Recent Advances in the cause and treatment of Parkinson disease

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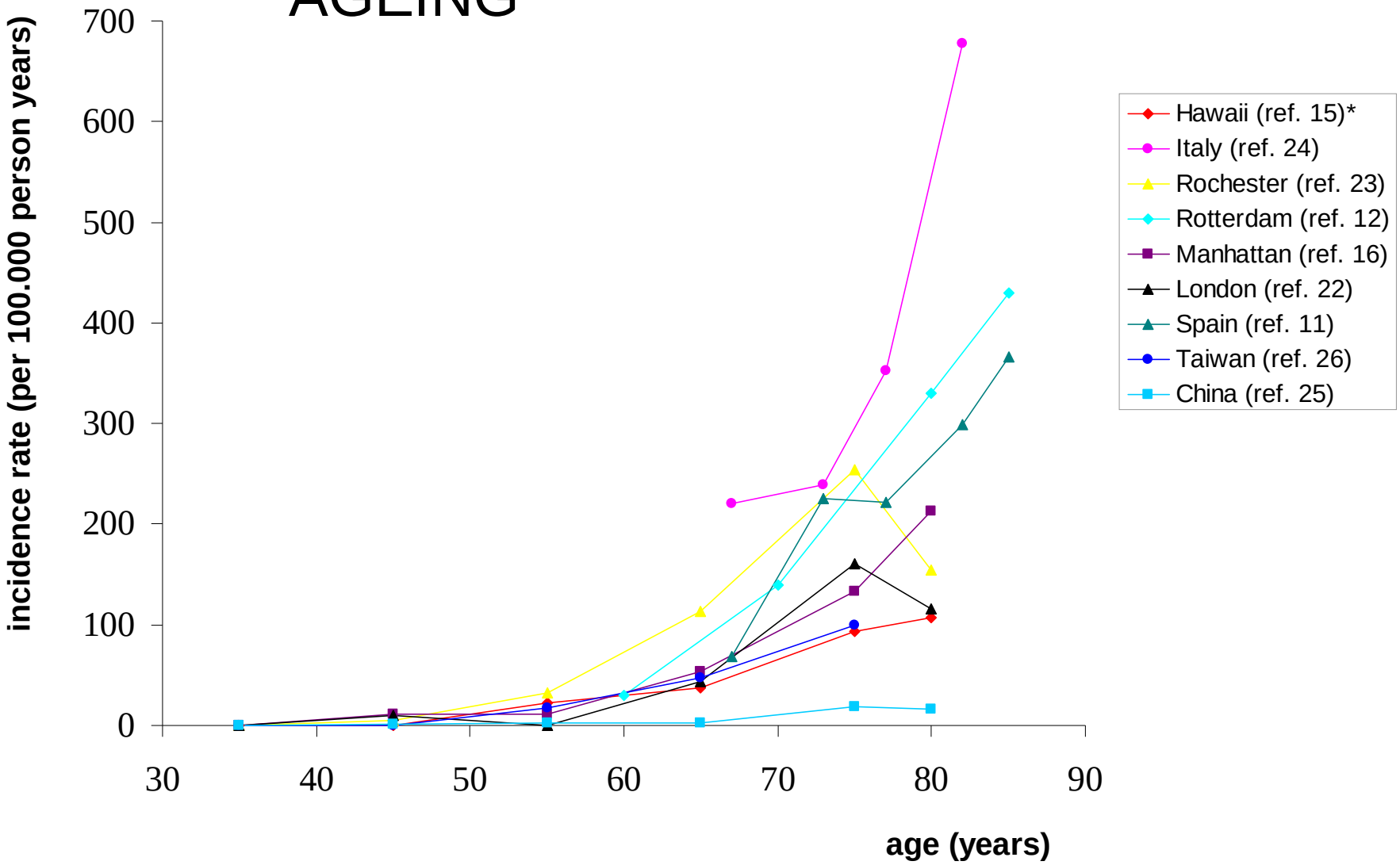
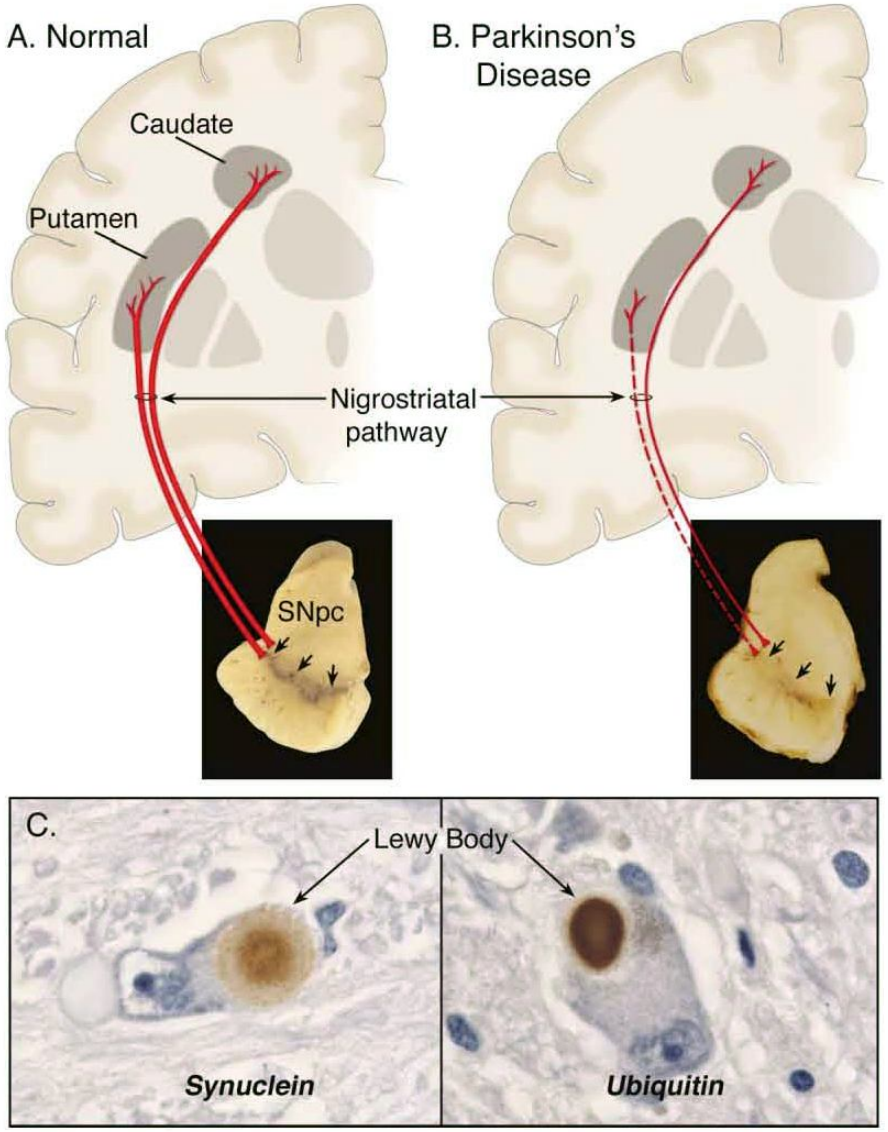
SOME BACKGROUND…

AGEING



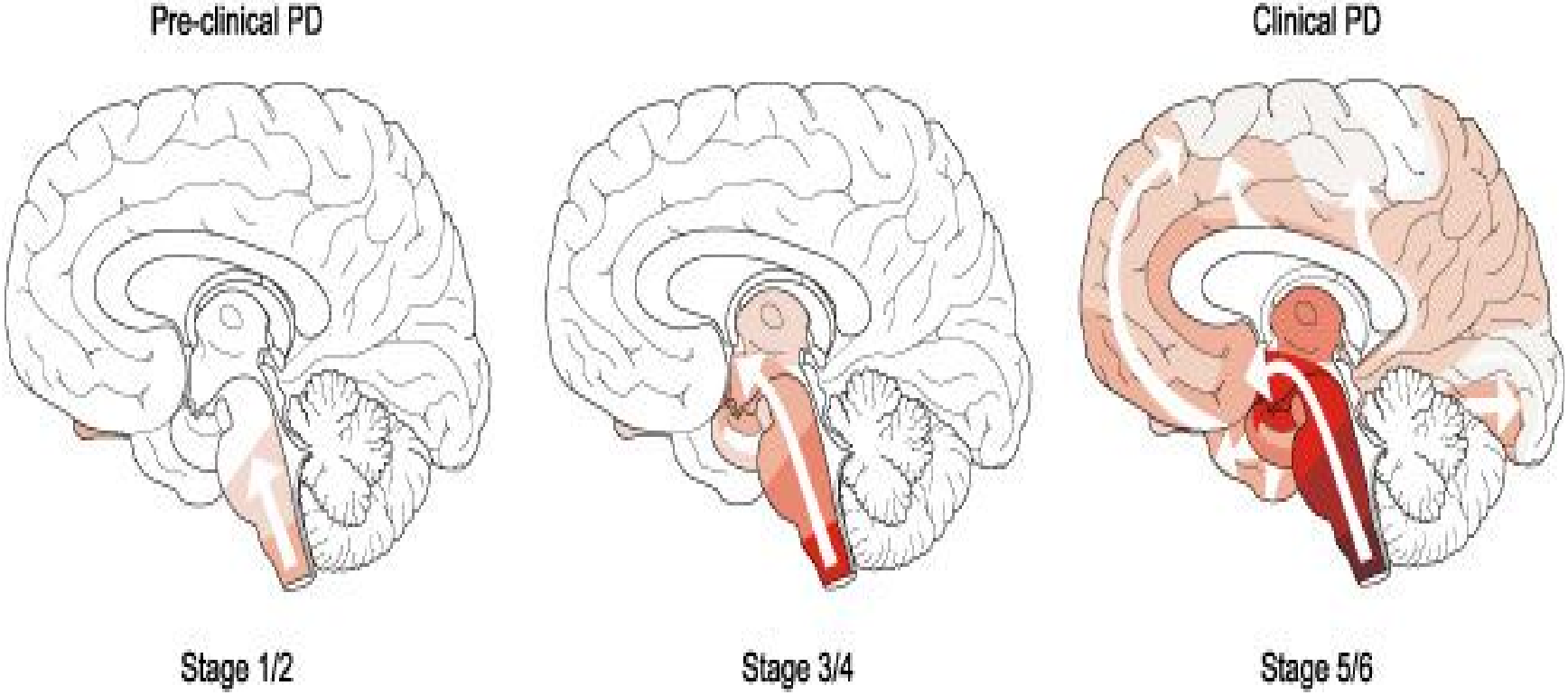
De Lau & Breteler Lancet Neurol 06

Pathological changes in PD



Disease Progression

Evolution of Lewy Body Pathology in PD



Aetiology

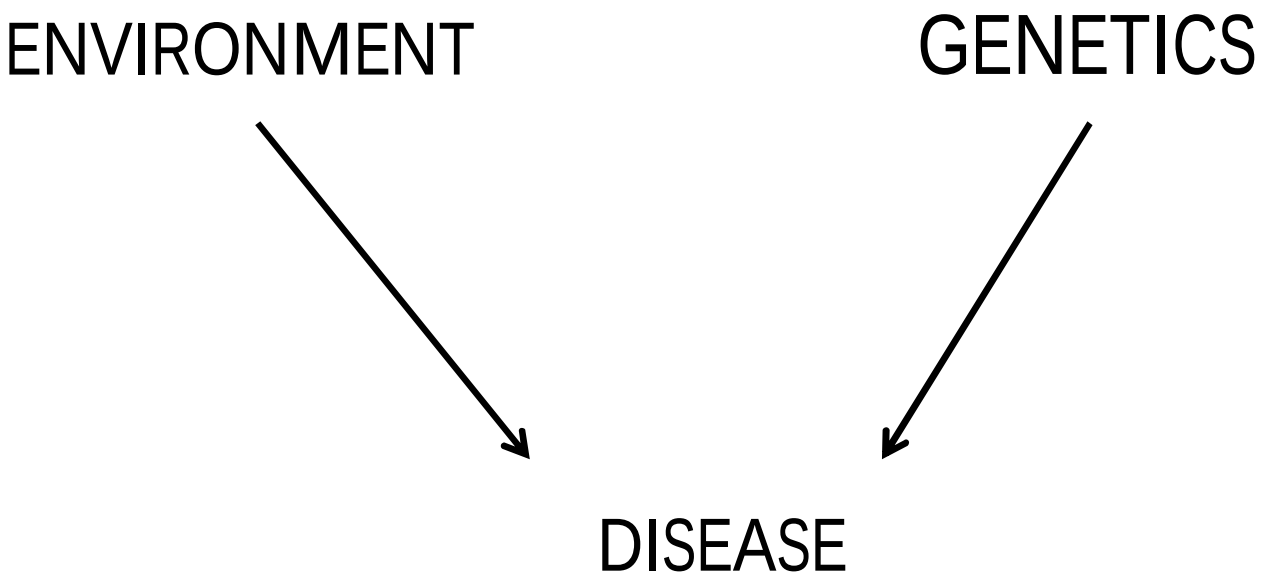
CAUSE - ENVIRONMENT

Environmental causes of PD

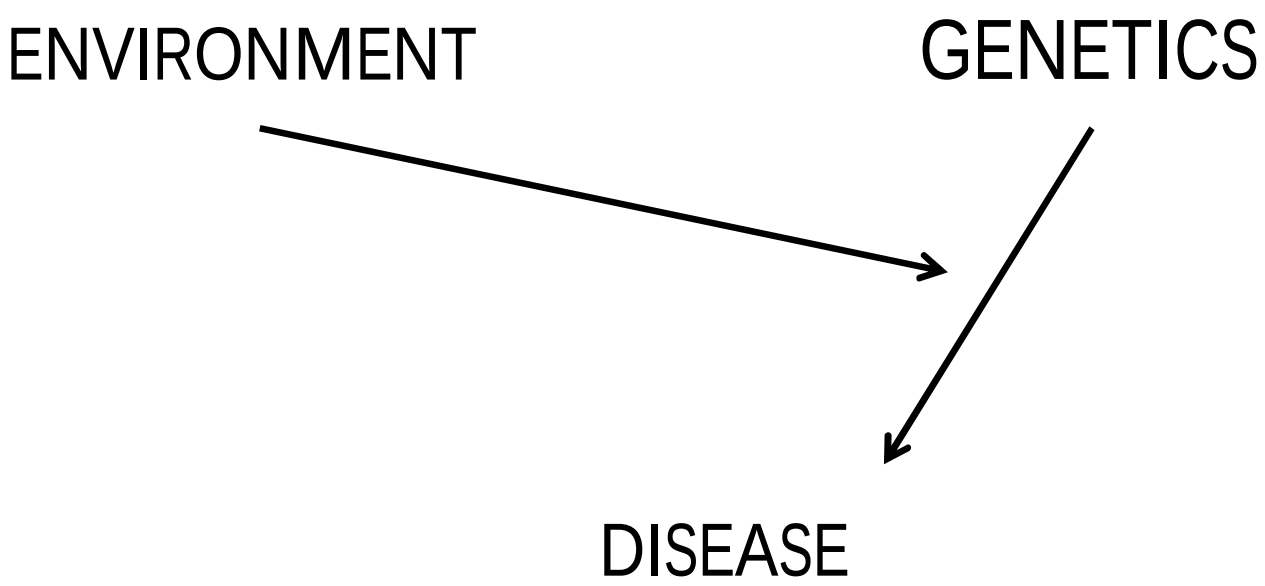
Modifying factors for PD risk

- Pesticides, herbicides, farming, rural living
- Solvent exposure
- Doctors, teachers
- Red hair
- Low vitamin D
- Smoking
- Coffee
- NSAIDS
- Isradipine
- Black hair
- High urate

Environment & Genetics in disease



Environment & Genetics in disease



CAUSE - GENETICS

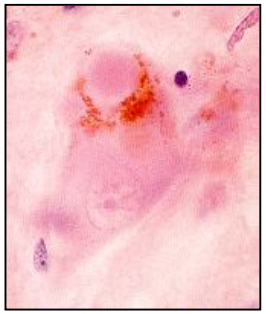
Genetic causes of PD

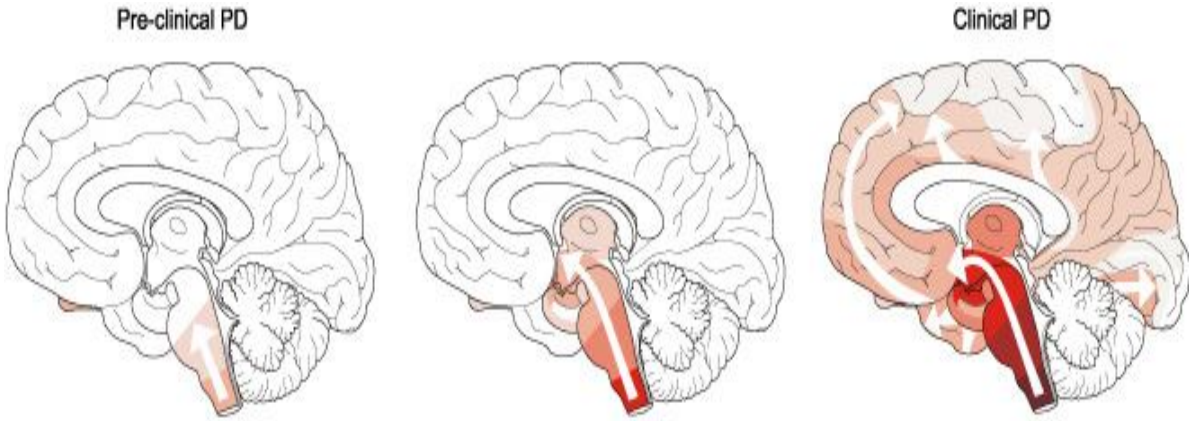
- GWAS – SNCA, tau, HLA-DR2, LRRK2
- Alpha-synuclein mutations – point, multiplications
- Parkin mutations
- DJ1 mutations
- PINK1 mutations
- LRRK2 mutations
- Others: HtrA2, UCHL1, ATP13A2, PLA2G6, GIGYF2
- Glucocerebrosidase: 7-20 fold increased risk

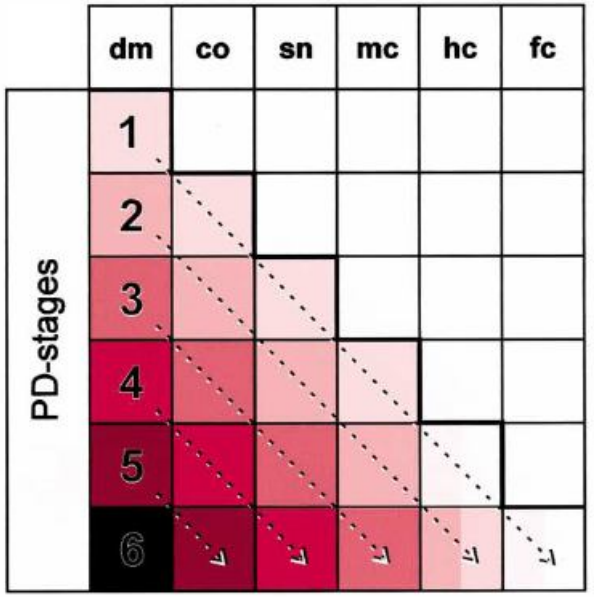
PD PATHOGENESIS

- Mitochondria
- Protein folding, aggregation, propagation
- Lysosomes

Braak hypothesis for spread of Lewy bodies

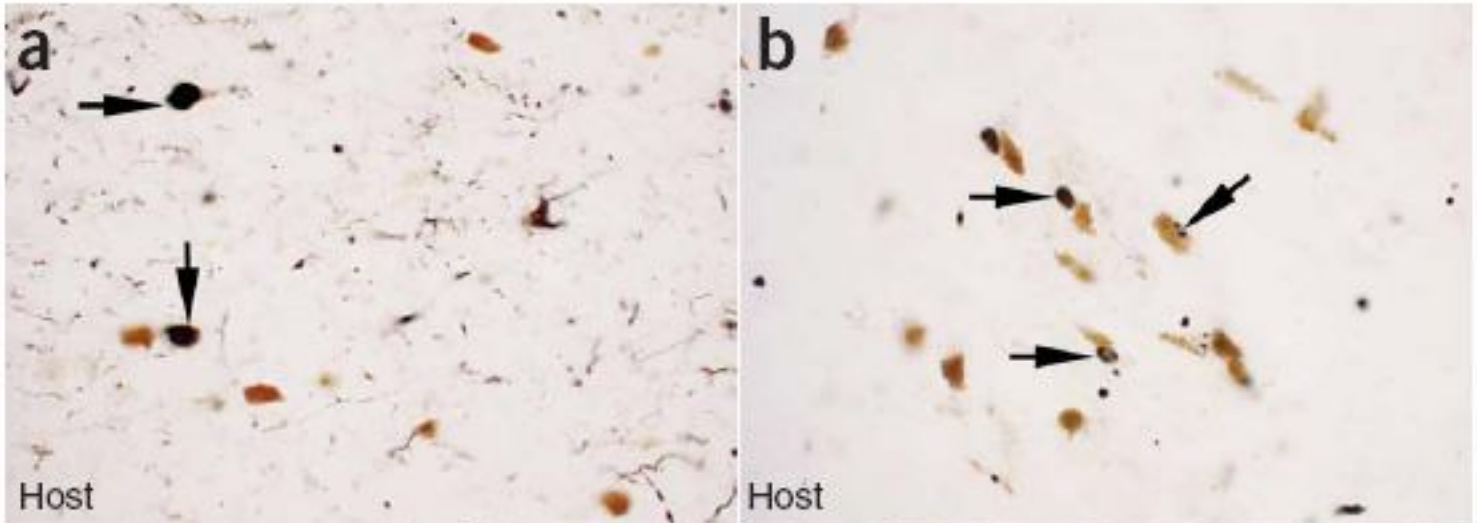






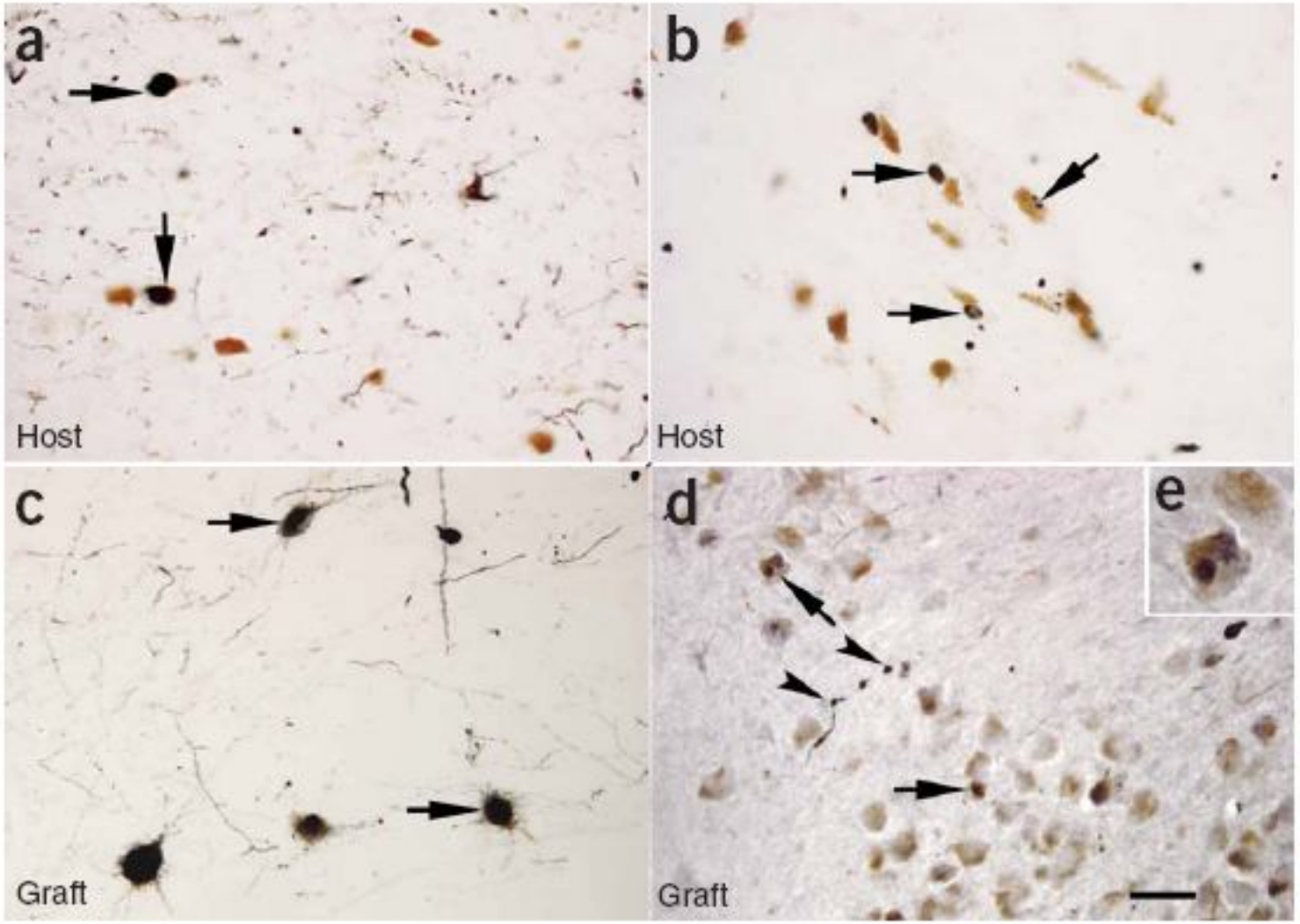
Braak et coll., 2003

Fetal graft cells develop PD pathology



Kordower et al Nat Med 2008

Fetal graft cells develop PD pathology



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PD PATHOGENESIS

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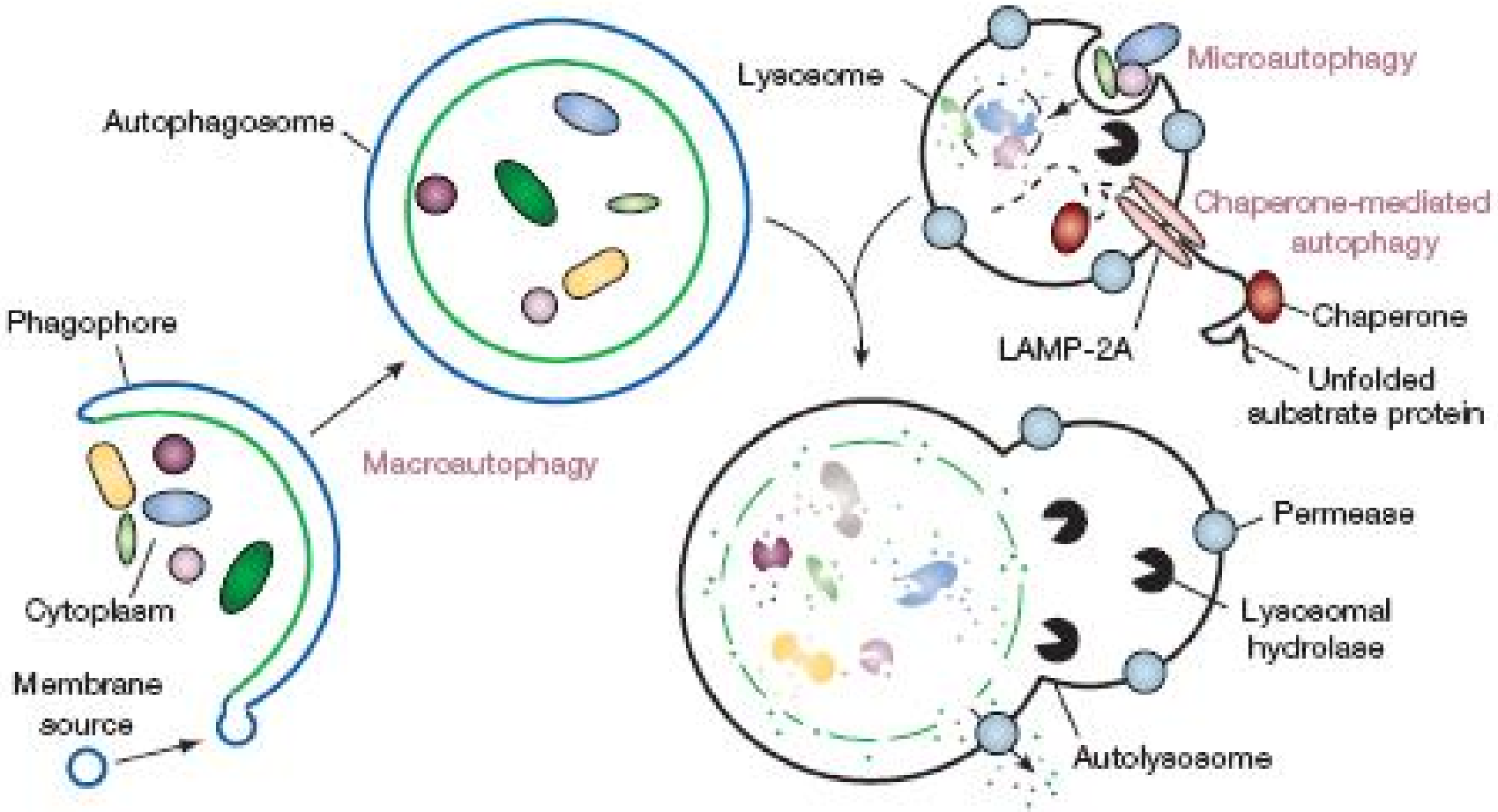
- Lysosomes


Autophagosome
Phagophore
Cytoplasm
Membrane source
Macroautophagy
Lysosome
Microautophagy
Chaperone-mediated autophagy
Chaperone
LAMP-2A
Unfolded substrate protein
Permease
Lysosomal hydrolase
Autolysosome

Glucocerebrosidase

- AuR, >300 mutations, ↓GBA activity
- Gaucher disease, lysosomal enzyme
- Commonest in Ashkenazi Jews
- Typical PD, mean age onset 55y, FH in 24%*
- Lewy body positive: 4.5 fold increase in GBA mutations in LB-PD in QS PDBB (Neumann Brain 2009)
- Lifetime risk for PD in GD patients ~20x (Bultron J Inh Met Dis 2010)

GCase in PD Brain

- 58%* ↓ GCase in GBA mutation positive SNc
- 48%* ↓ GCase in GBA mutation positive striatum

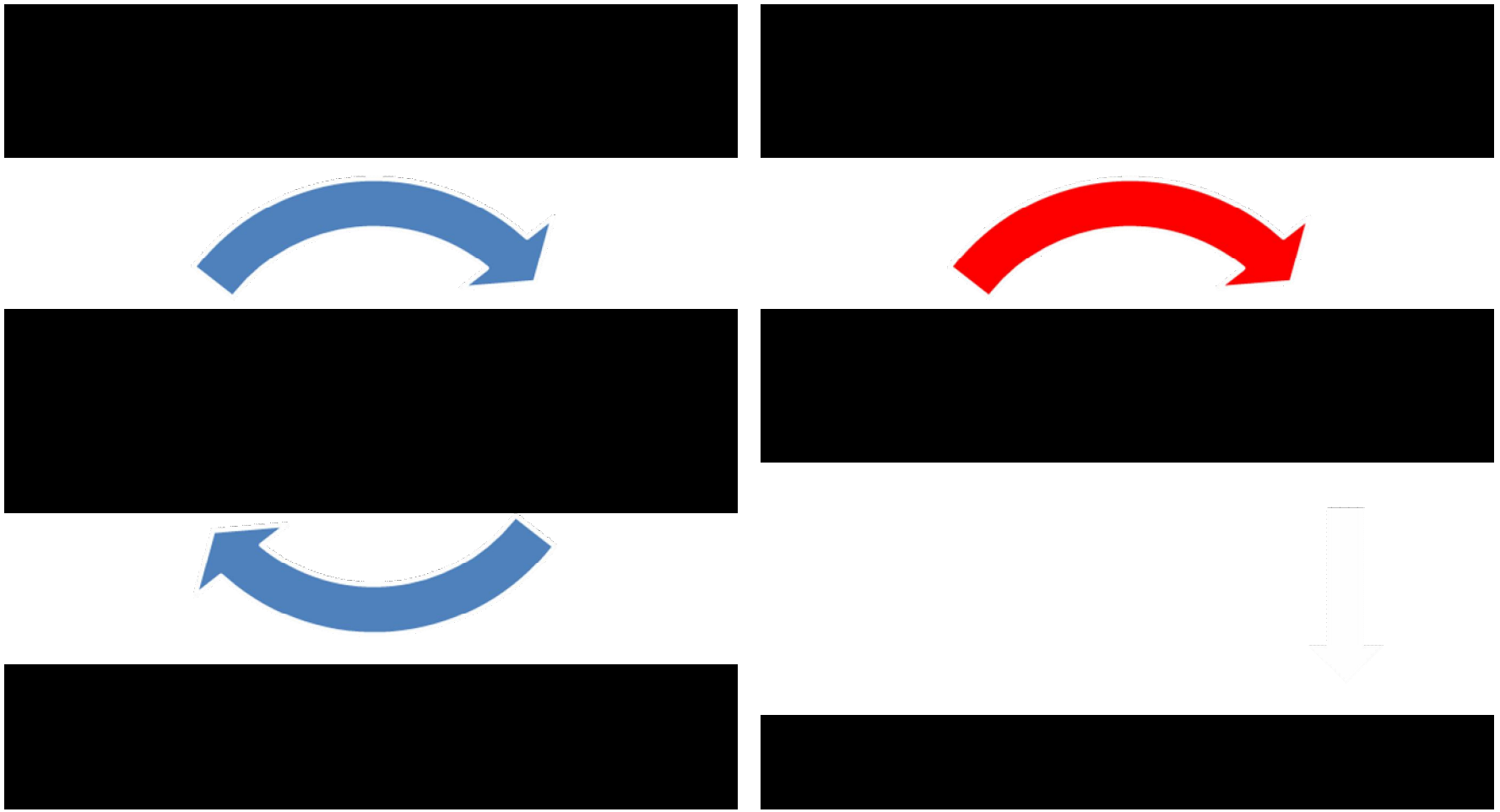
*p<0.01

GCase in PD Brain

- 58%* ↓ GCase in GBA mutation positive SNc
- 48%* ↓ GCase in GBA mutation positive striatum
- 33%* ↓ GCase in GBA mutation negative sporadic PD SNc

*p<0.01

The GCase - alpha-synuclein connection



Schapira Lancet 2014

Symptomatic treatments for Parkinson disease

Drug treatment of Parkinson's disease

- L-dopa
- Decarboxylase inhibitors – carbidopa, benserazide

- MAO-B inhibitors – selegiline, rasagiline
- COMT inhibitors – entacapone, tolcapone
- Combination forms – Stalevo
- Controlled release – Sinemet CR
- Dispersible – Madopar dispersible
- Liquid formulations – L-dopa methyl ester

- Intraduodenal administration - DuoDopa

- Ropinirole
- Pramipexole

- Pergolide
- Bromocriptine
- Cabergoline

- Extended release – Requip XL
- Transdermal administration – NeuPro

- Subcutaneous infusion - apomorphine

Safinamide

- Reversible MAOB inhibitor
- May have Na-channel, anti-glutamatergic activity
- Once daily 50-100mg
- Adjunct to levodopa (+) or dopamine agonist
- Reduces OFF-time, improves ON-time without increasing troublesome dyskinesia.

Non-dopaminergic approaches to the treatment of Parkinson's disease

- Motor symptoms – amantadine, anticholinergics
- Dementia – cholinesterase inhibitors
- Psychosis – atypical antipsychotics
- Neuropsychiatric – anxiolytics, antidepressants
- Somnolence – modafinil
- Autonomic signs – mineralocorticosteroids, oxybutynin

Neuroprotection

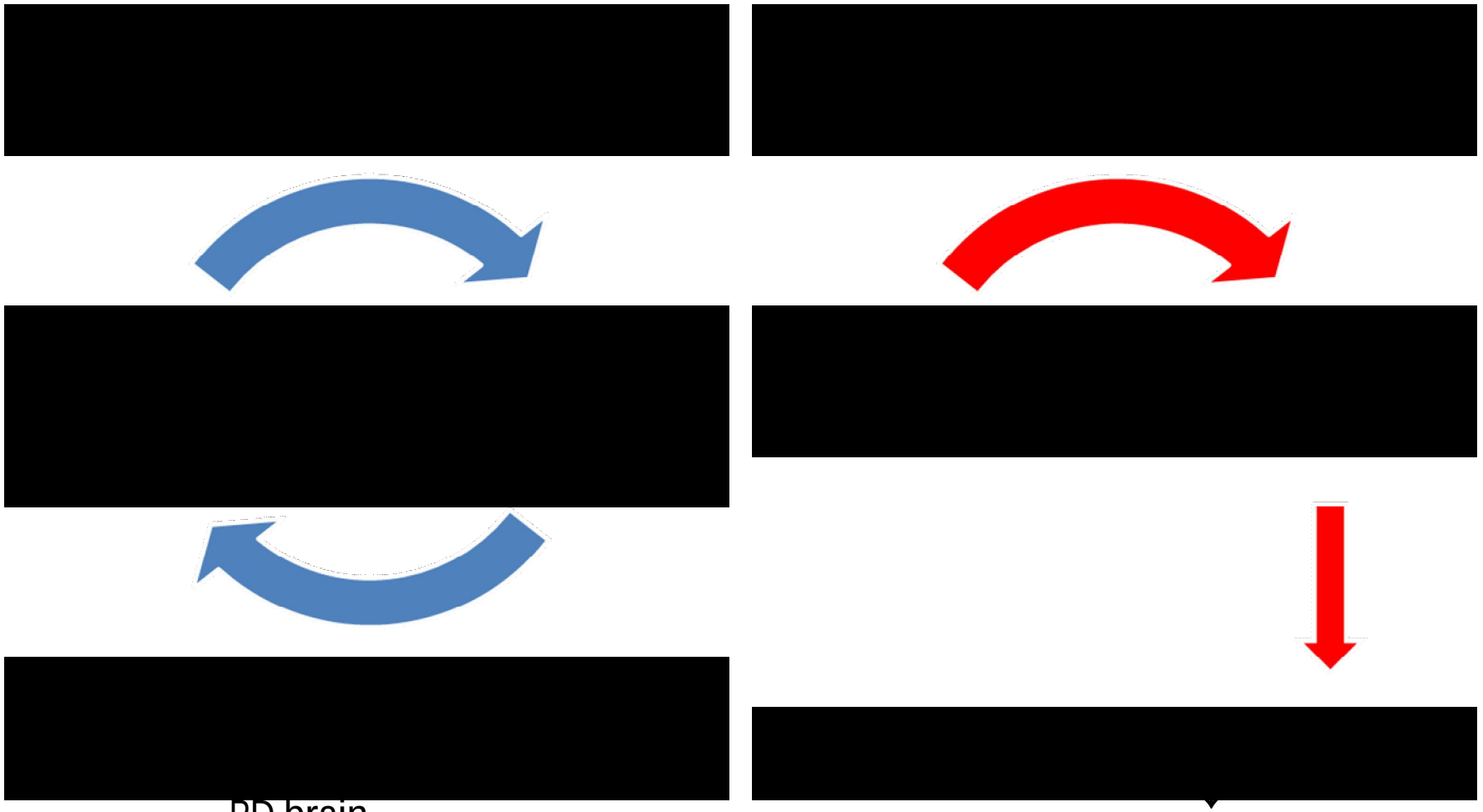
Slowing the course of Parkinson disease

Potential therapeutic targets

- Mitochondria: CoQ +/- vit E, creatine, PGC-1α, rasagiline, exenetide
- Anti-oxidants: Fe-chelators, inosine
- LRRK2 kinase inhibitors
- Growth factor stimulants: GDNF, BDNF
- Autophagy/mitophagy stimulants: rapamycin
- Protein disaggregation
- Calcium channel modulators: isradipine
- SNCA modulators
- GBA enhancers – chaperones

Schapira Lancet 2014

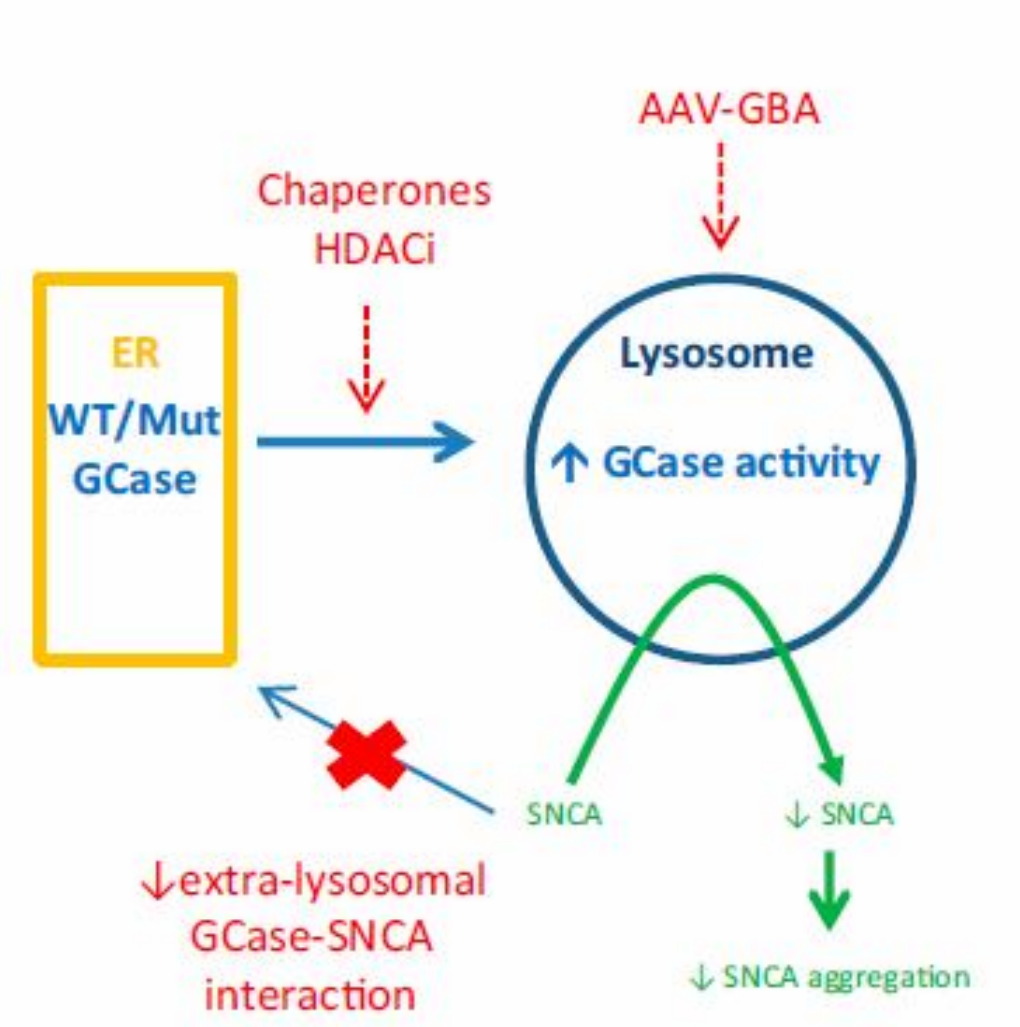
The GCase - alpha-synuclein connection



PD brain

Schapira Lancet 2014

GCase-alpha-synuclein as a target for PD



Schapira & Gegg PNAS 2013

Hypothesis

- Increasing GCase activity will reduce SNCA levels and slow the progression of PD
- This will be relevant to those with and without PD

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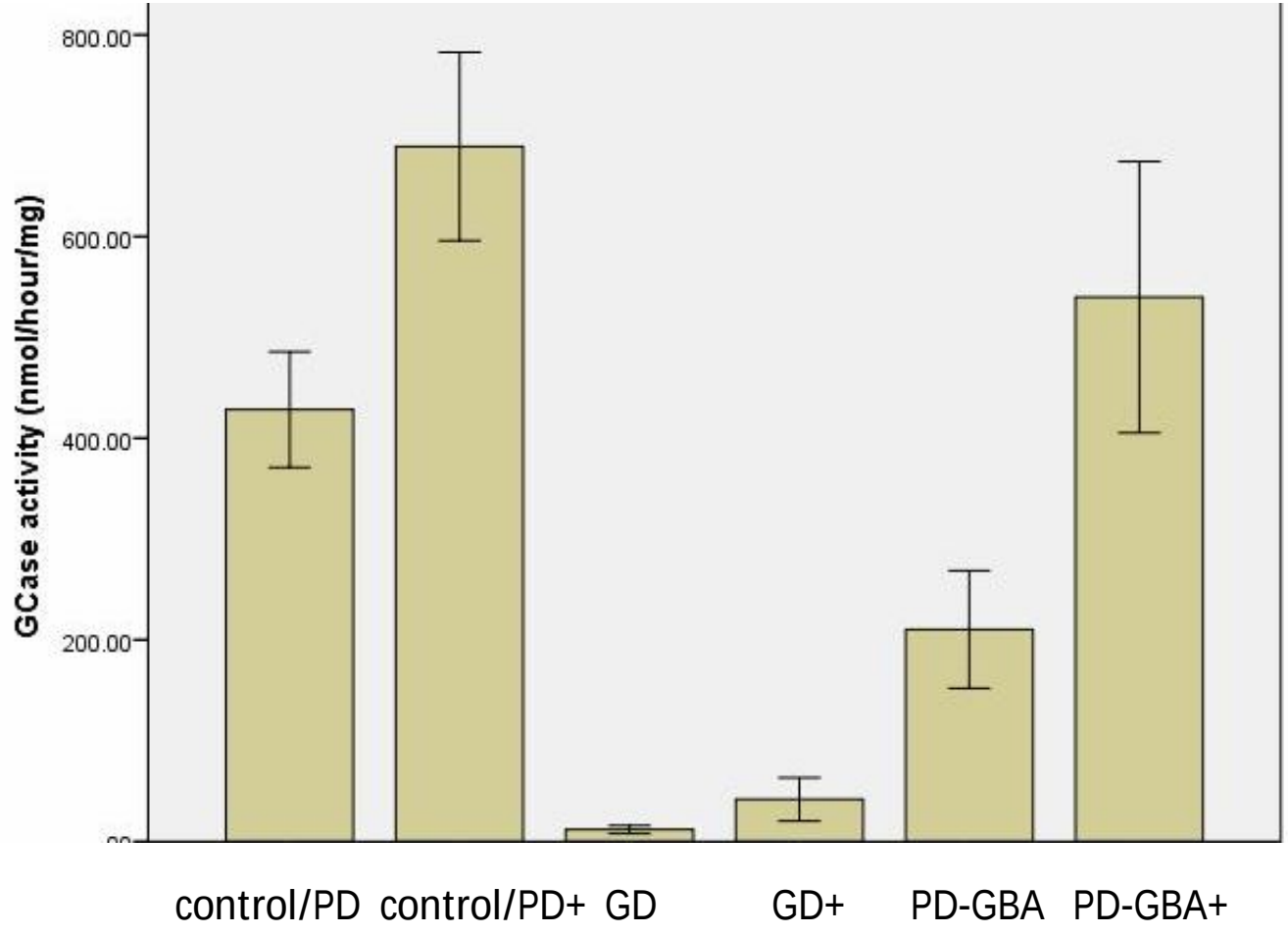
BRAIN
A JOURNAL OF NEUROLOGY

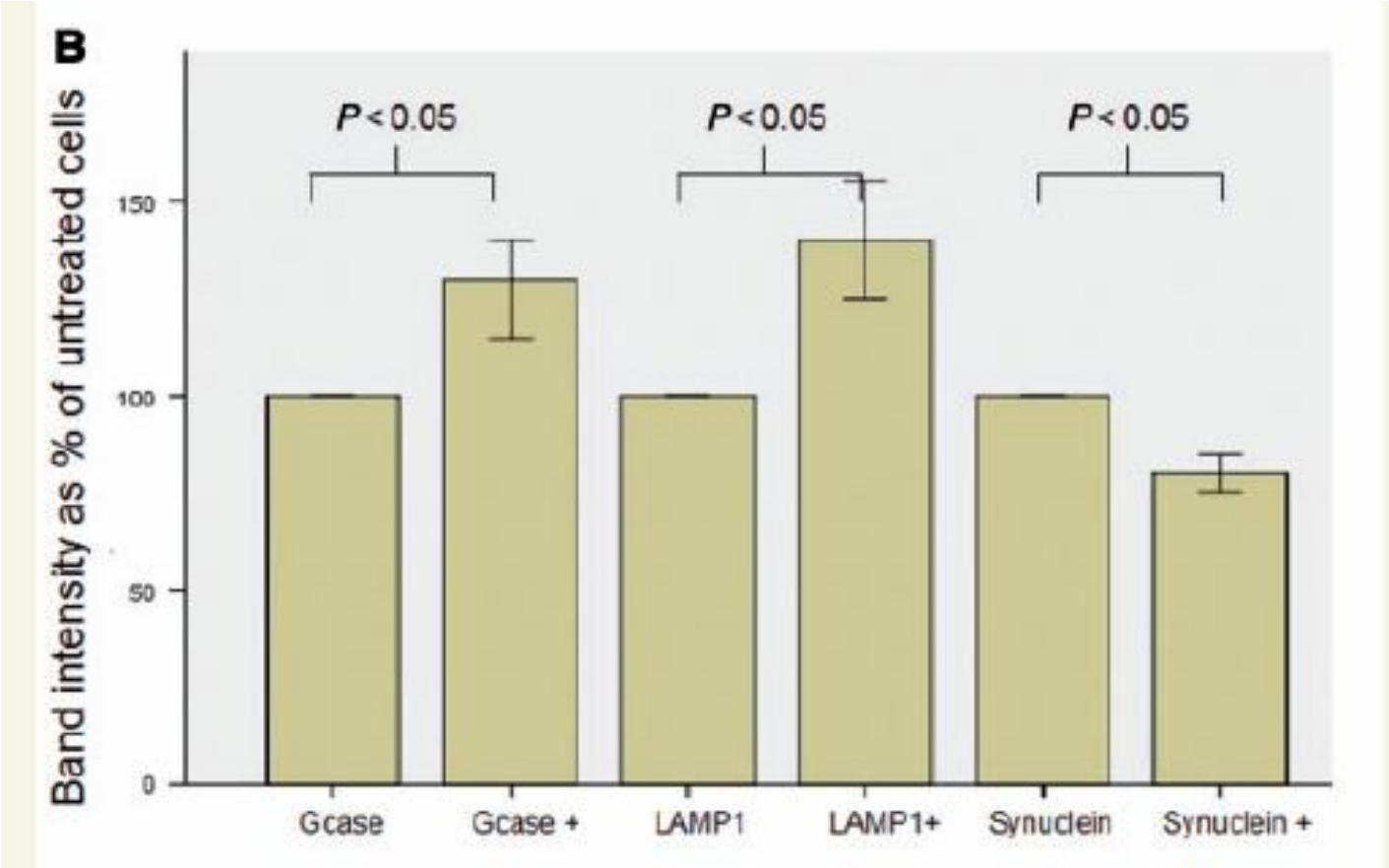
Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells

Alisdair McNeill,[1] Joana Magalhaes,[1] Chengguo Shen,[2] Kai-Yin Chau,[1] Derralyn Hughes,[3] Atul Mehta,[3] Tom Foltynie,[4] J. Mark Cooper,[1] Andrey Y. Abramov,[5] Matthew Gegg[1] and Anthony H.V. Schapira[1]

Proof of principle



Ambroxol reduces alpha-synuclein levels in cells after 5 days



AN

ESSAY

ON THE

SHAKING PALSY.

BY

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