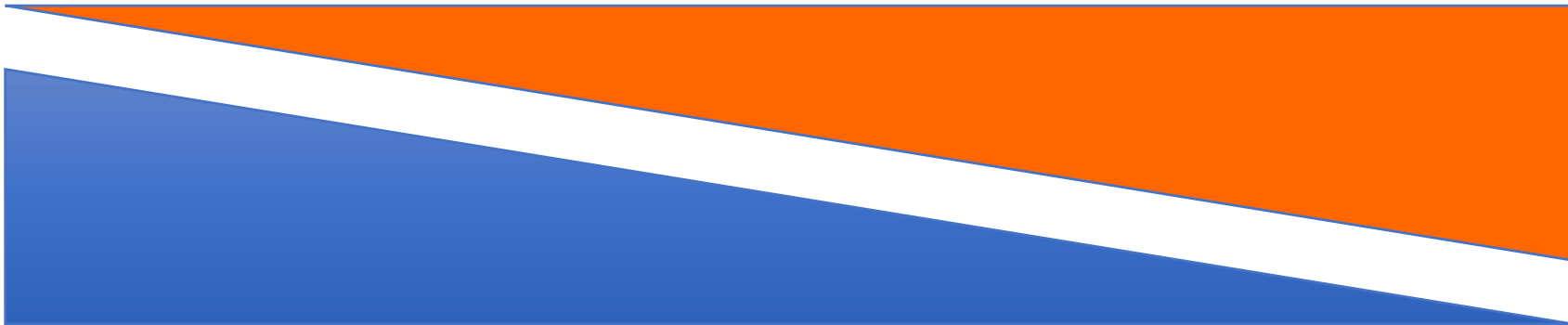


**What have we learned about Parkinson's
disease over the last 40 years?**

PD, acquired or innate disorder?

80's
Acquired
Toxic

90's-2000's
Innate
Genetic



PD in the 80's

- Movement disorders, motor symptoms
- Focus on dopamine and *substantia nigra*
- No genetic factors
- Toxic hypothesis
- Role of mitochondria

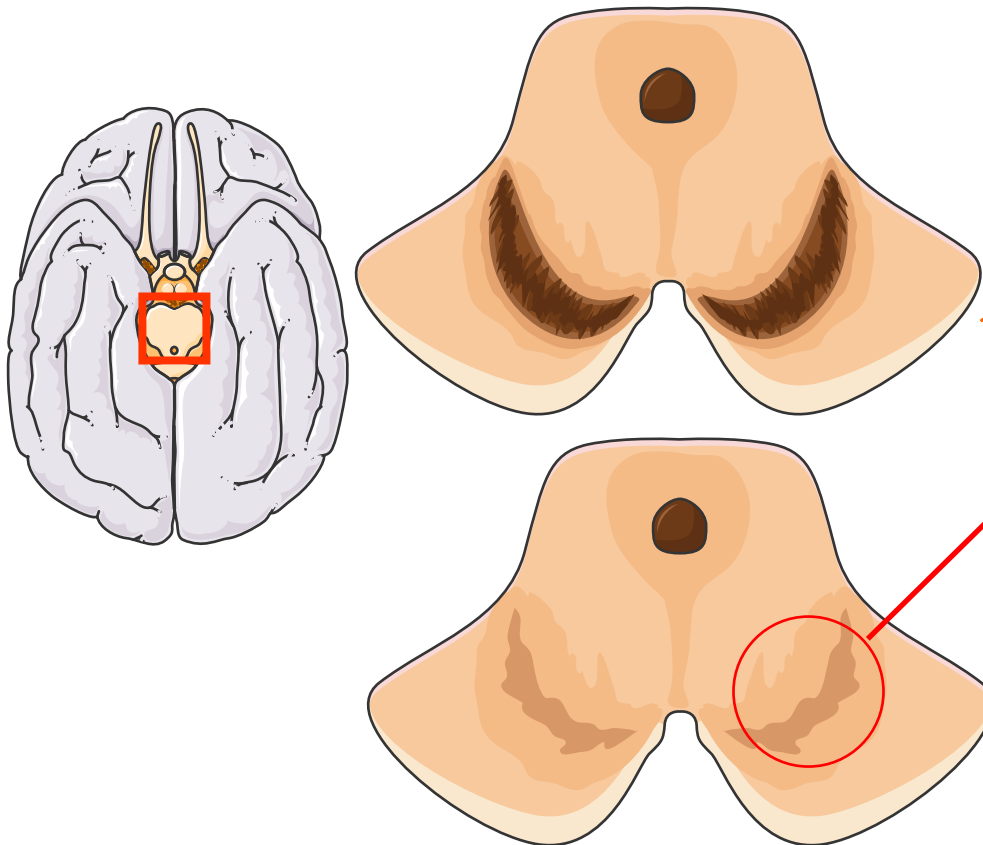
In the 80's, PD was primarily regarded as a movement disorder...

3 cardinal symptoms

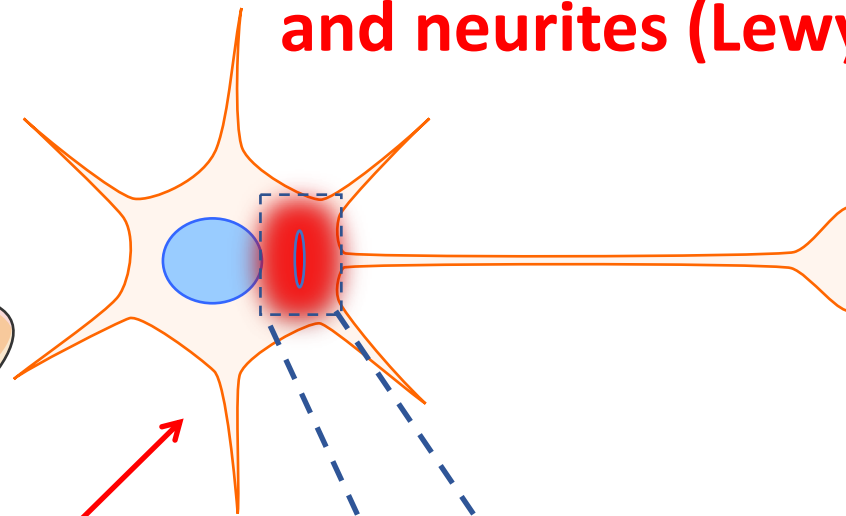
- Resting tremor
- Slowness of movement
- Muscle rigidity

...and a disorder of the *substantia nigra*

1. Loss of dopamine-secreting neurons

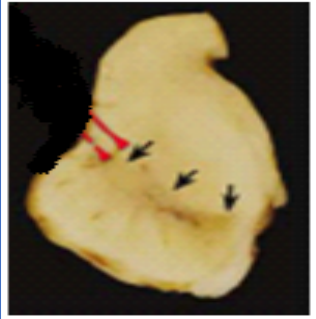


2. Lewy bodies and neurites (Lewy pathology)

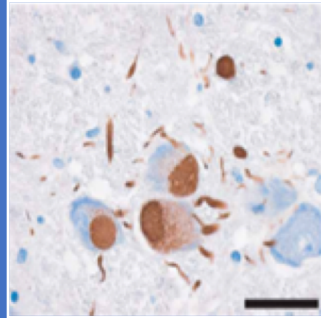


More than 100 hundred components identified but no definite marker in the 80's

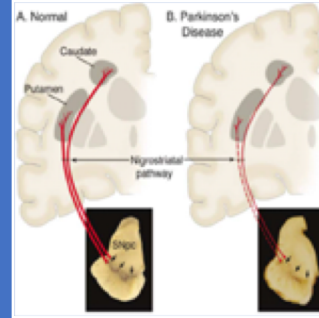
Pathophysiology of motor symptoms in PD



Substantia nigra,
neuronal
loss



Lewy bodies
and neurites



Dopamine
deficiency



Motor
symptoms

- Bradykinesia
- Hypertony

Lesion and neuronal loss = dysfunction = clinical signs

PD in the 80's, of toxic origin with the mitochondria at the forefront

PD in the 80's: genetic factors do not seem to play a major role

- Zero concordance for Parkinson disease was found in 12 monozygotic twin pairs
- These preliminary findings suggest that genetic factors do not play a major role in the etiology of Parkinson disease

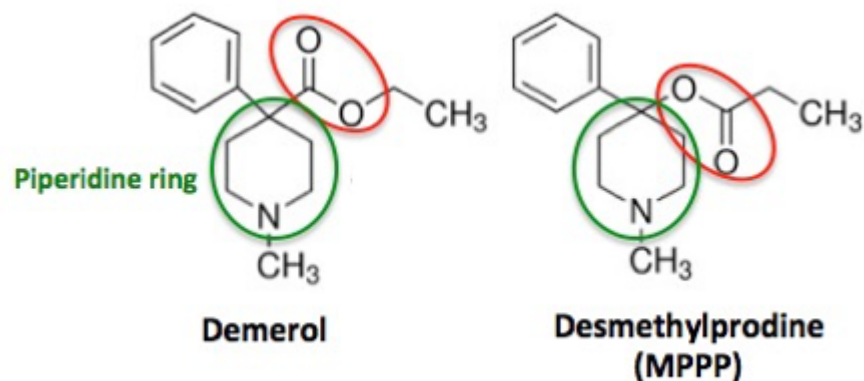
Duvoisin et al., Neurology 1981

1982: Toxic origin of PD, Parkinsonism in drug addicts

- 1 female, 3 males (2 brothers)
- 26 to 42 years old
- Santa Clara County
- Severe parkinsonism 4 to 14 days after iv injection of synthetic heroin (street drug)

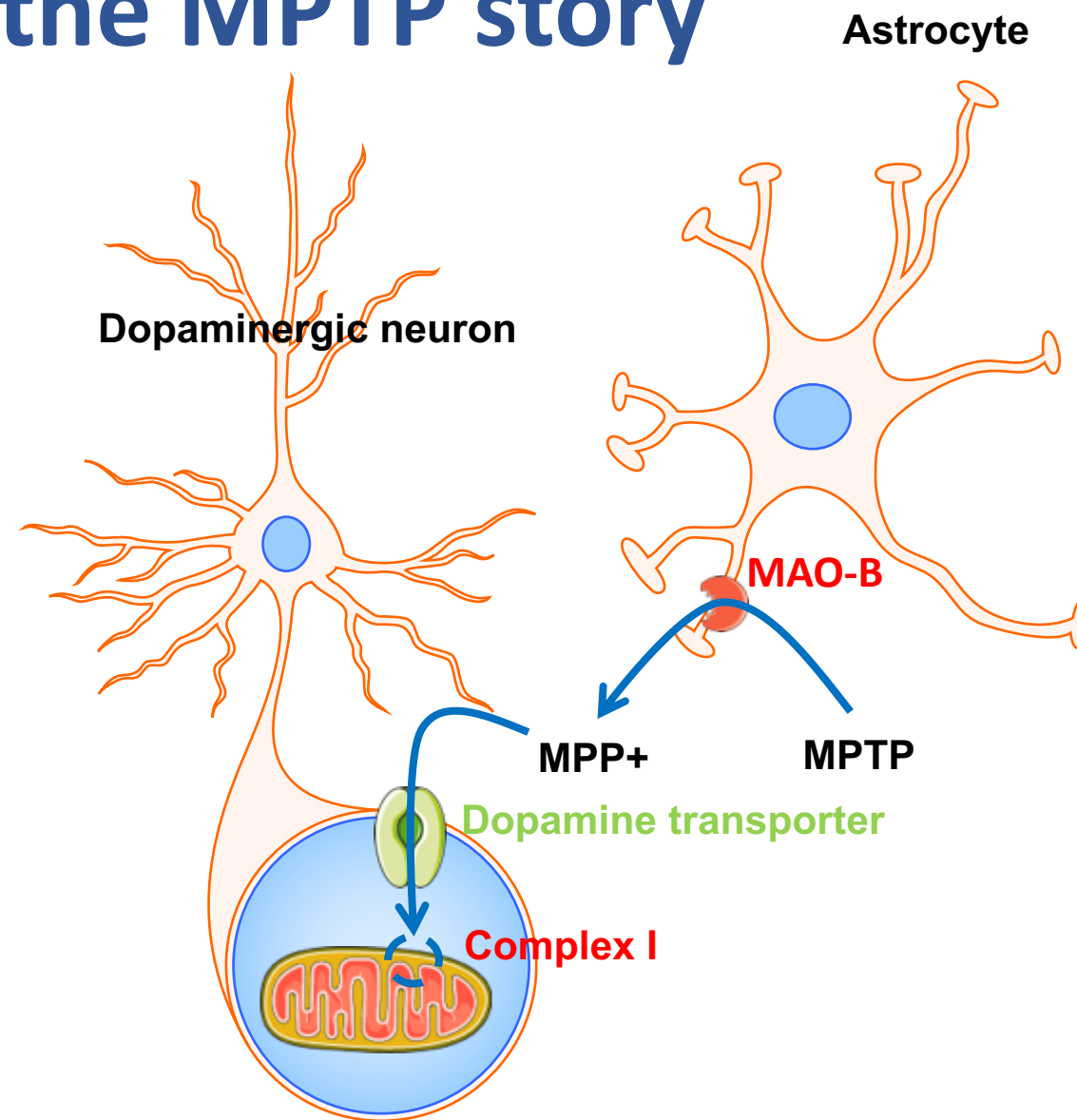


Toxic hypothesis of PD, the MPTP story

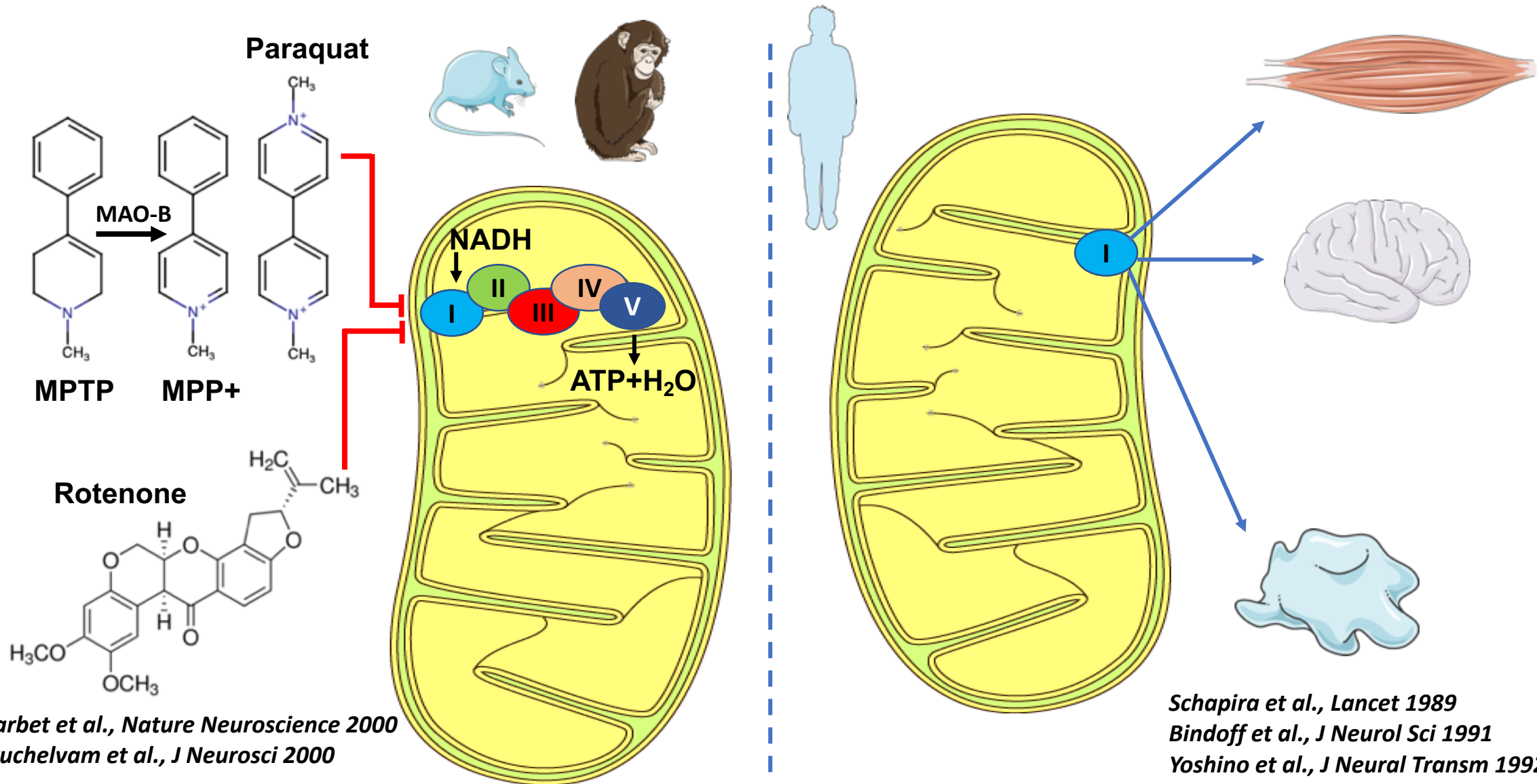


**Errors in temperature
and/or pH**

Langston et al., Science 1983



Additional data support a role for toxics and mitochondria



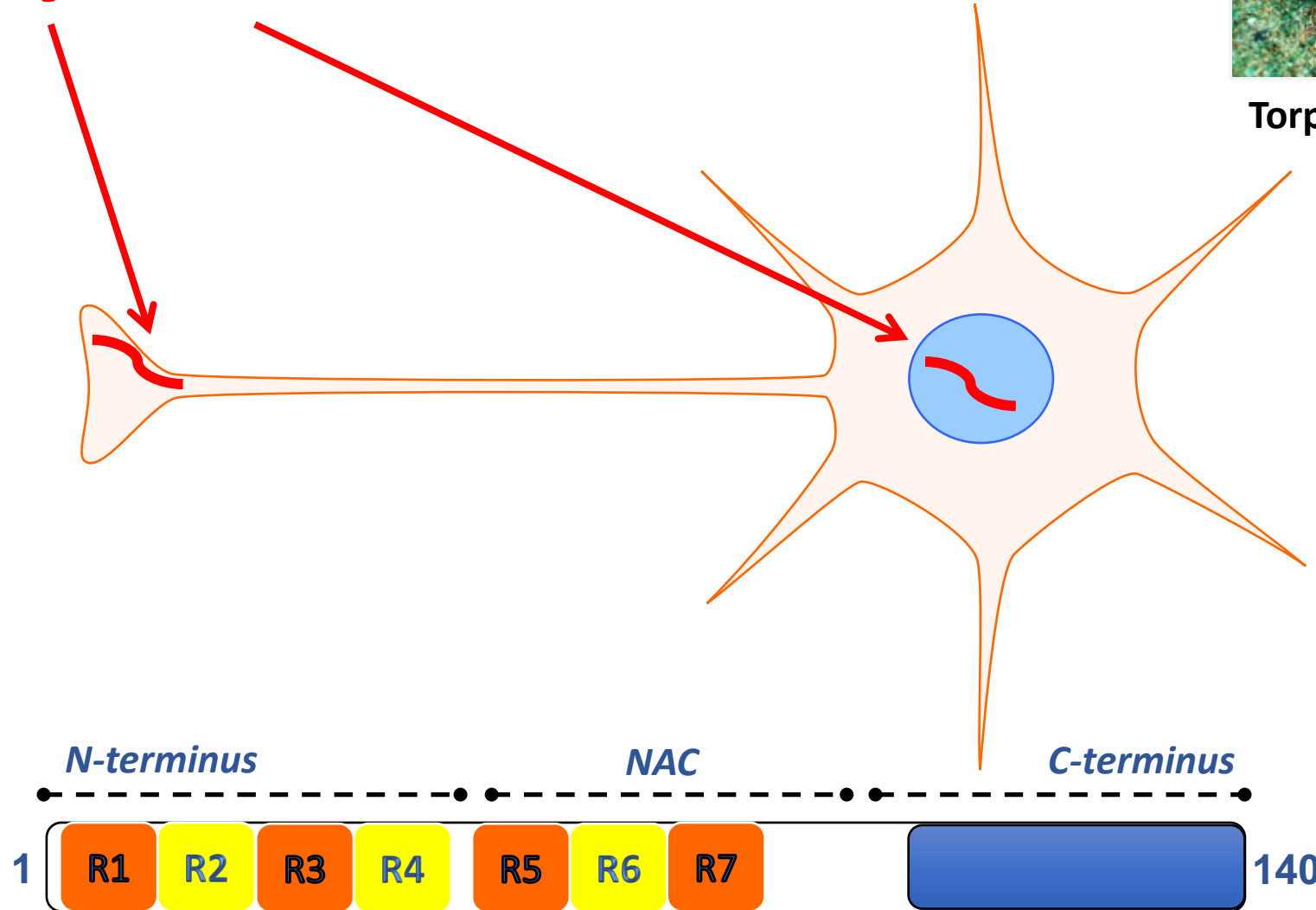
PD in the 90's

- Systemic and multifaceted disorder
- Genetic contribution
- Role of alpha-synuclein

Alpha-**syn**nuclein: 1988

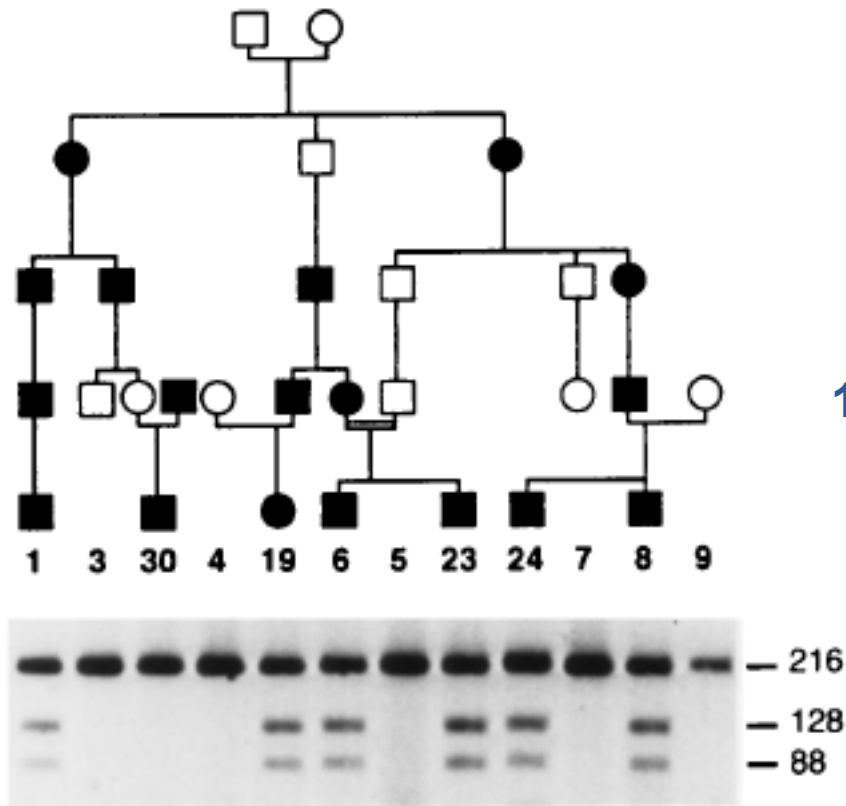


Torpedo californica



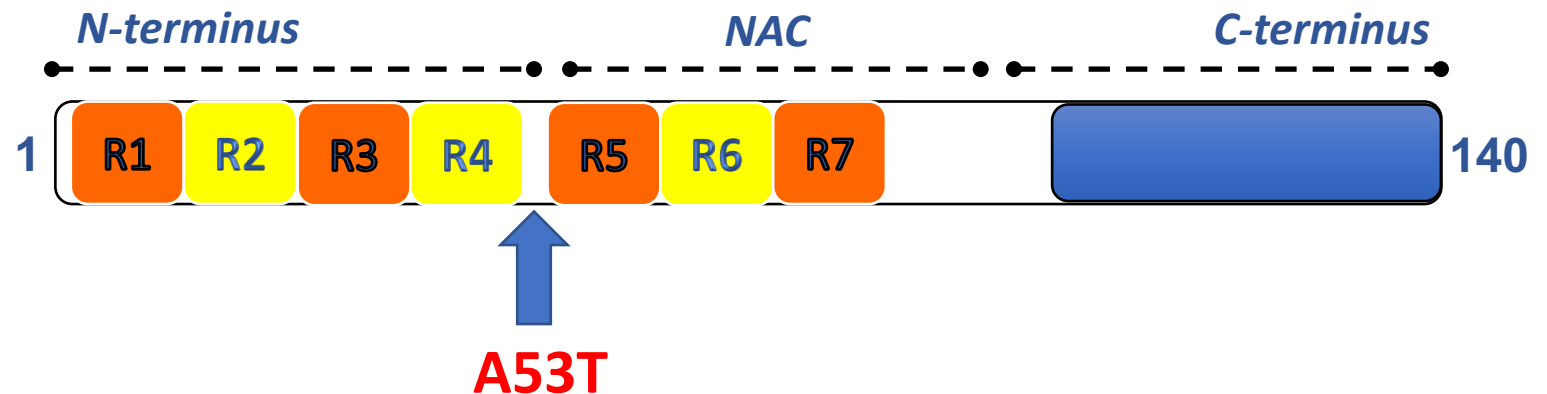
Maroteaux et al., J Neurosci. 1988

Alpha-synuclein: 1997, first gene with mutations reported to cause autosomal-dominant PD



Tsp45I PCR digestion products
G209A mutation

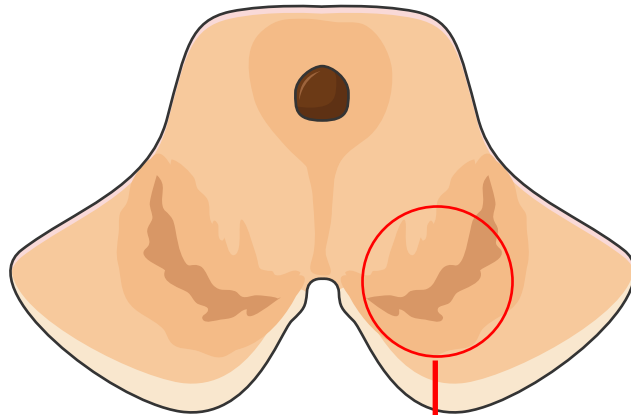
Mutation in the α -Synuclein Gene Identified in Families with Parkinson's Disease



Polymeropoulos et al., Science 1997

1997: alpha-synuclein, one main component of Lewy bodies

Before 1997



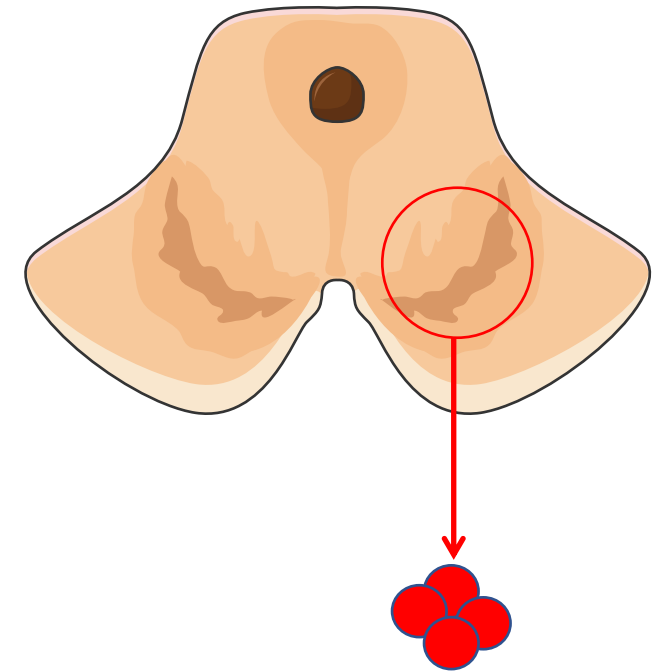
More than 100 hundred components identified but no definite marker

Spillantini et al., Nature 1997
Fujiwara et al., Nat Cell Biol 2002

6 PD and 4 DLB cases
sporadic



Alpha-synuclein IHC



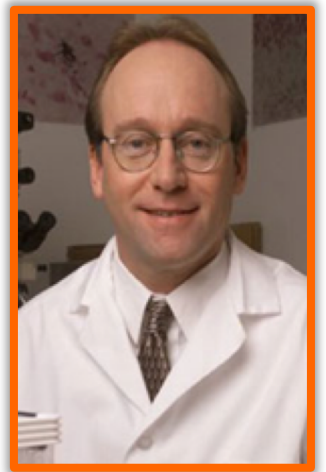
Phosphorylated aggregated
alpha-synuclein

Alpha-synuclein from 1997

- **1. Alpha-synuclein immunostaining became the method of choice for the detection of Lewy bodies and neurites. Reappraisal of Lewy pathology in PD**
- **2. Better understanding of the cellular biology and biochemical properties of alpha-synuclein**

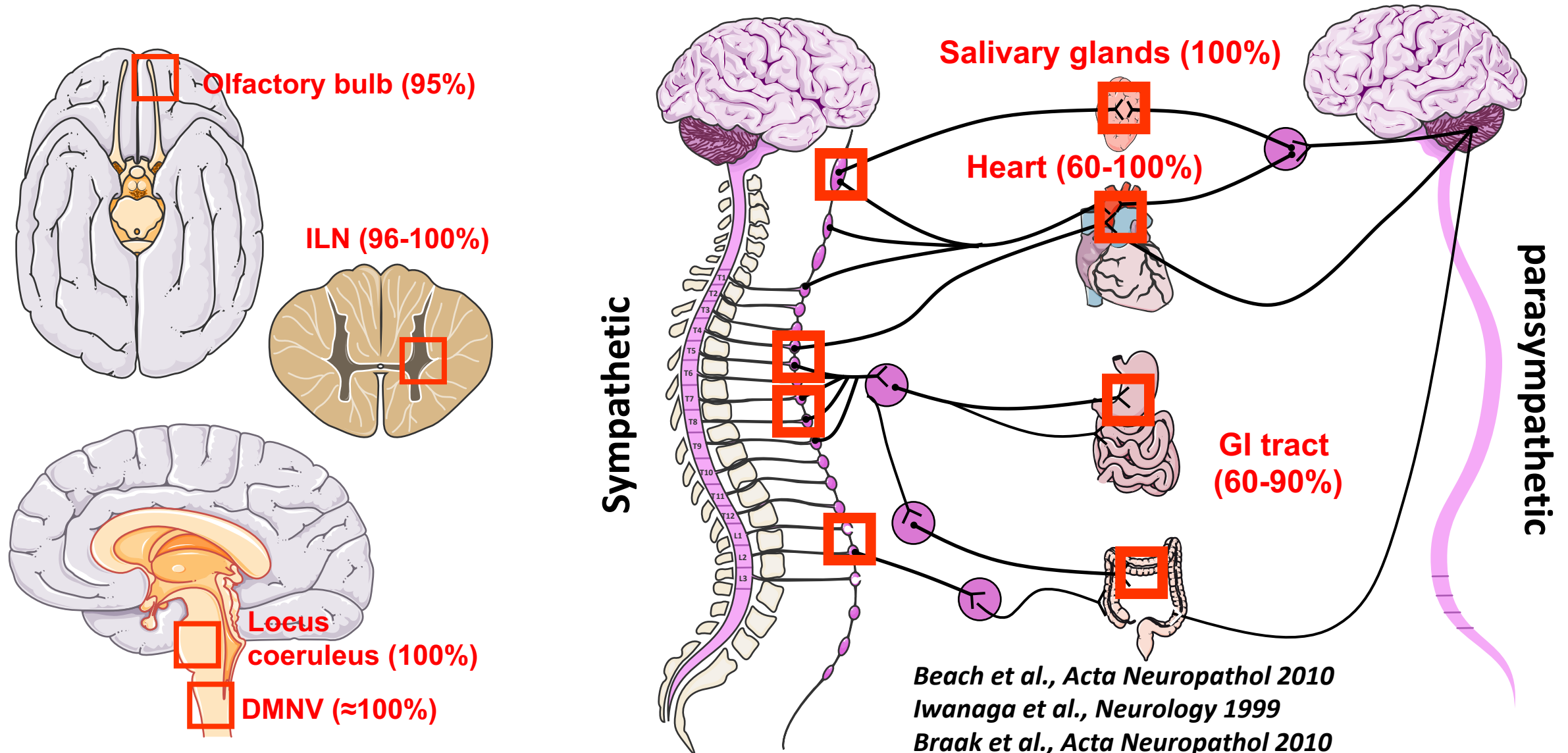


Heiko Braak



Thomas Beach

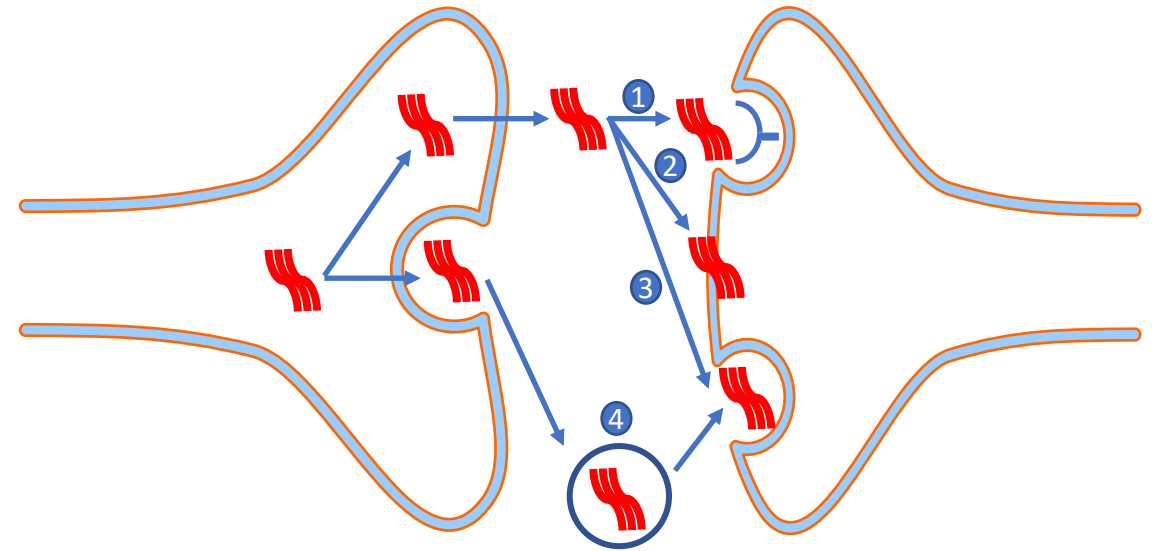
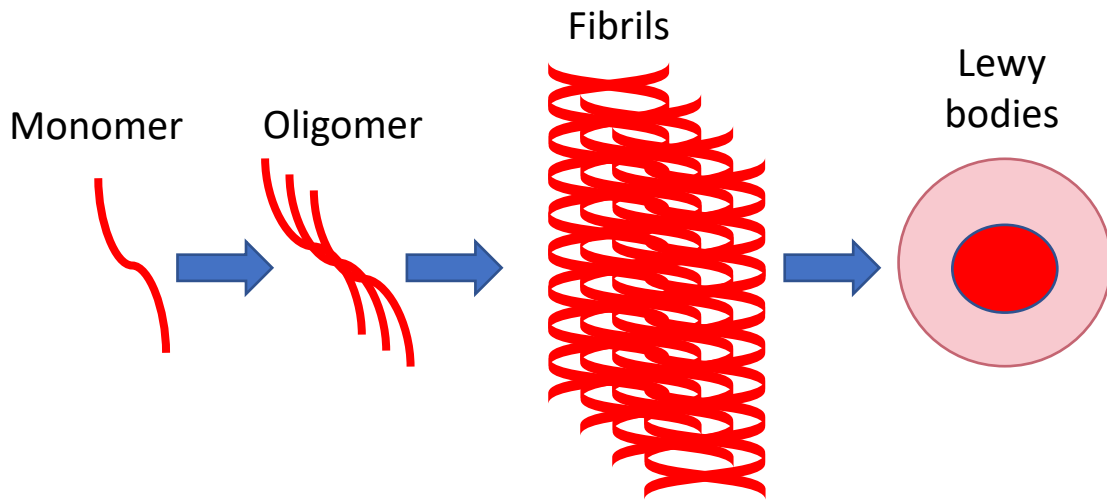
Lewy pathology extends well beyond the *substantia nigra*



Extranigral lesions are likely to manifest as non-motor symptoms

Region	Clinical symptoms
Autonomic nervous system Sympathetic ganglia ENS	Orthostasis (35%) GI symptoms (60%)
Olfactory system	Hyposmia (70%)
Medulla Dorsal motor nucleus vagus	GI symptoms (70%)
Pons Locus ceruleus Locus subceruleus	Depression REM Sleep behavior (60%)
Midbrain, substantia nigra	Motor symptoms
Subcortical structures	Dementia? (30-80%)
Neocortex	Dementia? (30-80%)

Alpha-synuclein, a natural propensity to aggregate and spread



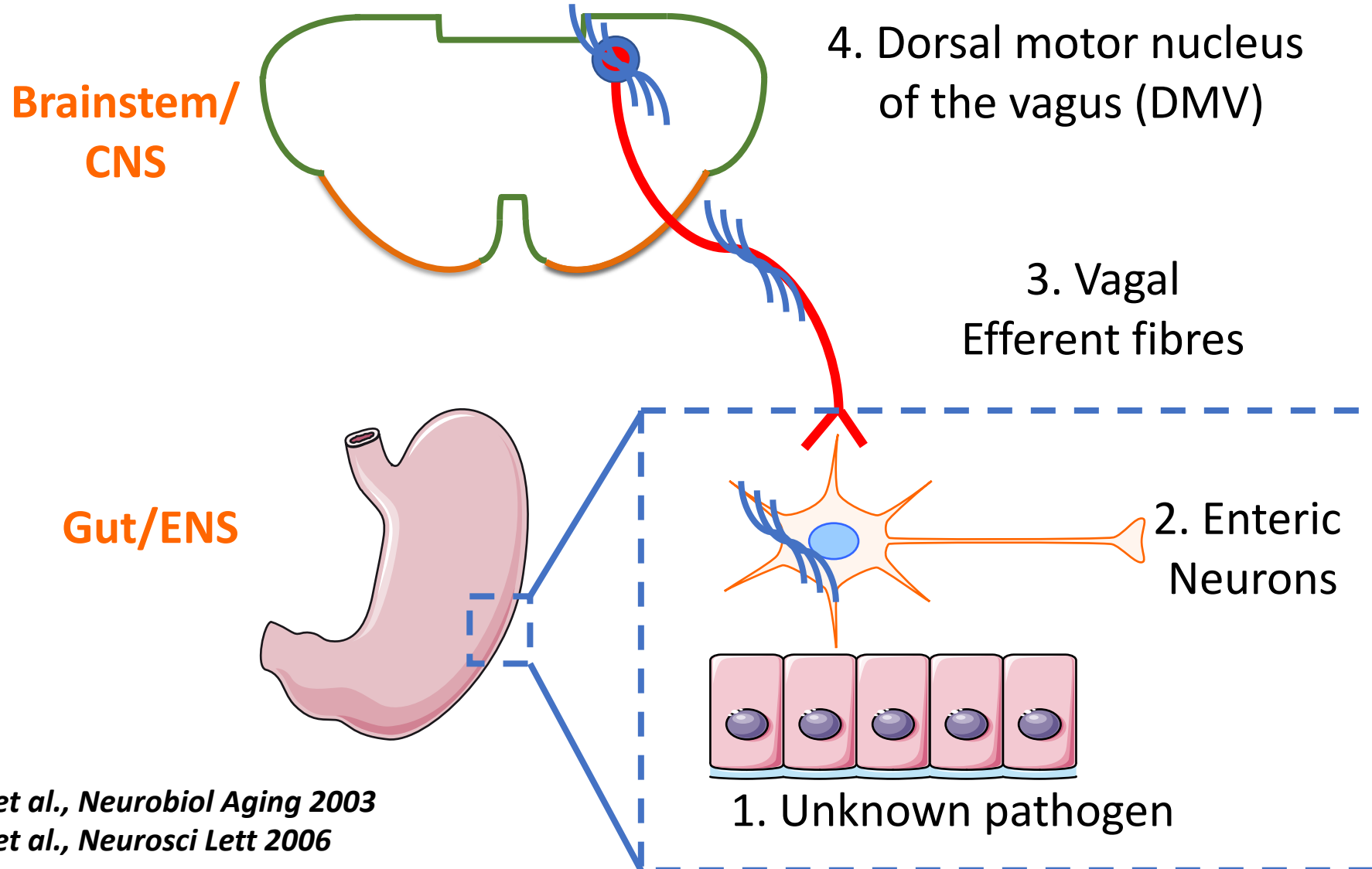
Prion-like hypothesis

Lee et al., J Neurosci 2005

Emmanouilidou et al., J Neurosci 2010

Hansen et al., JCI 2011

2003-2006: PD initiates in the gut and synuclein could be the culprit, Braak's hypothesis

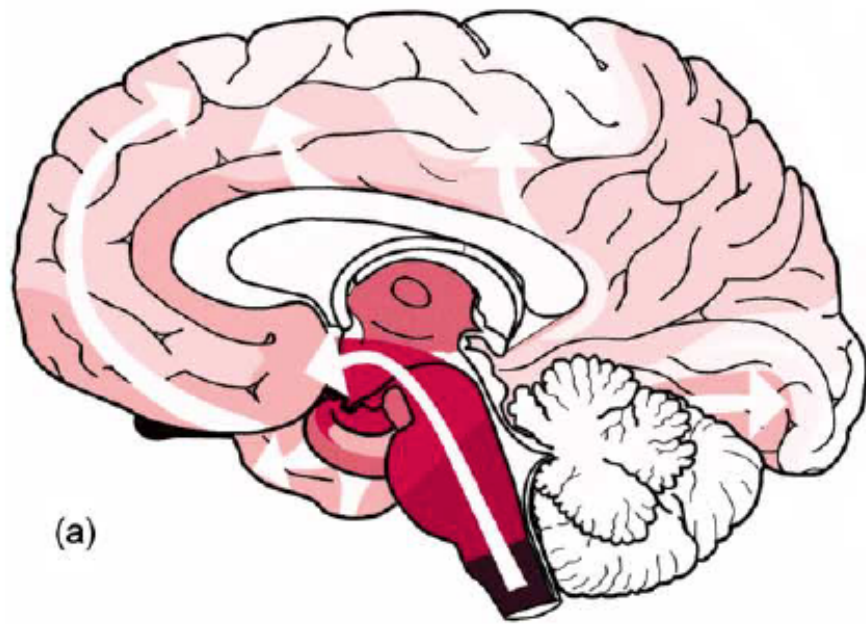


Braak et al., Neurobiol Aging 2003
Braak et al., Neurosci Lett 2006

Current trends in PD:

- 1. Gut and alpha-synuclein, not that simple...**
- 2. The disease starts earlier than originally thought**
- 3. More genes, back to mitochondria**

Braak's hypothesis, not that simple...

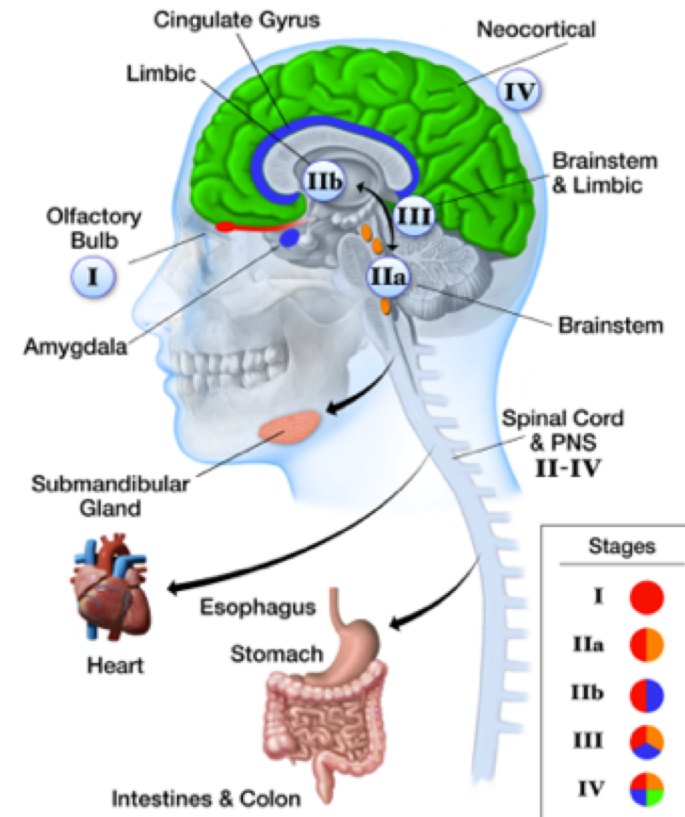


Braak

Braak et al., Neurobiol Aging 2003

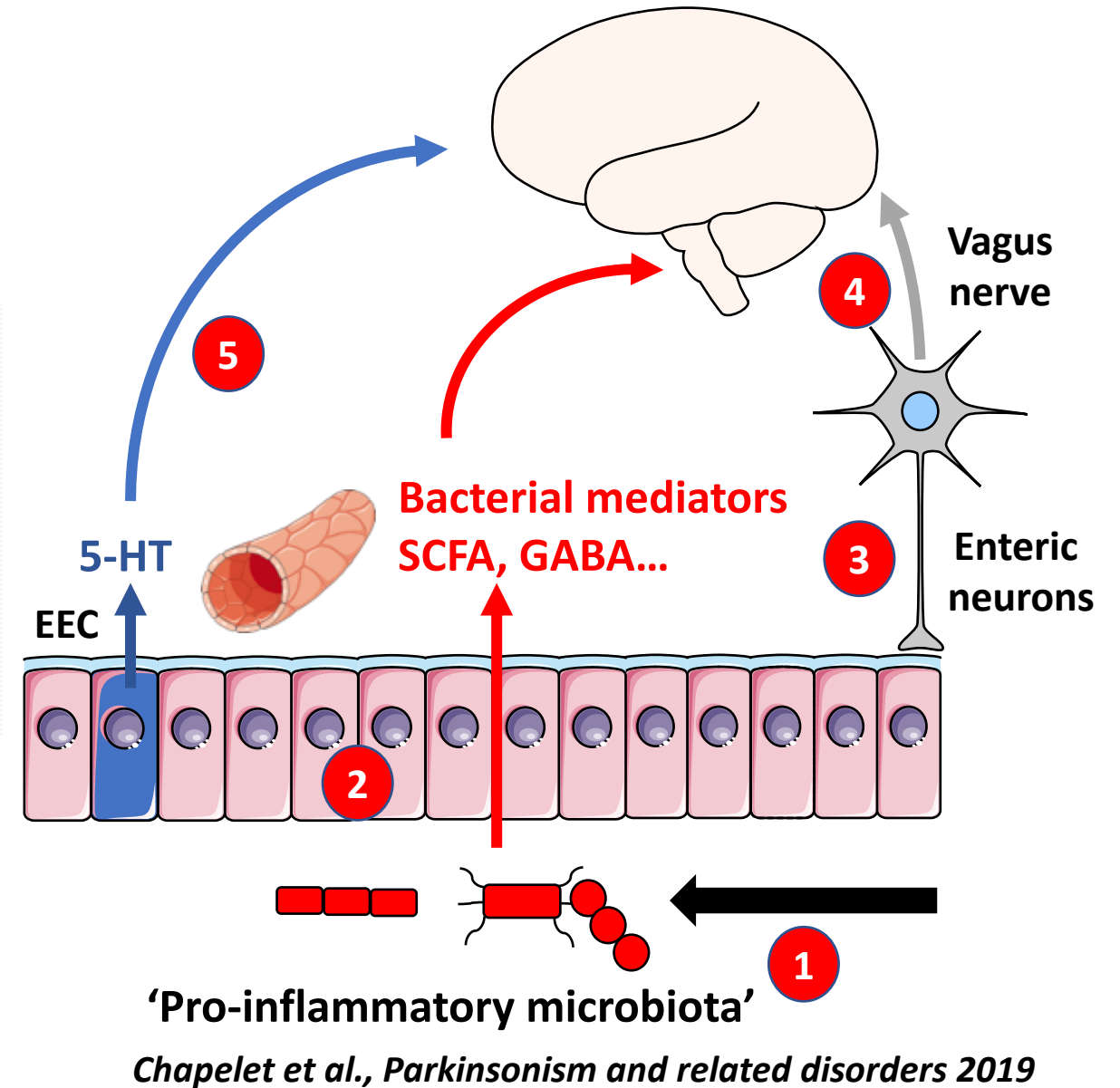
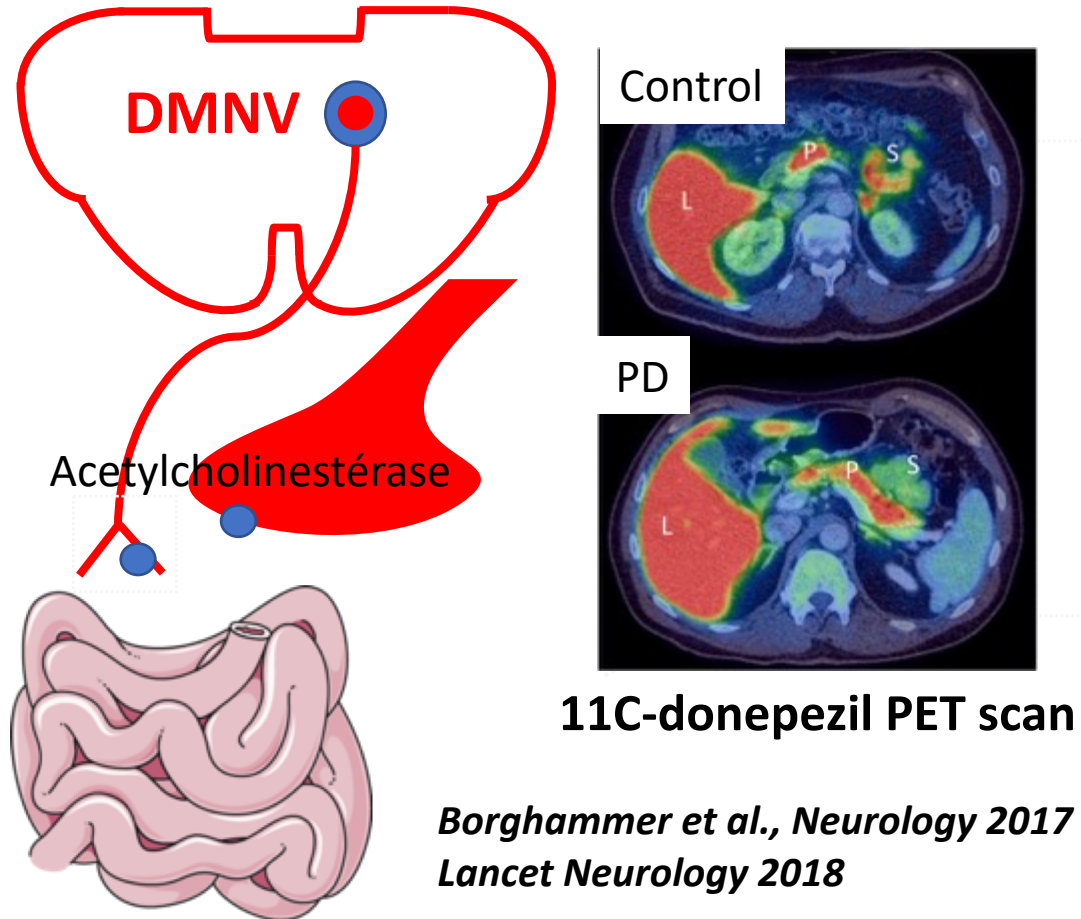
Adler and Beach, Movement Disorders 2016

Unified Staging System for Lewy Body Disorders



Beach

The gut might be involved, a bit more complicated than initially thought...



Alpha-synuclein, not that simple

The Journal of Neuroscience, October 11, 2017 • 37(41):9799–9807 • 9799

Dual Perspectives

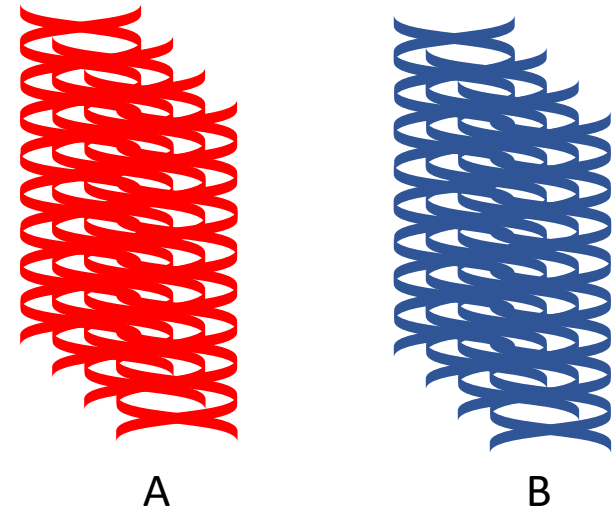
Dual Perspectives Companion Paper: Prying into the Prion Hypothesis for Parkinson's Disease, by Patrik Brundin and Ronald Melki

Parkinson's Disease Is Not Simply a Prion Disorder

D. James Surmeier,¹ José A. Obeso,^{2,3} and Glenda M. Halliday^{4,5}

¹Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, ²CINAC, HM Puerta del Sur, Hospitales de Madrid, Mostoles and CEU-San Pablo University, 28938 Madrid, Spain, ³Network Center for Biomedical Research on Neurodegenerative Diseases, Instituto Carlos III, 28029 Madrid, Spain, ⁴Brain and Mind Centre, Sydney Medical School, University of Sydney, Sydney, 2006 New South Wales, Australia, and

⁵School of Medical Sciences, University of New South Wales and Neuroscience Research Australia, Sydney, 2052 New South Wales, Australia

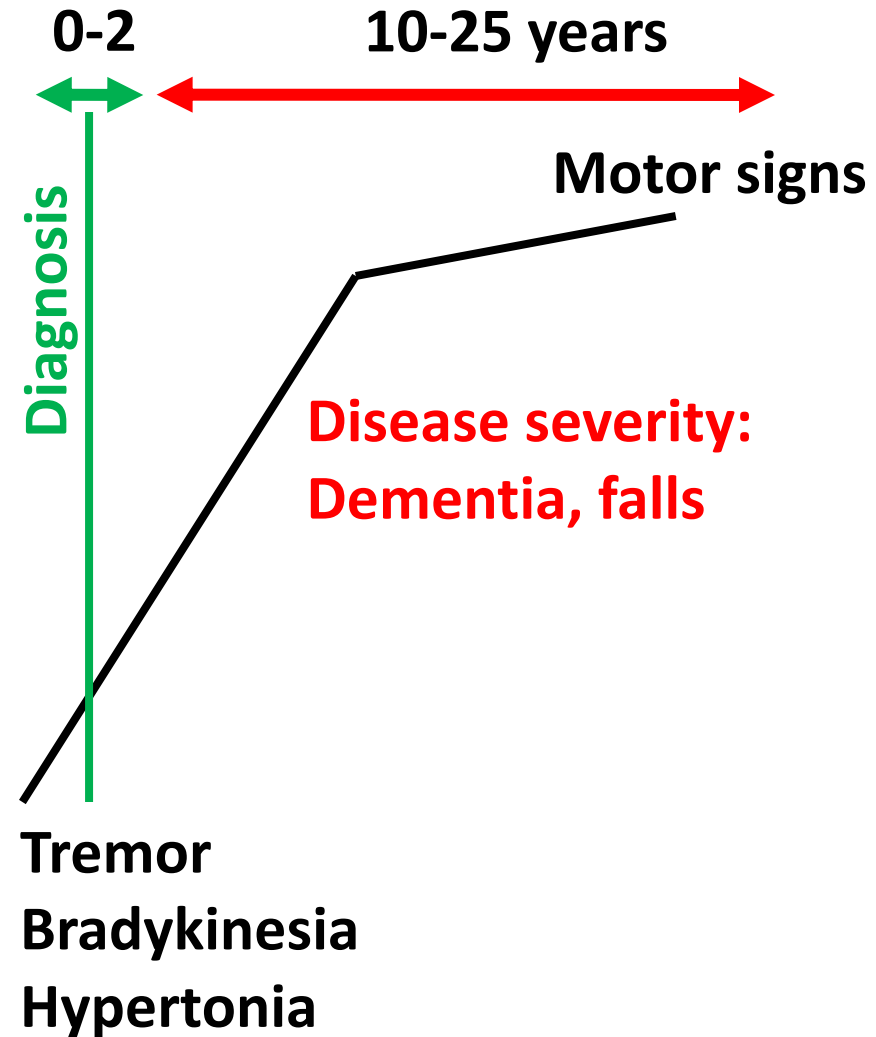


**Different strains or conformers
Different disease phenotypes**

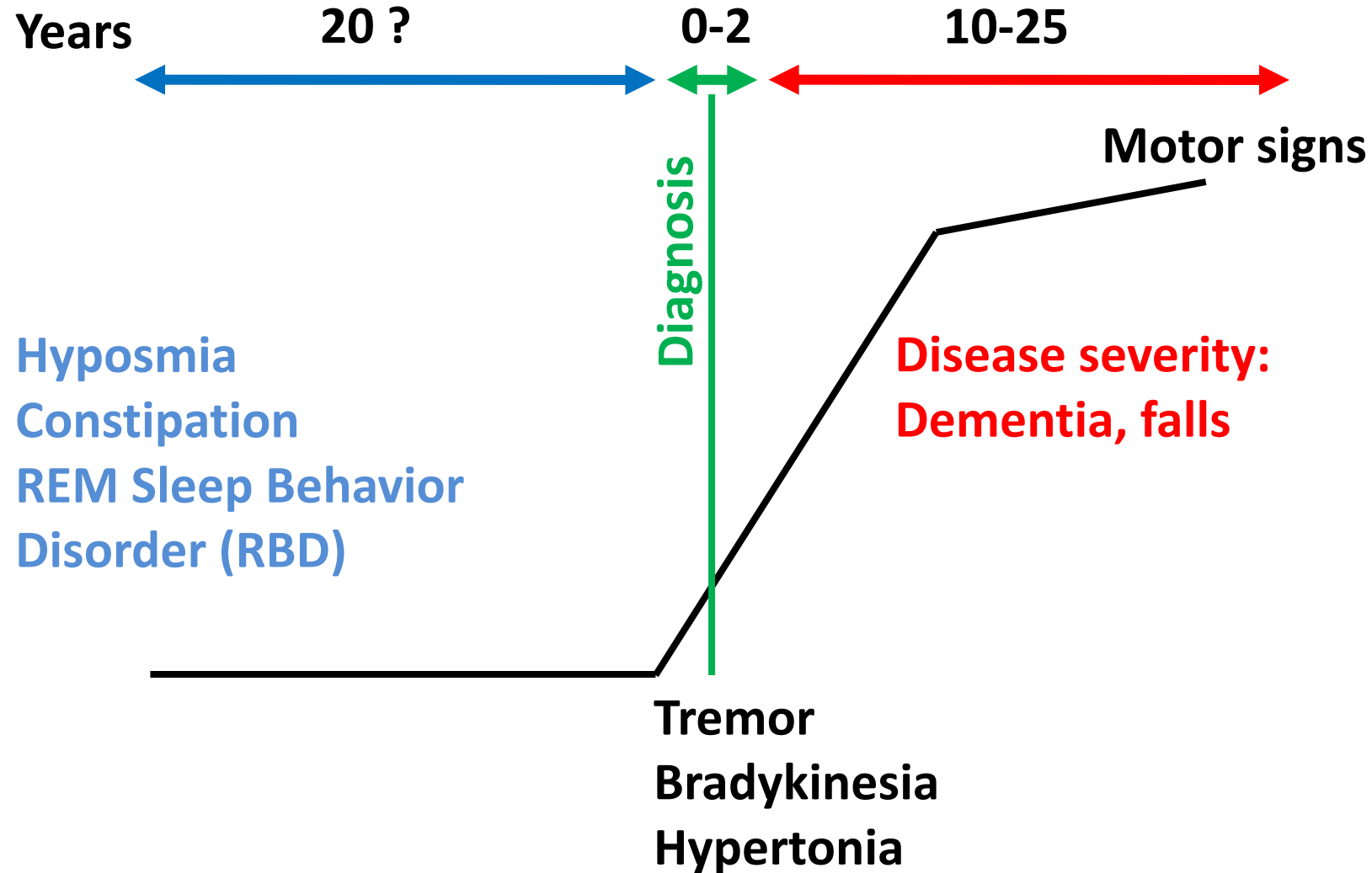
Peelaerts et al., Nature 2015

Van der Perren et al., Acta Neuropathol 2020

The classical view of PD



The actual view of PD



RBD antedates motor symptoms in PD

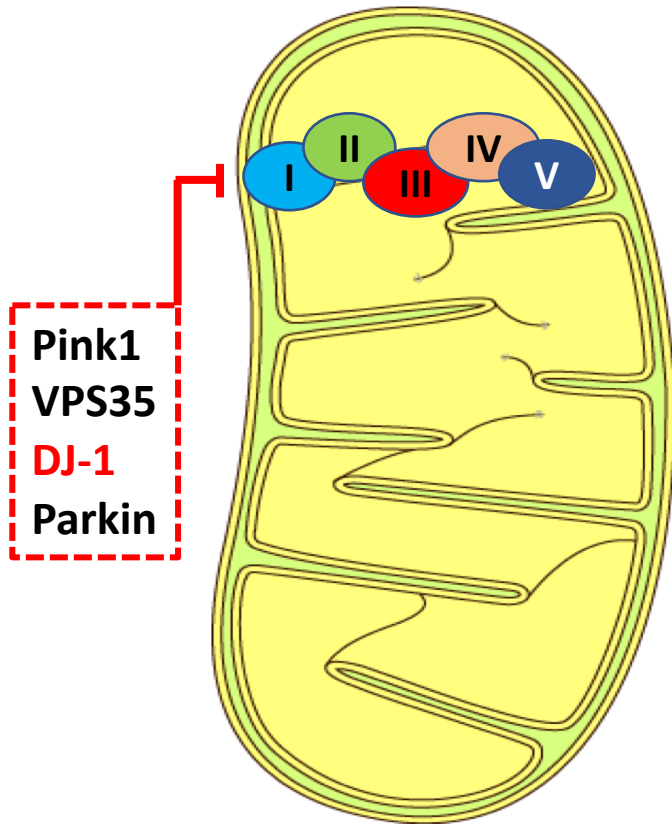
- Bed partner complaint
- Incomplete loss muscle tone during REM sleep
- Dream-enacting behaviors
 - Violent, kicking, fighting, shouting, crying...90%
 - Pleasant activity only 20%
 - Vocalizations, mumbling, speaking, singing
- Longitudinal series of patients with RBD showed that they have a later conversion to synucleinopathy and especially PD
- Median time between RBD and motor symptoms of PD varies from 5 to 15 years

Iranzo et al., Lancet Neurol 2012

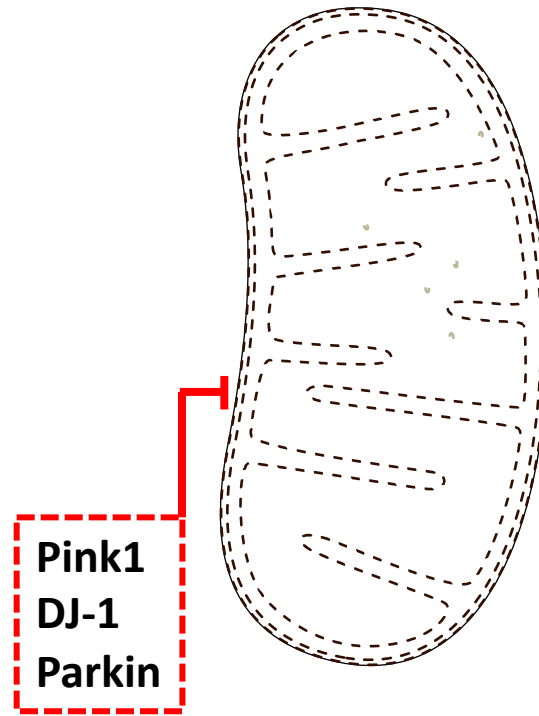
Schenck et al., Neurology 1996

More genes, mitochondria and the endosome/lysosome system

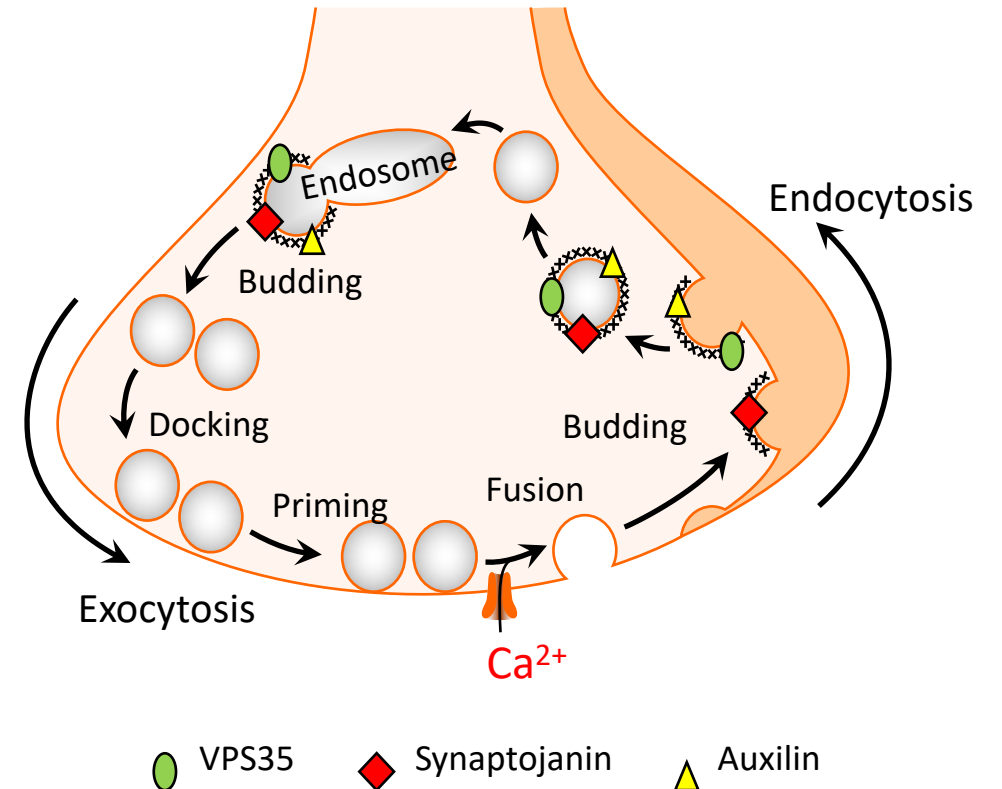
Electron transport chain



Mitophagy



Endosomal system



DJ-1: new role in carbohydrate metabolite, Heremans...Bommer, PNAS 2022

Conclusion and perspectives

- Pathophysiology
 - More pieces of the jigsaw
 - Unable to draw a straightforward scenario
- Reasons for hope
 - Capable of detecting the disease earlier
 - RBD
 - New markers based on peripheral alpha-synuclein
 - New disease modifying therapies
 - Immunotherapies targeting alpha-synuclein (strains or conformers specific?)
 - Repurposing of antidiabetic drugs for a systemic anti-inflammatory effect