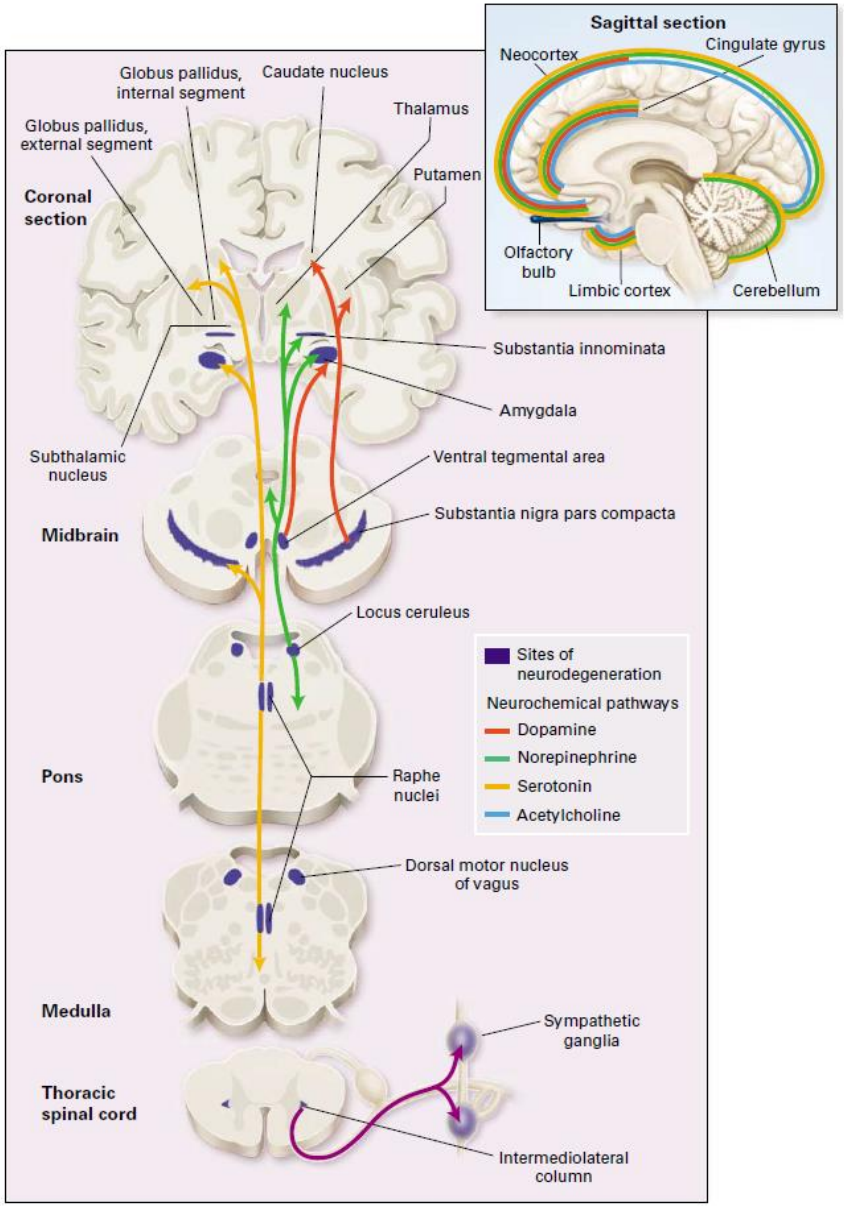


Non-motor symptoms
(premotor?)

- Olfactory dysfunction
- Constipation
- Drowsiness
- Pain
- Anxiety- beyond the normal response to stress
- Sleep disturbances (vivid dreams, talking and moving during night sleep)
- Depression

PD is a really complex disease affecting several neurotransmitter circuitries

Olfactory bulb -> non DA cells
Raphe -> serotonergic neurons
Locus ceruleus -> noradrenergic neurons
Substantia Innominata -> cholinergic neurons



PD, Anthony Lang and Andres Lozano, JNM 1998

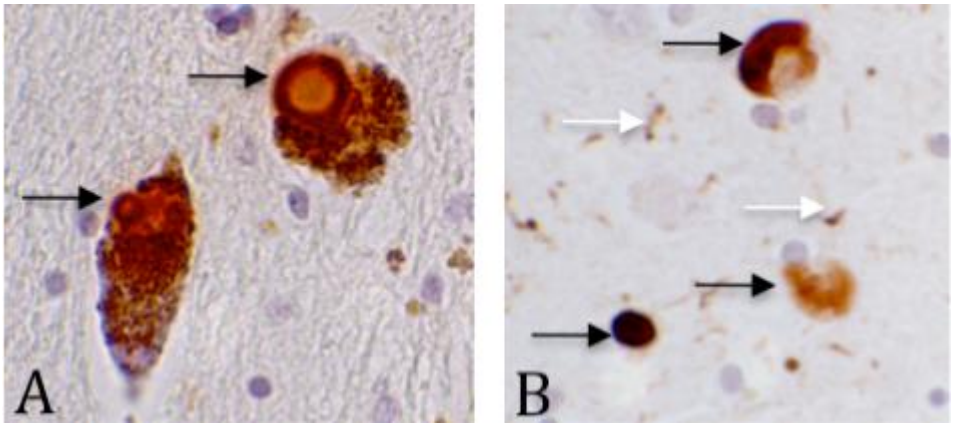
Hallmark of the disease – protein aggregates

- Intracytoplasmic inclusions

  Lewy bodies (black arrows)

  Lewy neurites (white arrows)

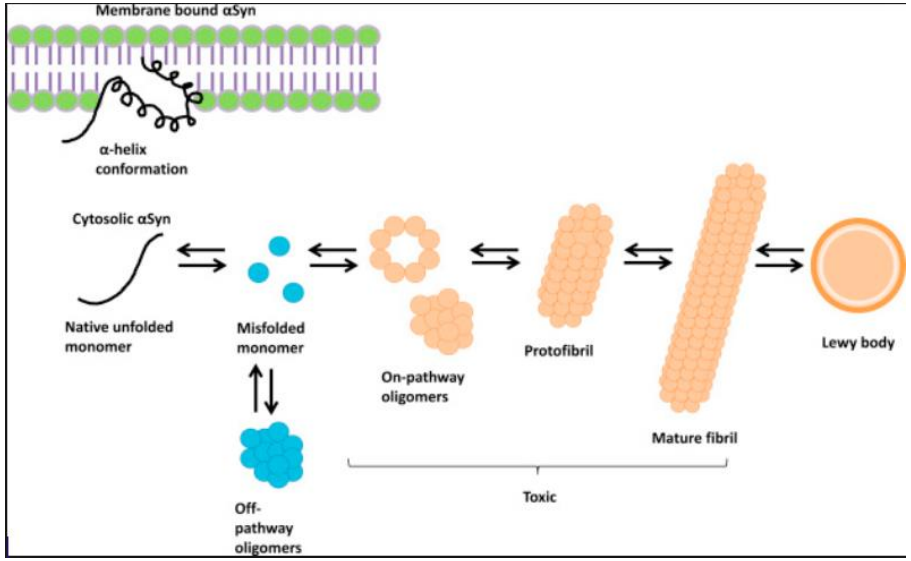
Konstantine Tetriakoff, 1919



From UKPDC

- Major component: α-Synuclein
  - 140aa, synaptic protein – role: neurotransmission?
  - Molecular chaperon for SNARE
  - Genetic mutations in gene results

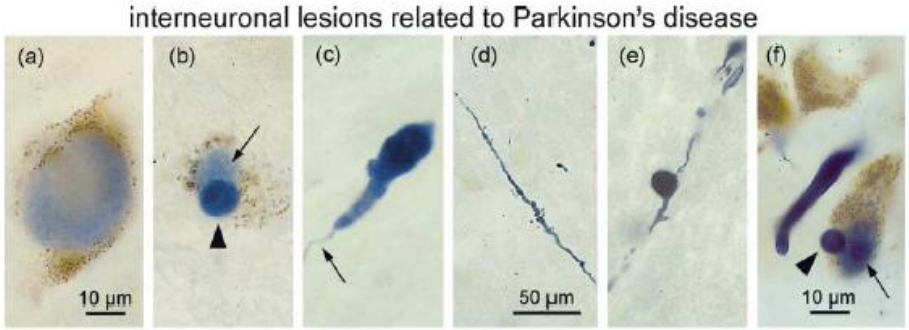
  in increased aggregates, more «sticky»



A possible course of the disease

Braak et al.
Staging of brain pathology related to sporadic Parkinson's disease

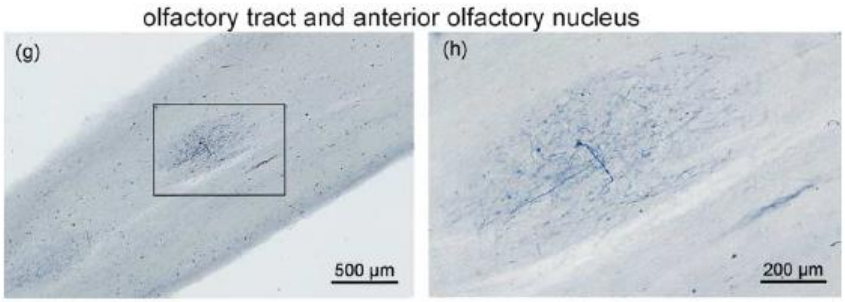
What did they look for:

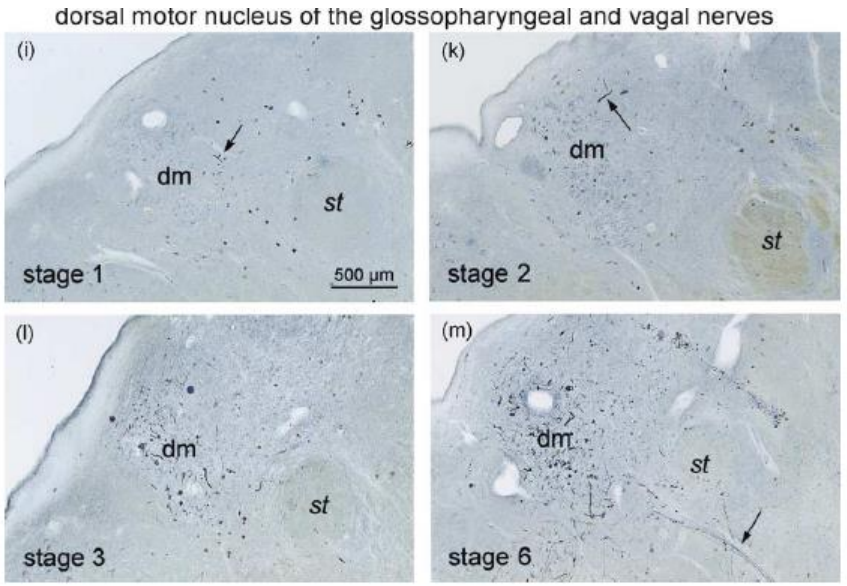


Where:

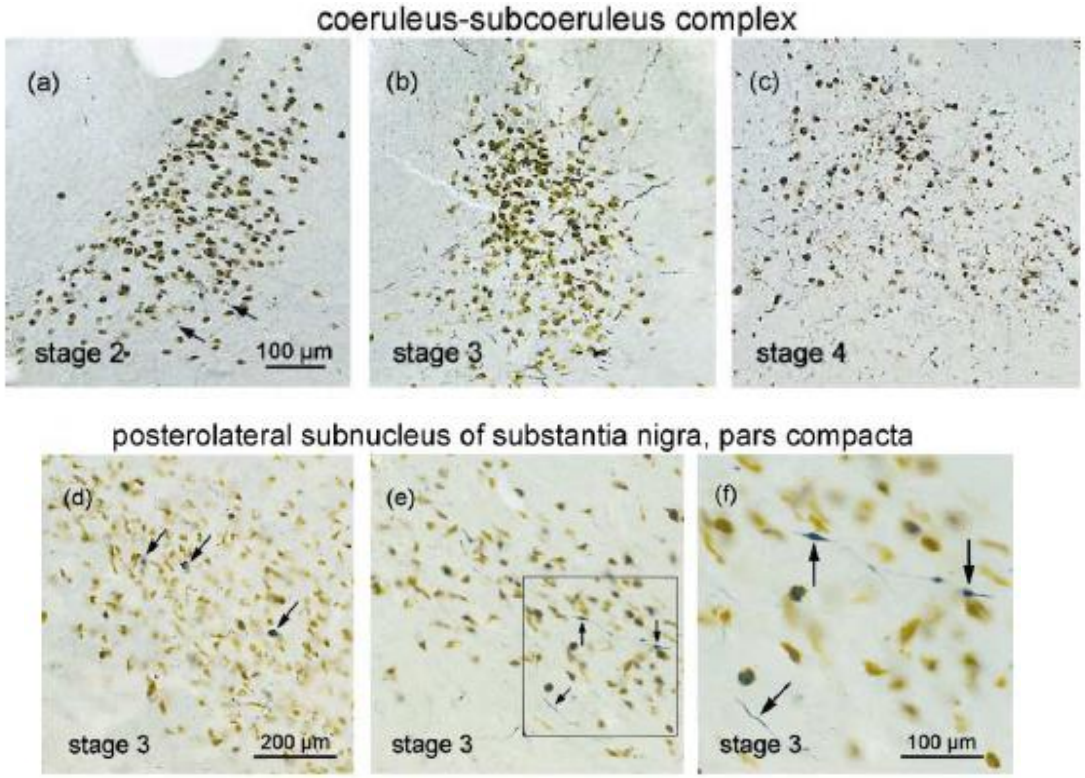
- 41 individuals with clinically diagnosed PD
- 69 individuals no clinical records but detected at autopsy
- 58 age- & gender- matched controls
  (no clinical history, no LB/LN detected at autopsy)

First signs in olfactory bulb and IX/X cranial nerves



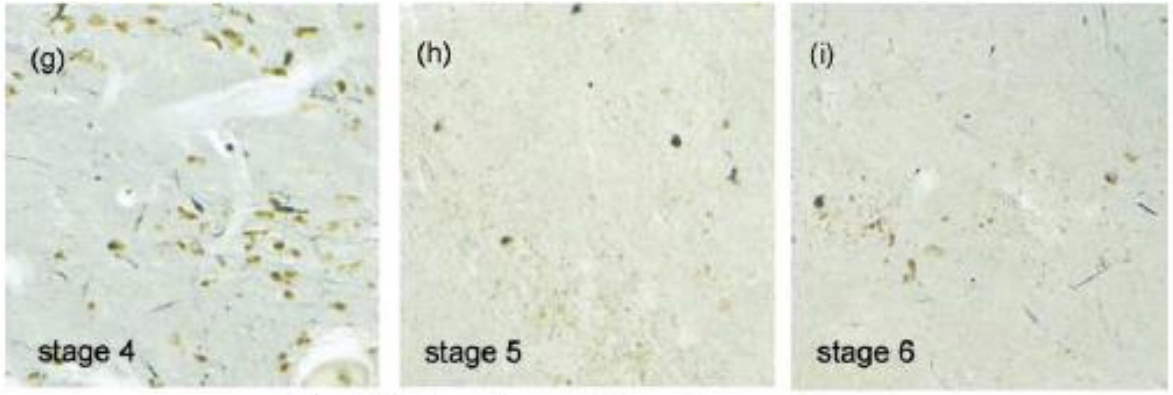


Lesions in structures other than dopamine neurons

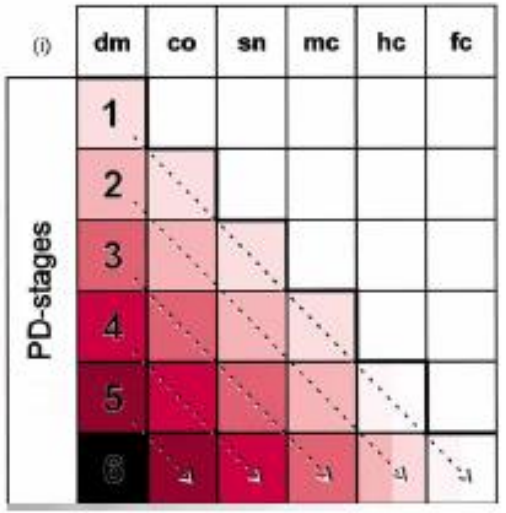


Norepinephrine
Locus coeruleus

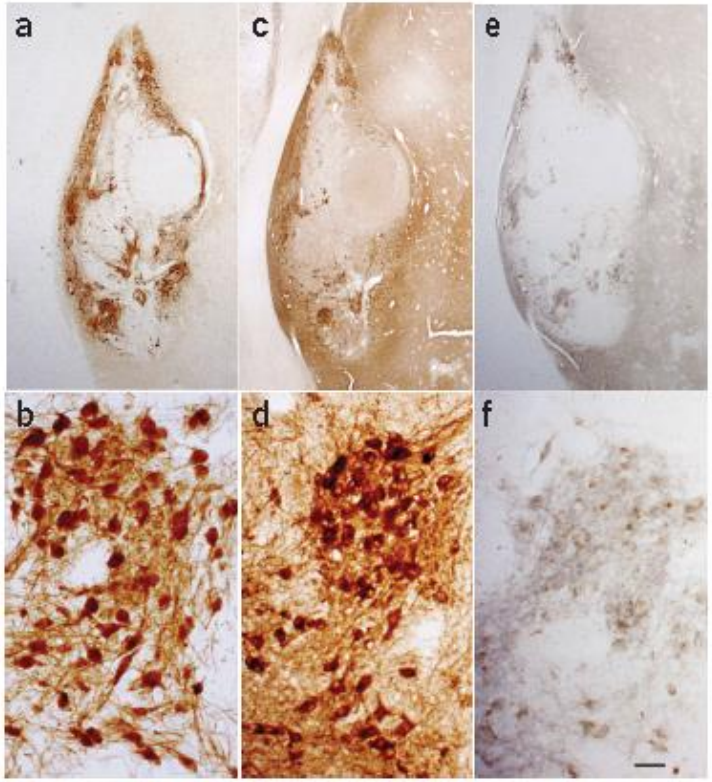
Until the total absence of Substantia nigra neurons

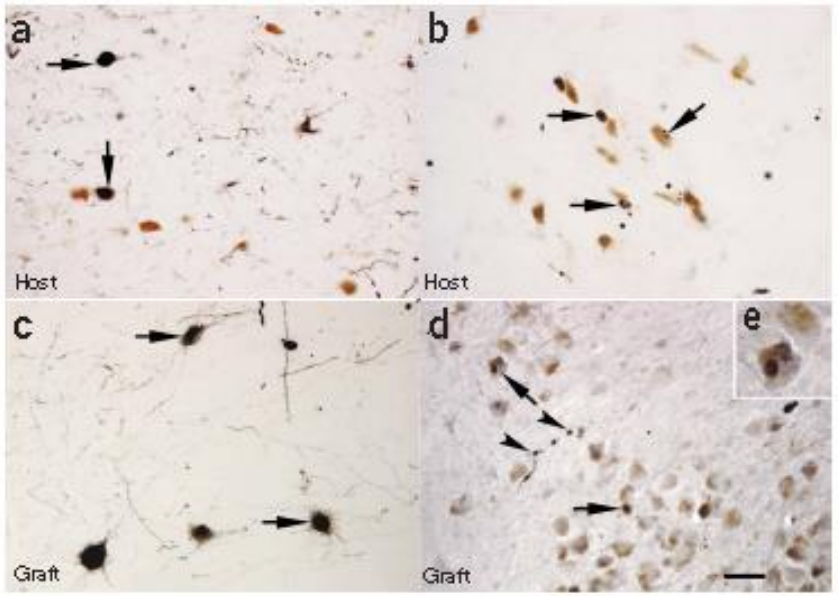


Spreading of the deposits seems to develop following a specific route



Is PD a prion-like disease?





Li J-Y et al, Nature Med 2008
Kordower et al, Nature Med 2008

Midbrain transplants show Lewy bodies -
the disease has spread from host to transplanted cells

Pathogenesis

- Genetics

  α-synuclein, PARK4, LRRK2

  Parkin, DJ-1, PINK1

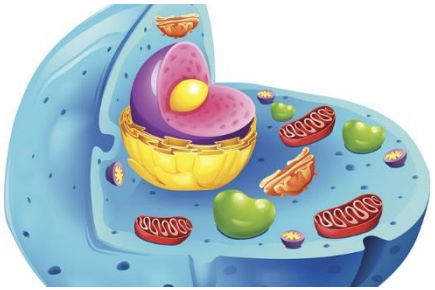
- Free radicals induce mitochondria dysfunction & oxidative stress

  Complex I deficiency in cellular respiration

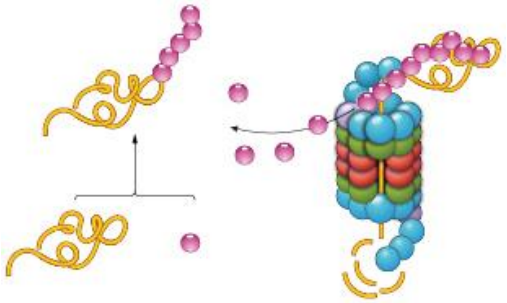
  Toxins - Pesticides

- Neuroinflammation

  activated microglia, pro-inflammatory cytokines, effects on neurotrophins



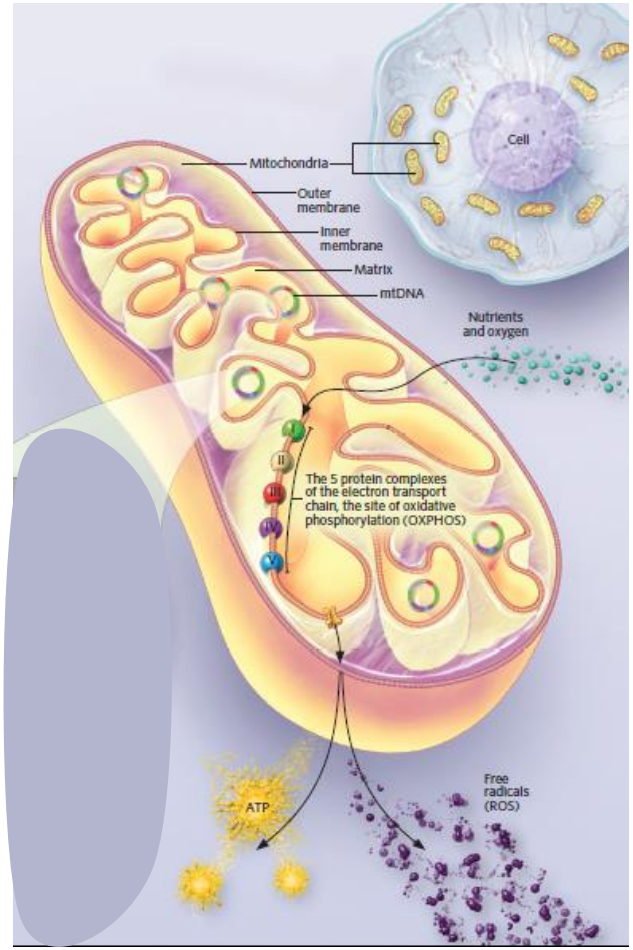
Lessons from Genetics



Mutations in the following genes have been correlated with development of Parkinson's disease (mostly familiar forms):

- SNCA — α-synuclein
- LRRK2 — leucine-rich repeat kinase 2/dardarin protein; autophagy-lysosome pathway
- UCH-L1 — ubiquitin-proteasome system
- PARKIN — mitochondria (ubiquitin-ligase)
- DJ-1 — mitochondria
- PINK1 — PD-PTEN-induced putative kinase 1; mitochondria

Mitochondrial dysfunction



Mitochondria are power houses:
- Nutrients plus oxygen to create ATP/energy via cellular respiration
- Reactive oxygen species (ROS) are toxic by-products

High energy production, low ROS; and viceversa

ROS induce oxidative stress and can damage lipids, DNA, proteins

Age, toxins, α-synuclein all contribute to ↑ROS

Why are dopaminergic neurons affected by mitochondria dysfunction?

Neurons have a high energy demand

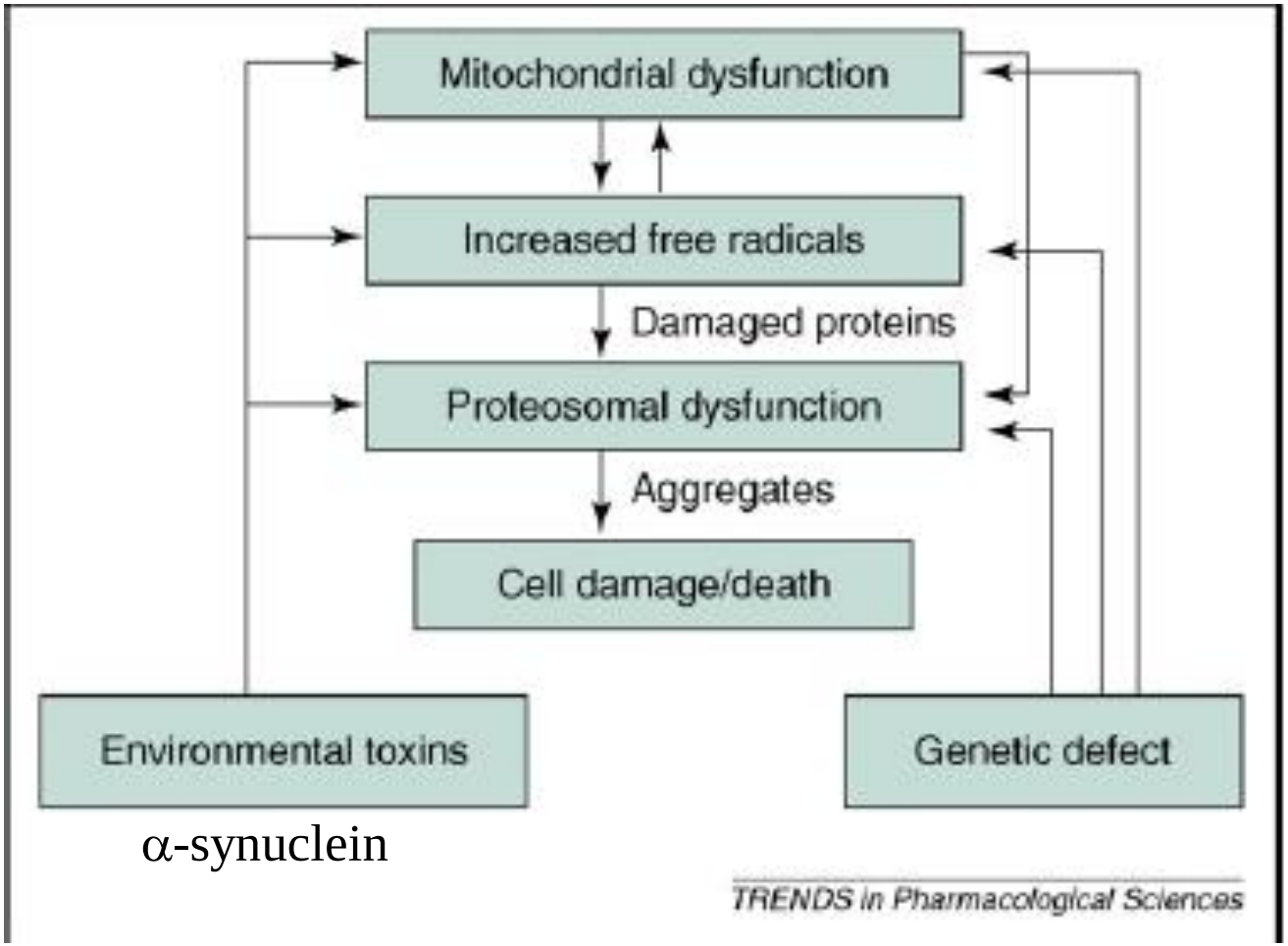
- maintain basic requirements for recurrent firing
- refill vesicles to prevent neurotransmitter oxidation
- long distance axon transport

Neurons die if their mitochondria are compromised

Dopaminergic neurons: pacemakers, long axons, many synapses

Dopamine metabolism creates highly reactive species and dopamine can auto-oxidize (melanin deposits from oxidative breakdown of dopamine)

A unified theory?

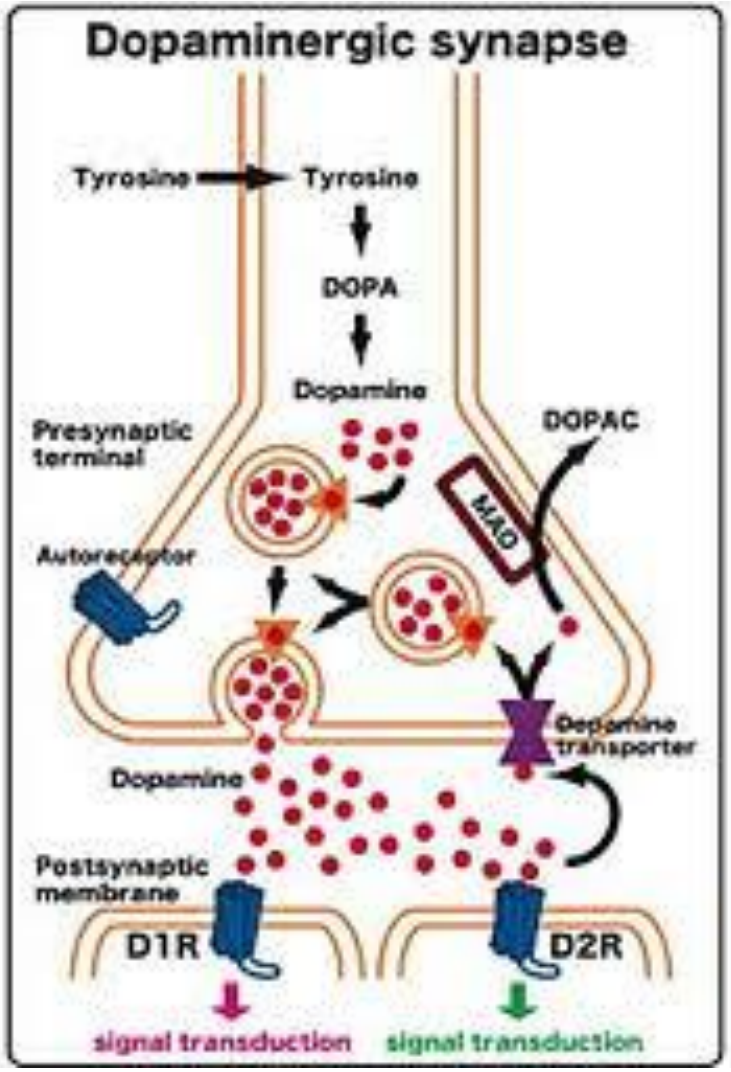


α-synuclein

Available and possible treatments
What are the problems in PD?

- Drugs
- Surgery
- Cell replacement therapy – stem cells
- Gene therapy *e.g. AAV-GAD, AAV-AADC*

What type of Drugs could work?



- Levodopa [+ carbidopa]

but fluctuations and dyskinesia

- MAO inhibitors - Seleginine/Deprenyl
- Dopamine agonists - Pramipexole/Ropinirole

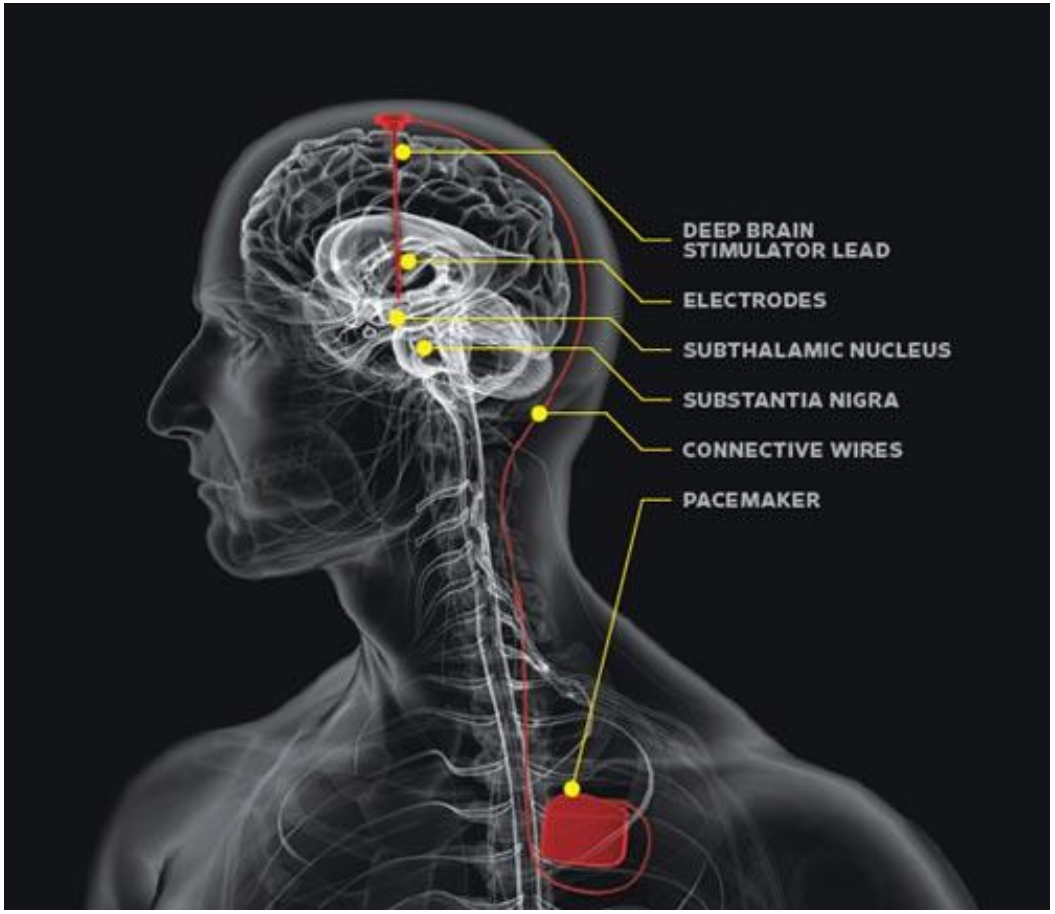
but side effects

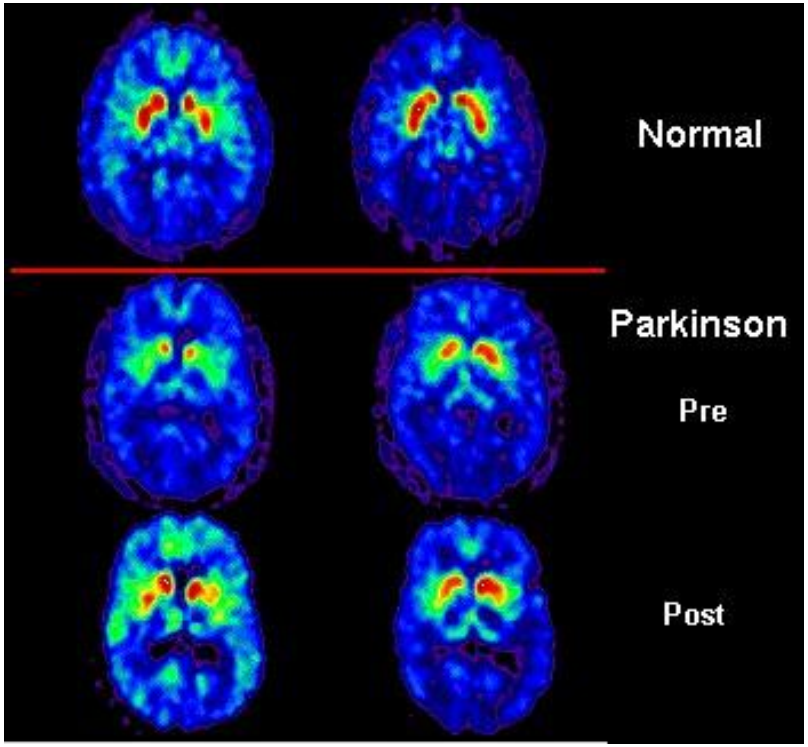
- Amantadine…? *reduces dyskinesia*

Surgery

Originally: Pallidotomy (tremor, rigidity, bradykinesia) and thalamotomy (Tremor)

Now: Deep Brain stimulation





Transplantations

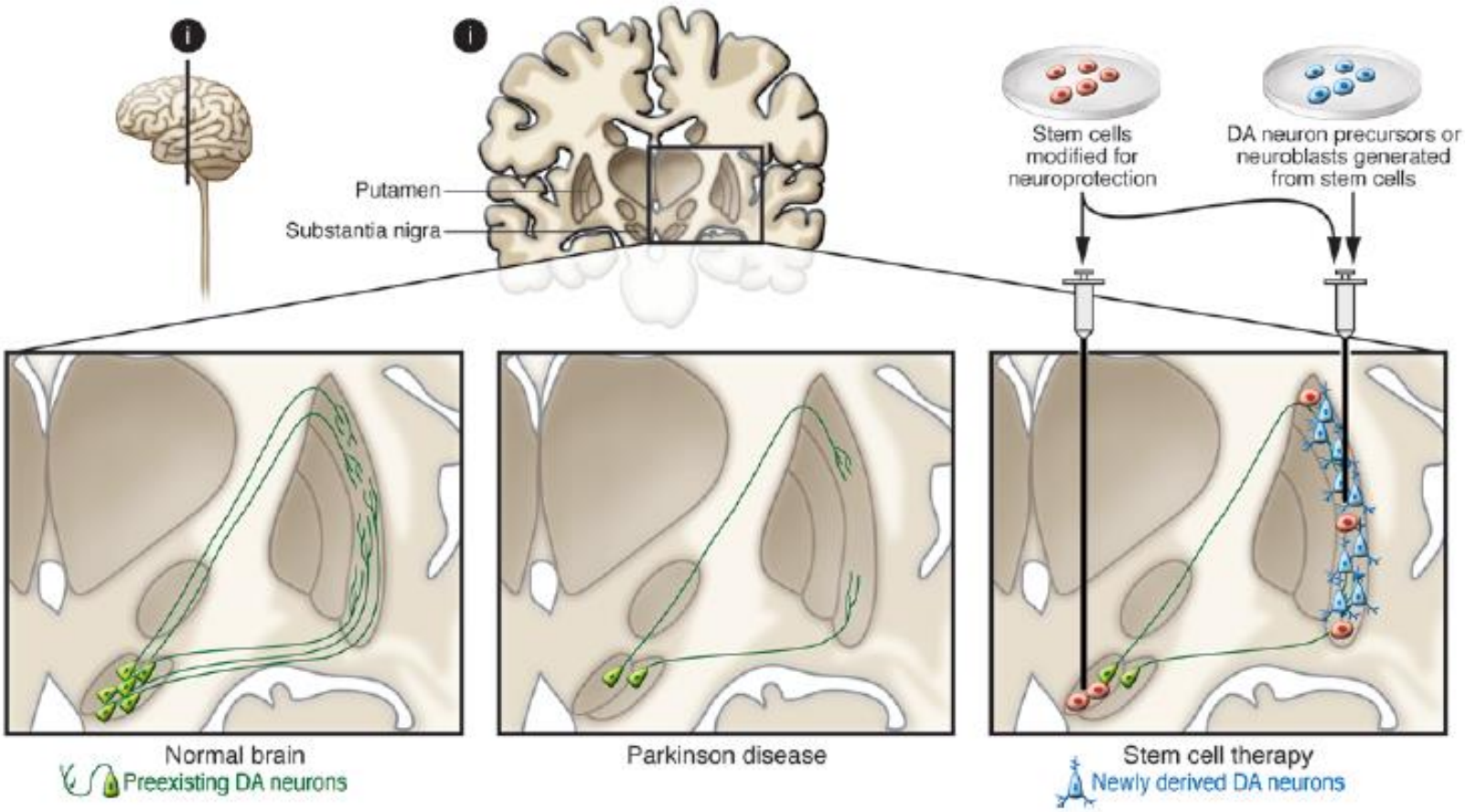
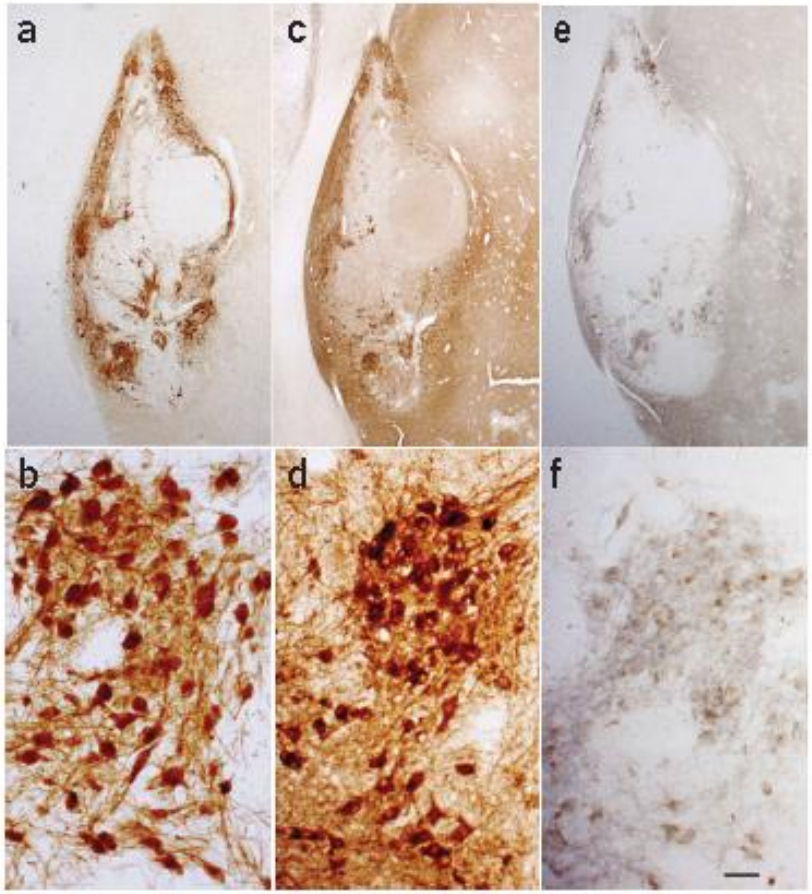


Figure 1
Stem cell–based therapies for PD. PD leads to the progressive death of DA neurons in the substantia nigra and decreased DA innervation of the striatum, primarily the putamen. Stem cell–based approaches could be used to provide therapeutic benefits in two ways: first, by implanting stem cells modified to release growth factors, which would protect existing neurons and/or neurons derived from other stem cell treatments; and second, by transplanting stem cell–derived DA neuron precursors/neuroblasts into the putamen, where they would generate new neurons to ameliorate disease-induced motor impairments.

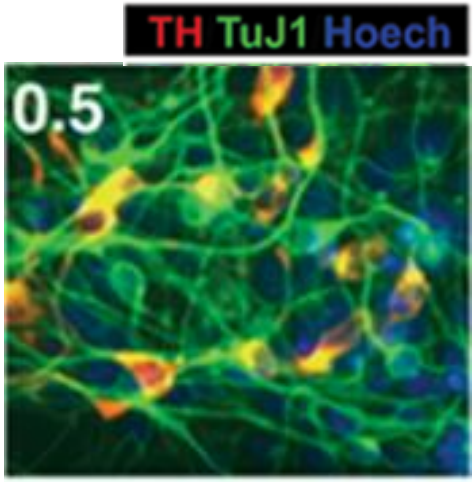
Olle Lindvall & Kokaia (2010) J. Clin. Invest. 120:29-40. doi:10.1172/JCI40543

Transplantations

Foetal tissue transplants

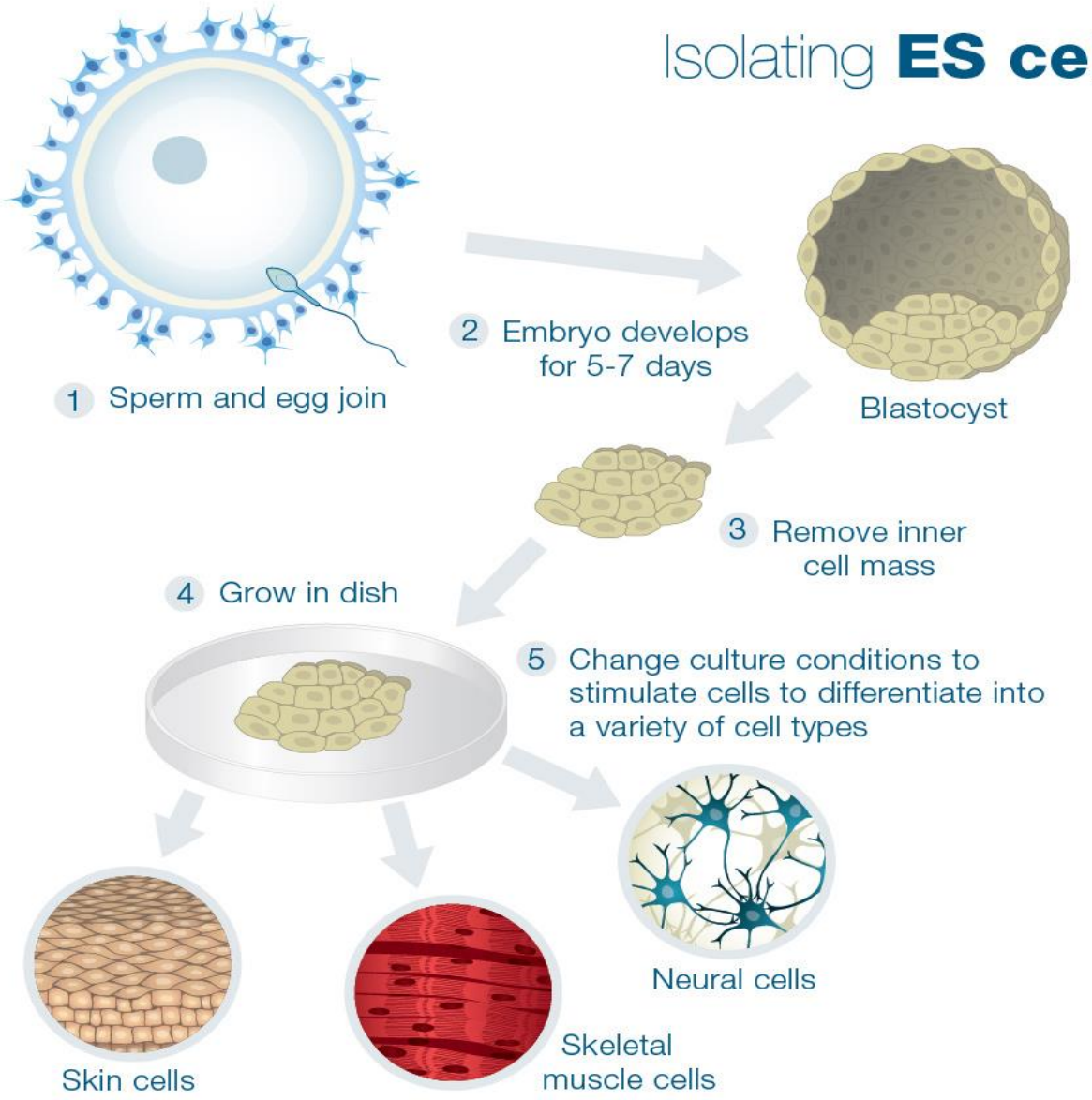


Stem cells transplants

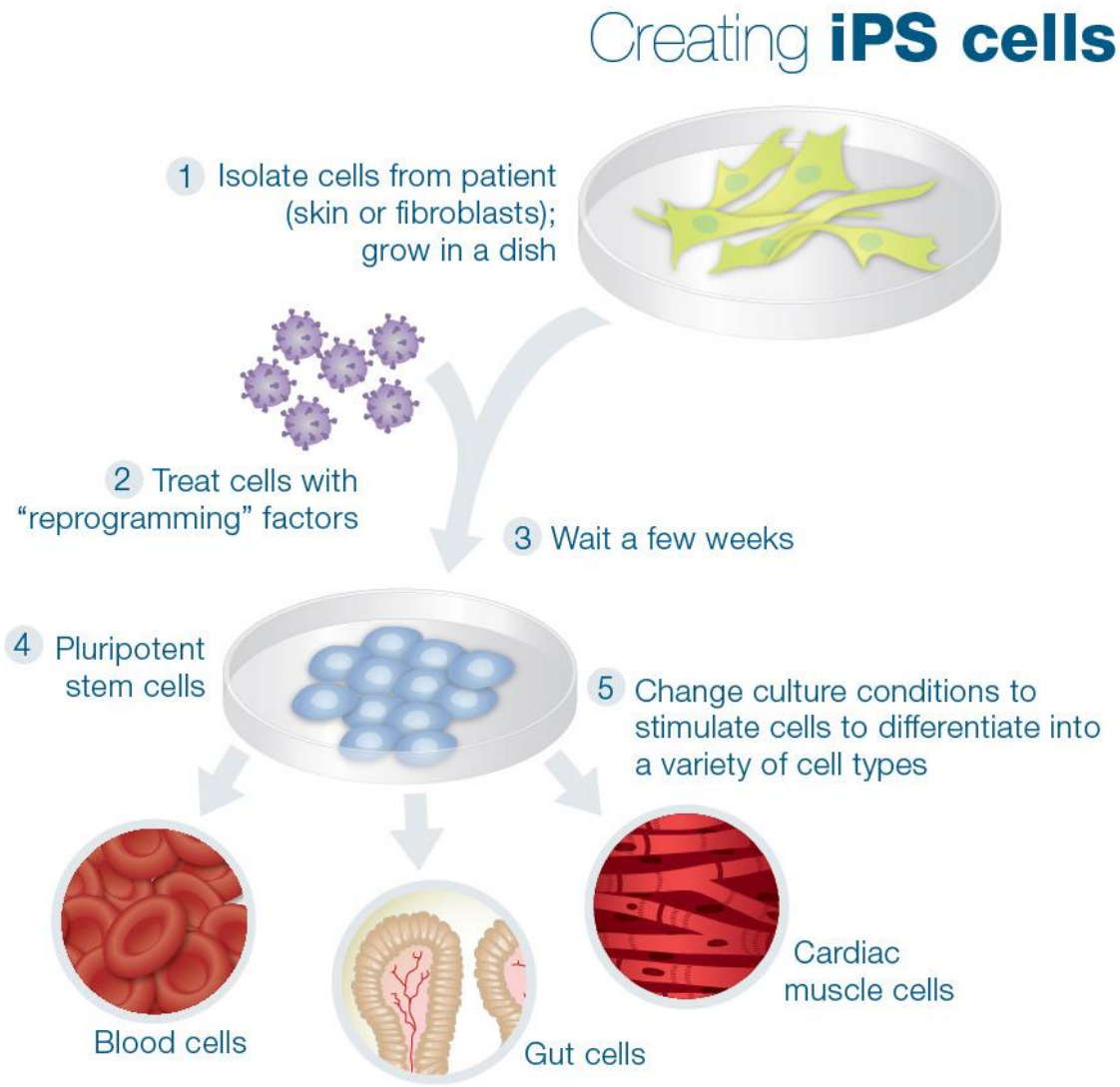


Sacchetti et al, 2009 CSC

Isolating **ES cells**



Ideally a hybrid would be necessary



Type of stem cells available

- Embryonic stem cells – ESC

  most potent capable of unlimited growth due to self-renewal; pluripotent

- Somatic stem cells or adult stem cells

  more fate restricted when specializing into specific tissue lineage. Some tissue are highly regenerative; multi-potent for all specialized cells within that lineage

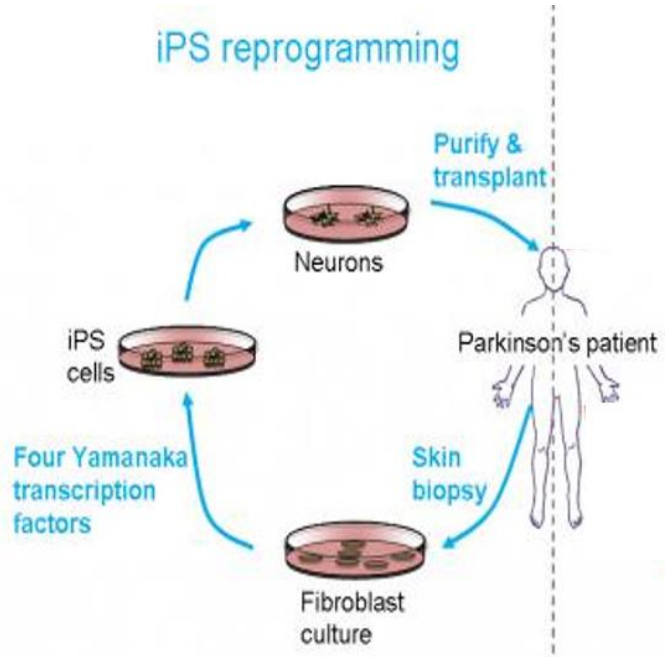
- Induced pluripotent stem cells – iPS

  Reprogrammed cells appear as ESCs

  Can generate pluripotency from patients directly

  Based on 4 Transcription factors

  (oct4,myc,klf4,Sox2) linked to pluripotency



Stem cells Trials (or soon to be)

❖ Japan 2017 - Takahashi (GForce-PD) – *proof of principle*

hiPSC progenitors (healthy or PD) in monkeys – ok for 2 years

No tumors, no immuno response; integration and increase spontaneous behavior ; MRI and PET scans show improvements

Future: Derived from human healthy individuals and then match immunoresponse with patients to avoid immunoresponse.

❖ China 2017 - Dopamine progenitor cells derived from ESCs

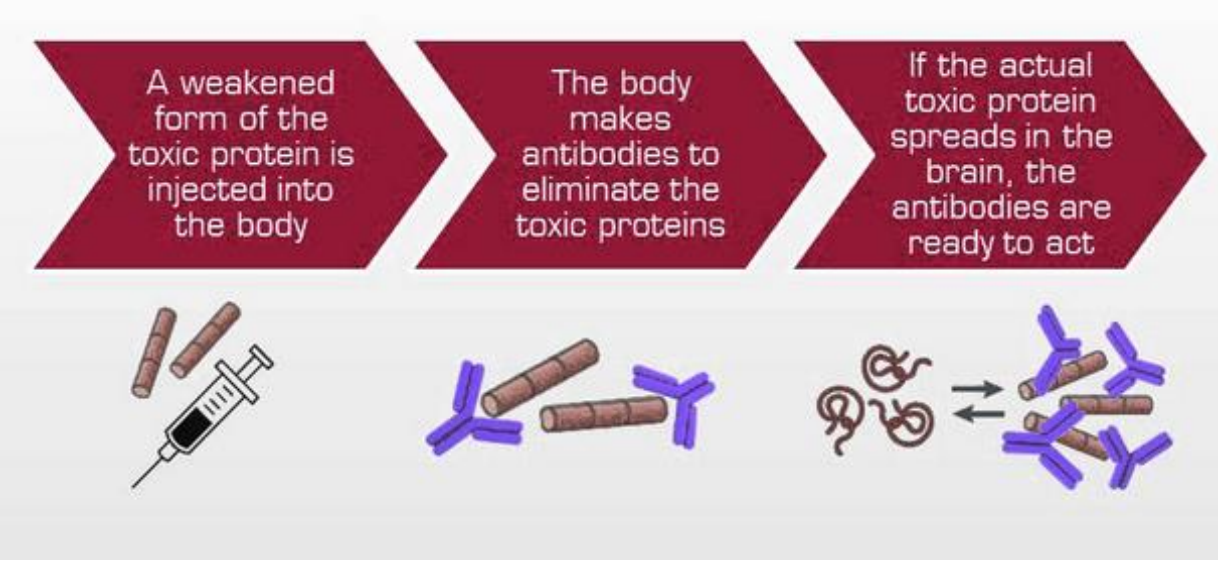
❖ US/Sweden/England - ESC-derived Dopamine neurons

❖ Scripps - iPSC from patients'own skin cells to avoid immunoresponse

Other trials:

Vaccines from AffiRis, Austria (Austria/Germany/France)
against alpha-synuclein AFFITOPE PD01A-03A

Phase I to test safety and immunoresponse in 36 patients
(high dose/low dose/placebo) with 5 injections.
Safe and good immunological response although no news on efficacy



Biomarkers

α-synuclein in Cerebral Spinal Fluid of PD patients is lower

Rush Univ Dr Goldman

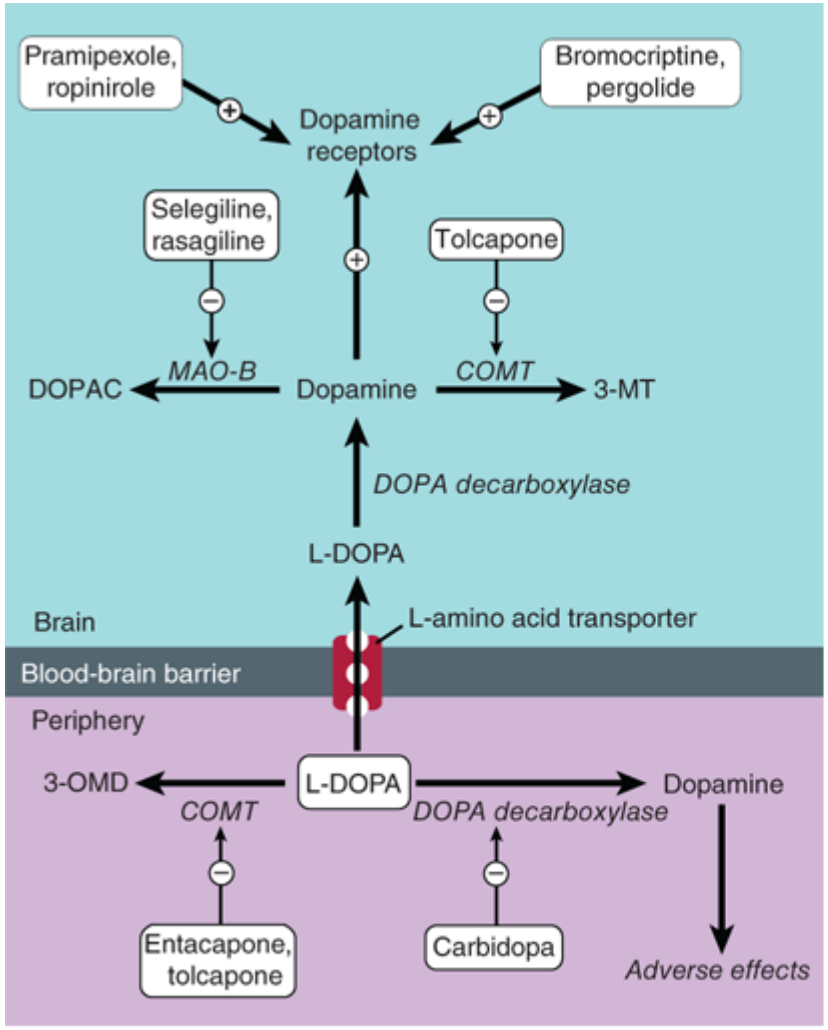
Detection of α-synuclein in CSF using α-synuclein real time quaking-induced conversion (αSyn RT-QuIC) assay that has similar sensitivity and specificity to the prion assays, but can be performed in 1–2 days with quantitation.

Blinded analysis of cerebrospinal fluid from 29 synucleinopathy cases [12 Parkinson's and 17 dementia with Lewy bodies] and 31 non-synucleinopathy controls, including 16 Alzheimer's cases, yielded 93% diagnostic sensitivity and 100% specificity for this test so far;

Acta Neuropathologica Communications Neuroscience of Disease 2018 **6**:7 https://doi.org/10.1186/s40478-018-0508-2

Readings and more:

- An essay on the shaking palsy, James Parkinson – http://www.gutenberg.org/files/23777/23777-h/23777-h.html
- Missing pieces in the Parkinson's disease puzzle, Obeso et al., (2010), Nature Med. 16(6) :653-661
- Staging of brain pathology related to sporadic Parkinson's disease, Braak et al., (2003), Neurobiology of ageing 24:197-211
- Parkinson's Disease and Alpha Synuclein: Is Parkinson's Disease a Prion-Like Disorder? C.W. Olanow and P. Brundin, Movement disorder (2013), 28(1):31-40
- The Case of the Frozen Addicts, J. William Langston and Jon Palfreman, Pantheon ed. (1995)
- Lucky man: a memoir, M.J. Fox, Hyperion ed. (2003)
- Does Parkinson's begins in the gut? https://www.scientificamerican.com/article/does-parkinsons-begin-in-the-gut/
- TED talk – What are stem cells? https://www.youtube.com/watch?v=evH0I7Coc54
- University of Utah - http://learn.genetics.utah.edu/content/stemcells/



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

Stem cells

Organs and tissues *highly specialized cells* originate from initial pool of **stem cells** formed shortly after fertilization.

"Cardinal properties of stem cells":

- ✓ Their capacity to **self-renew** (divide in a way that generates more stem cells)
- ✓ Their capacity to **differentiate** into any cell of your body (to turn into mature, specialized cells that make up tissues and organs).

Stem cells are used for

- Understanding how genetic information is translated into tissue formation and organogenesis

  knowledge

- Delivery of cells to diseased tissue for treatment of diseases of malformation, degeneration, trauma, genetic deficiency

  cell-based therapy and regenerative medicine

- Cell-based assays from stem cells for drug discovery and *in vitro* models of disease

  treatments and cures

Type of stem cells available for neuroscience

- Embryonic stem cells - *pluripotent*

  Limitations – expensive, limited % neurons of desired phenotype

- Somatic stem cells or adult stem cells – *multipotent*

  Limitations – limited differentiation potential