Parkinsons UK 2016
Edinburgh

Richard Davenport

Previous RJD talks

- 2013: Causation (after Roger Barker)
- 2014: ICD
- 2015: Fallow year
- 2016:?

What causes IPD?

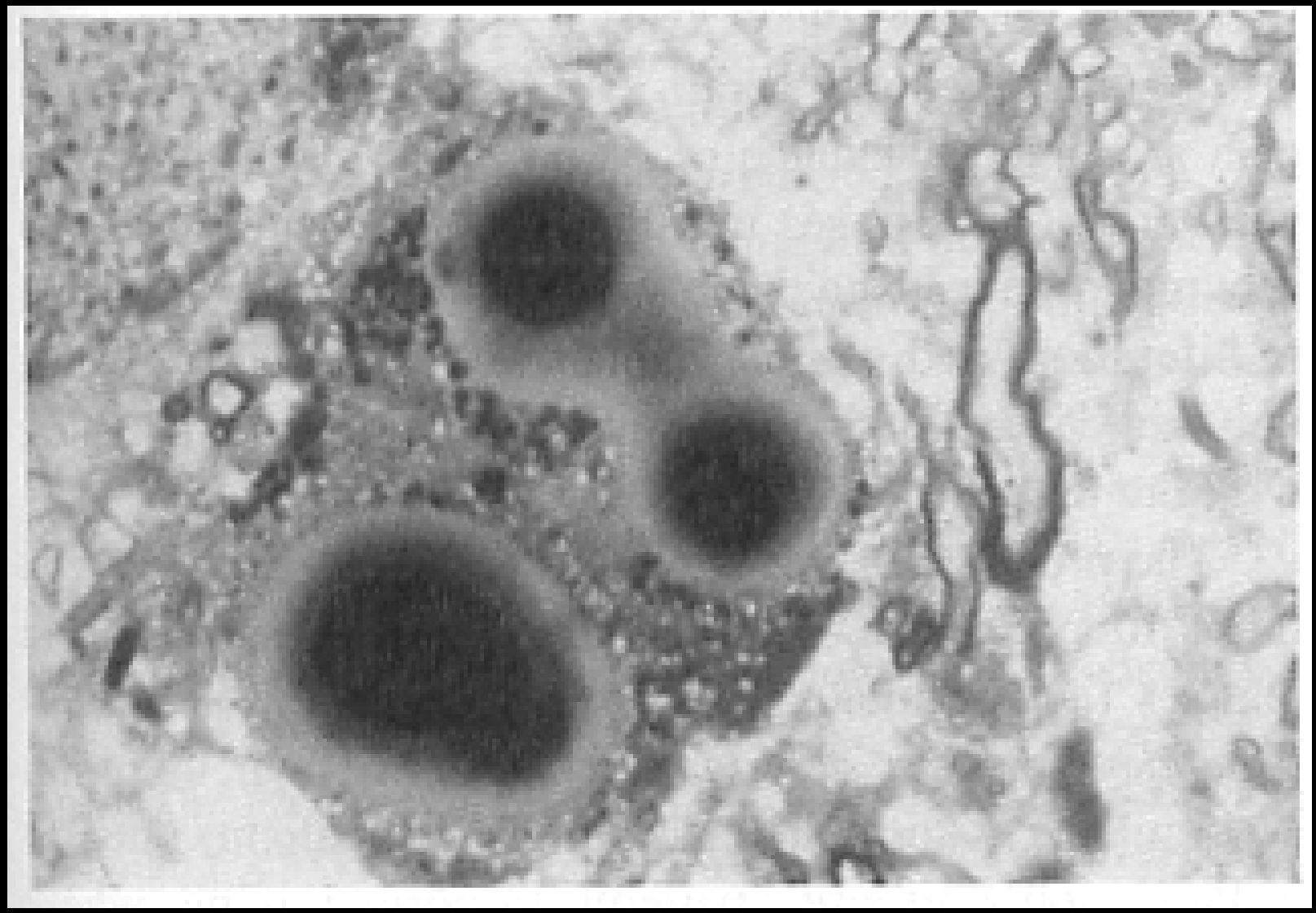
The story so far….

- 1817 - James Parkinson publication
- 1912 - Lewy describes inclusion body pathology

FIG. 4. In the laboratory of the neurology clinic, Munich: *1,* F. Lotmar; *2,* Frau Grombach; *3,* St. Rosenthal; *4,* Ugo Cerletti; *5,* Allers(?); *6,* F. Bonfiglio; *7,* A. Alzheimer; *8,* N. Achucarro; *9,* G. Perusini; *10,* F. H. Lewy.

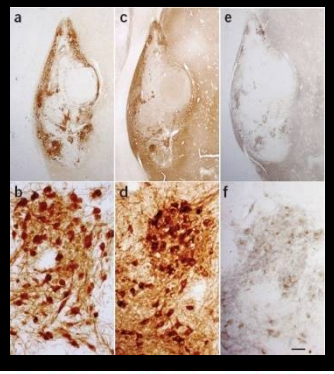
The Lewy body

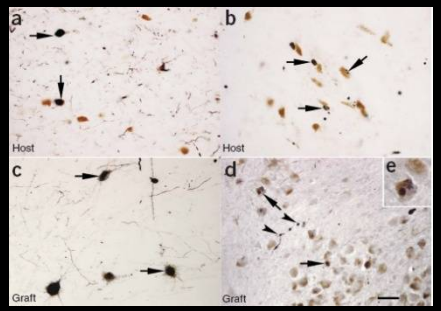
- Inclusions within neurones (microscopic)
- Found throughout brain
  - correlate with disease progression



The Lewy body

- 1980s/90s
  - ?irrelevant (bystander)
  - 1997
  - α-synuclein mutation linked
  - α-synuclein identified in LB
  - 2008: α-synuclein identified in fetal grafts





BRIEF COMMUNICATIONS

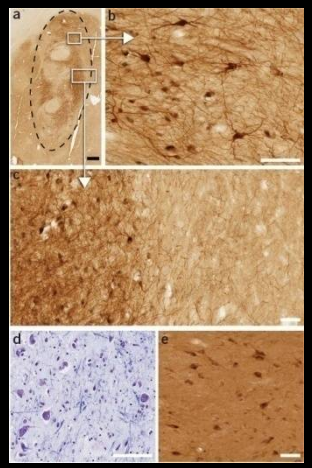
Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

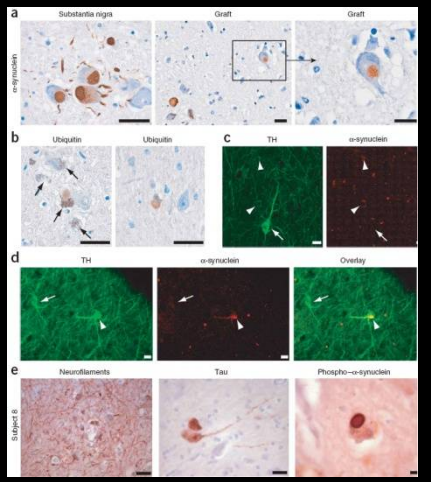
Jeffrey H Kordower[1], Yaping Chu[1], Robert A Hauser[2], Thomas B Freeman[3] & C Warren Olanow[4]

nature medicine

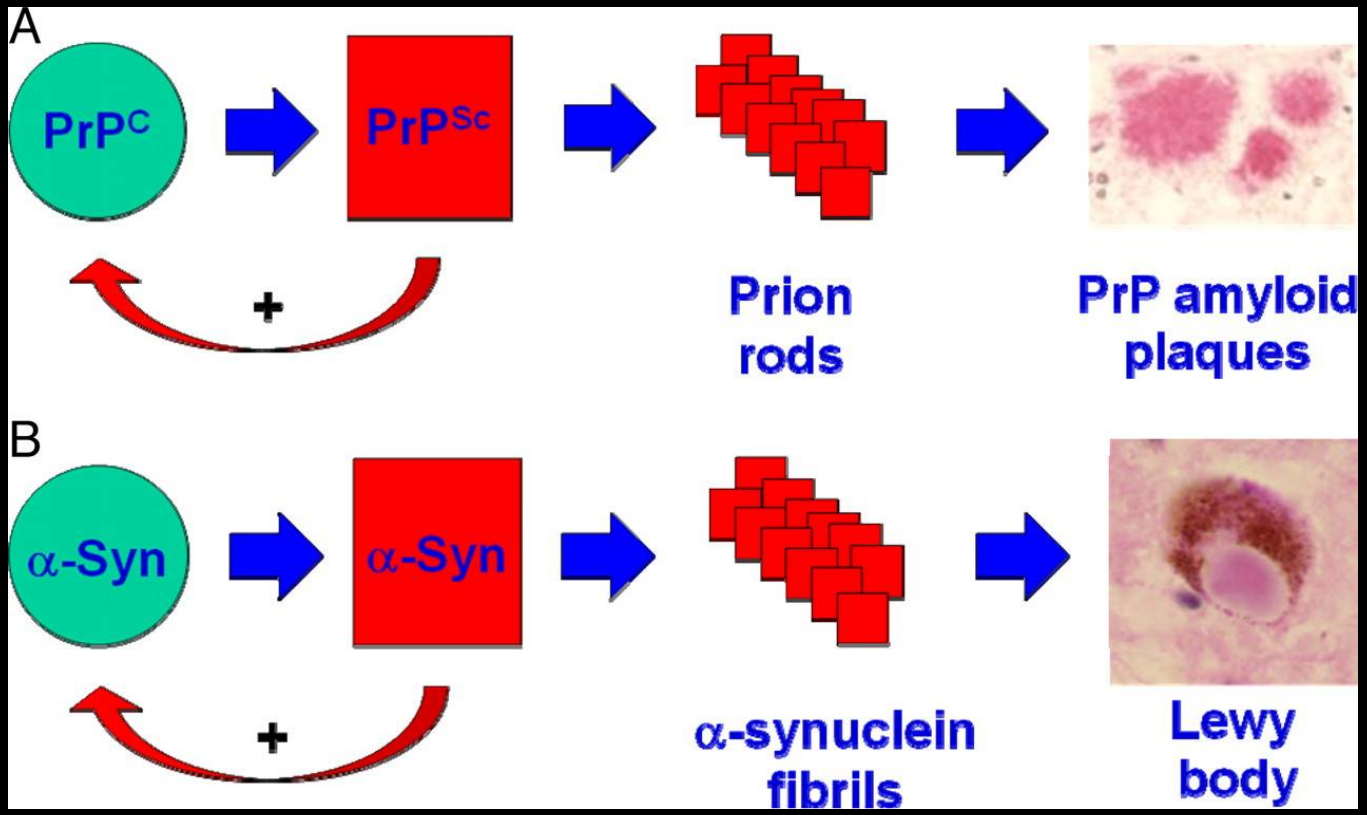
Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation

Jia-Yi Li[1], Elisabet Englund[2], Janice L Holton[3], Denis Soulet[1], Peter Hagell[4], Andrew J Lees[3], Tammaryn Lashley[3], Niall P Quinn[5], Stig Rehncrona[6], Anders Björklund[7], Håkan Widner[4], Tamas Revesz[3,9], Olle Lindvall[4,8,9] & Patrik Brundin[1,9]

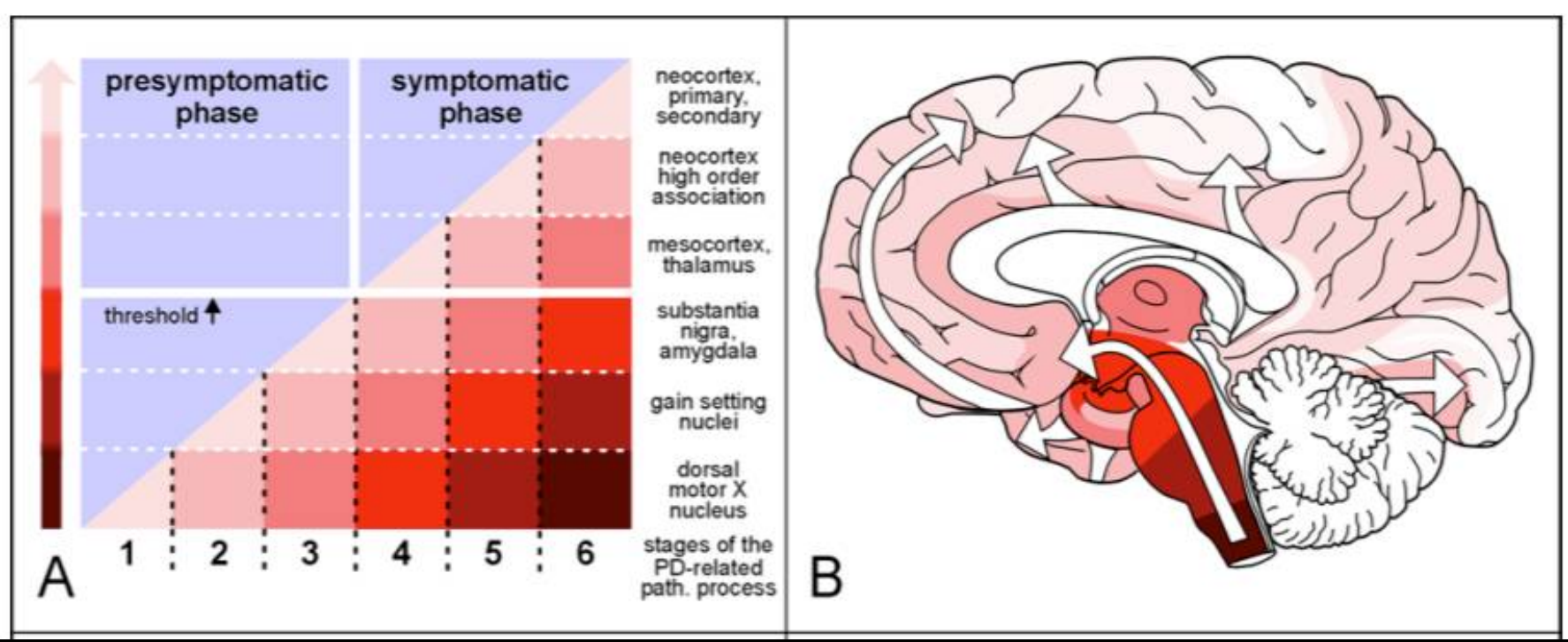




Is PD a prion disease?



Braak Hypothesis 2003



Stage 6: Neocortex

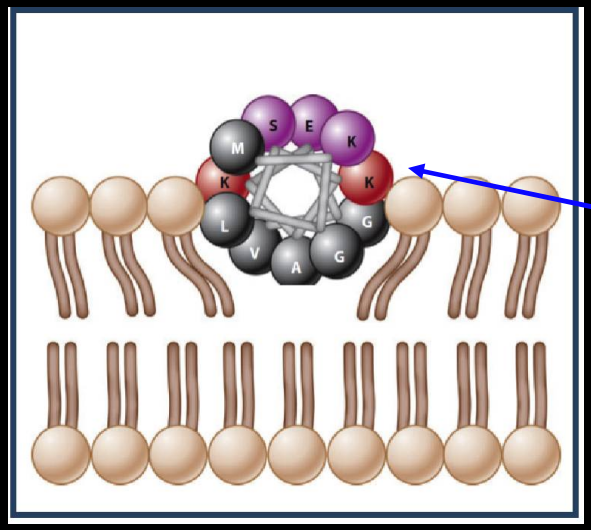
Stage 1: Olfactory bulb/medulla

α-Synucleinopathy

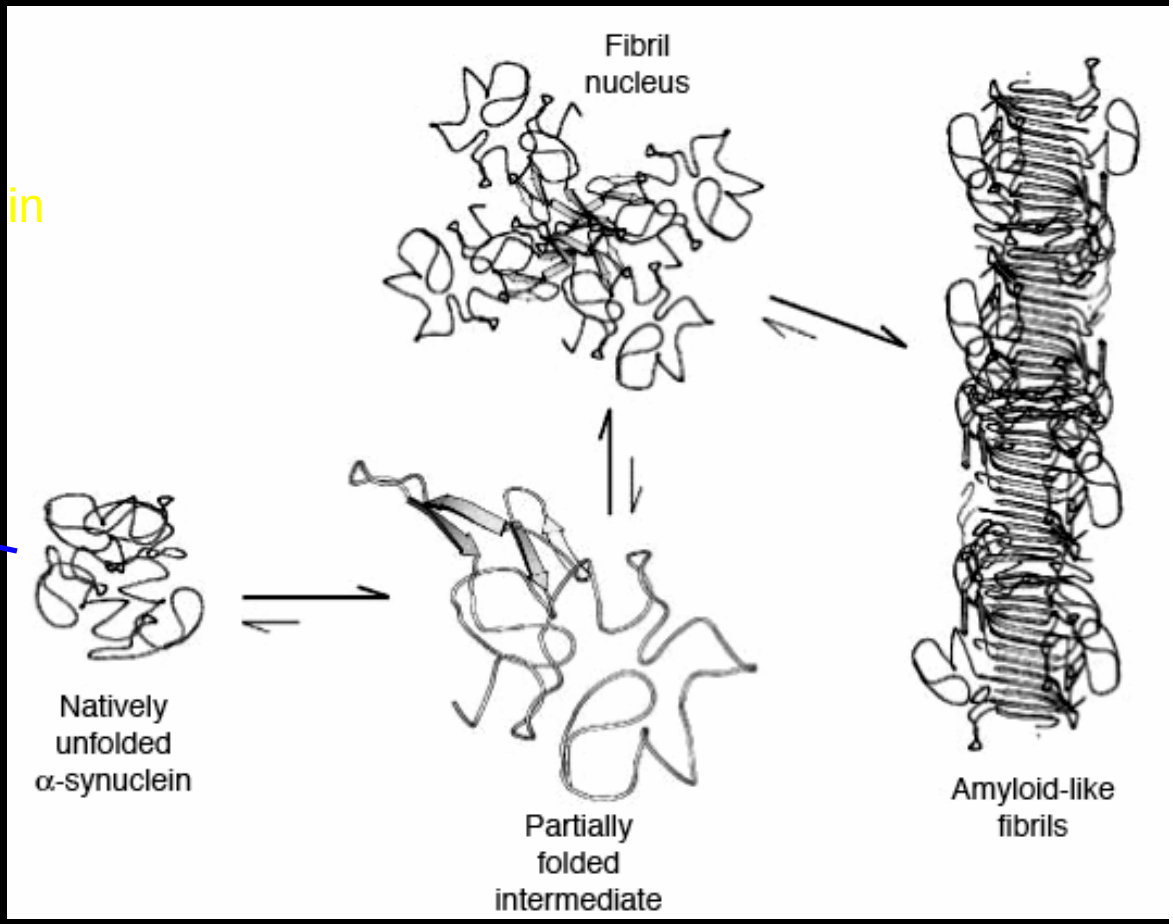
Natively
unfolded
α-synuclein

α-Synucleinopathy

α-Synuclein can form α-helices when in contact with membranes

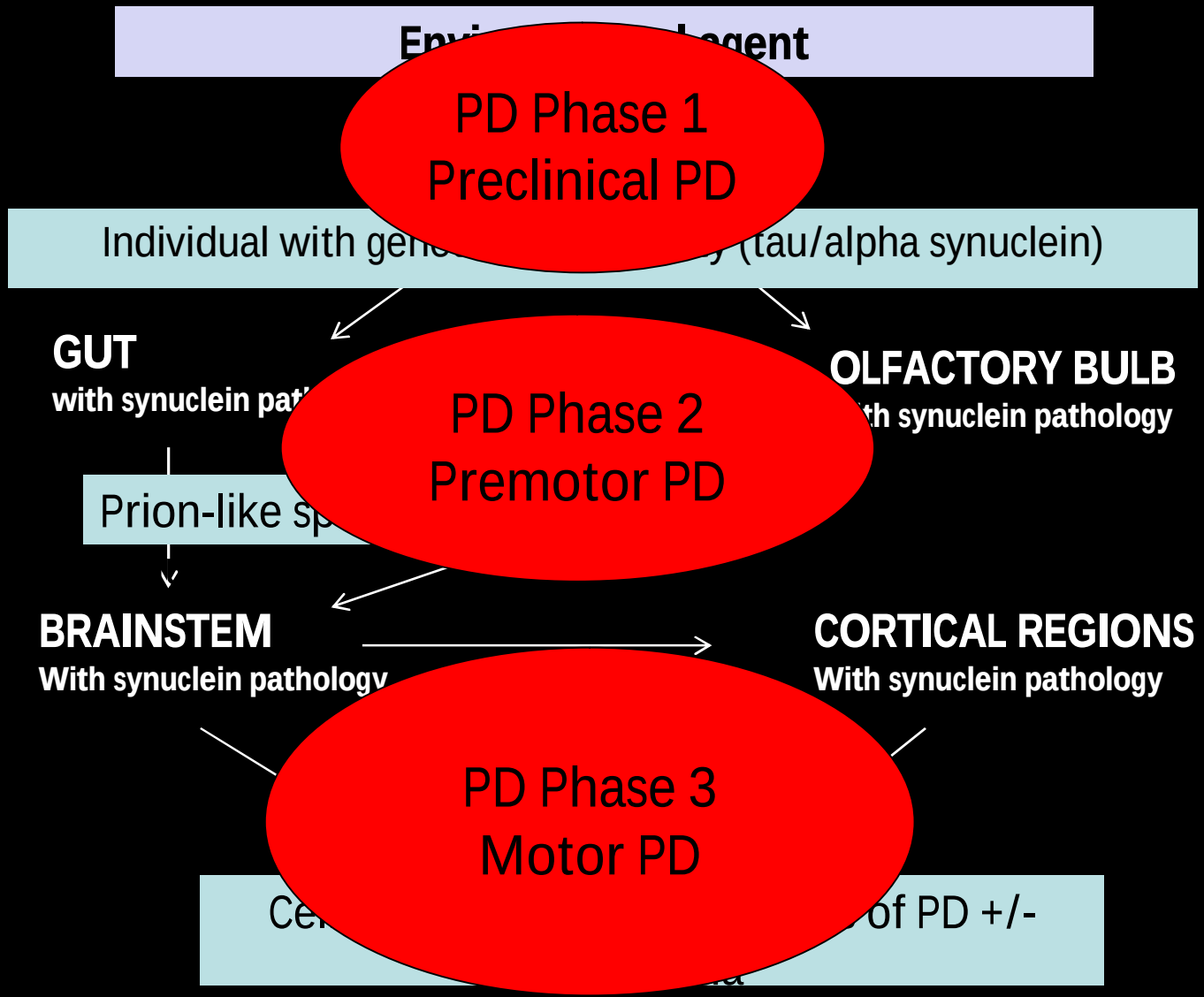


Normal function



Pathogenic versions found in synucleinopathies

Hypothesis for PD



1. Pre-clinical phase

- No symptoms or signs
- PD pathology assumed to be present
  - ?biomarkers
- Decades prior to motor symptoms?

2. Pre-motor phase

- Hyposmia (reduced smell)
- Depression/anxiety
- Constipation
- REM Behavioural disturbance
- Within decade prior to motor symptoms?

3. Motor (and non-motor) phase

- Tremor
- Akinetic/rigidity (stiffness/slowness)
- Postural problems
- Etc…..

How does the causative "toxin" gain access to body?

- Prion disease
  - Ingested (variant CJD)
  - Implanted (iatrogenic CJD)
  - Genetic causes
  - Sporadic

Toxin entry in PD

- Nose (hyposmia?)
- Gut (constipation?) via vagus nerve

OPEN ACCESS Freely available online

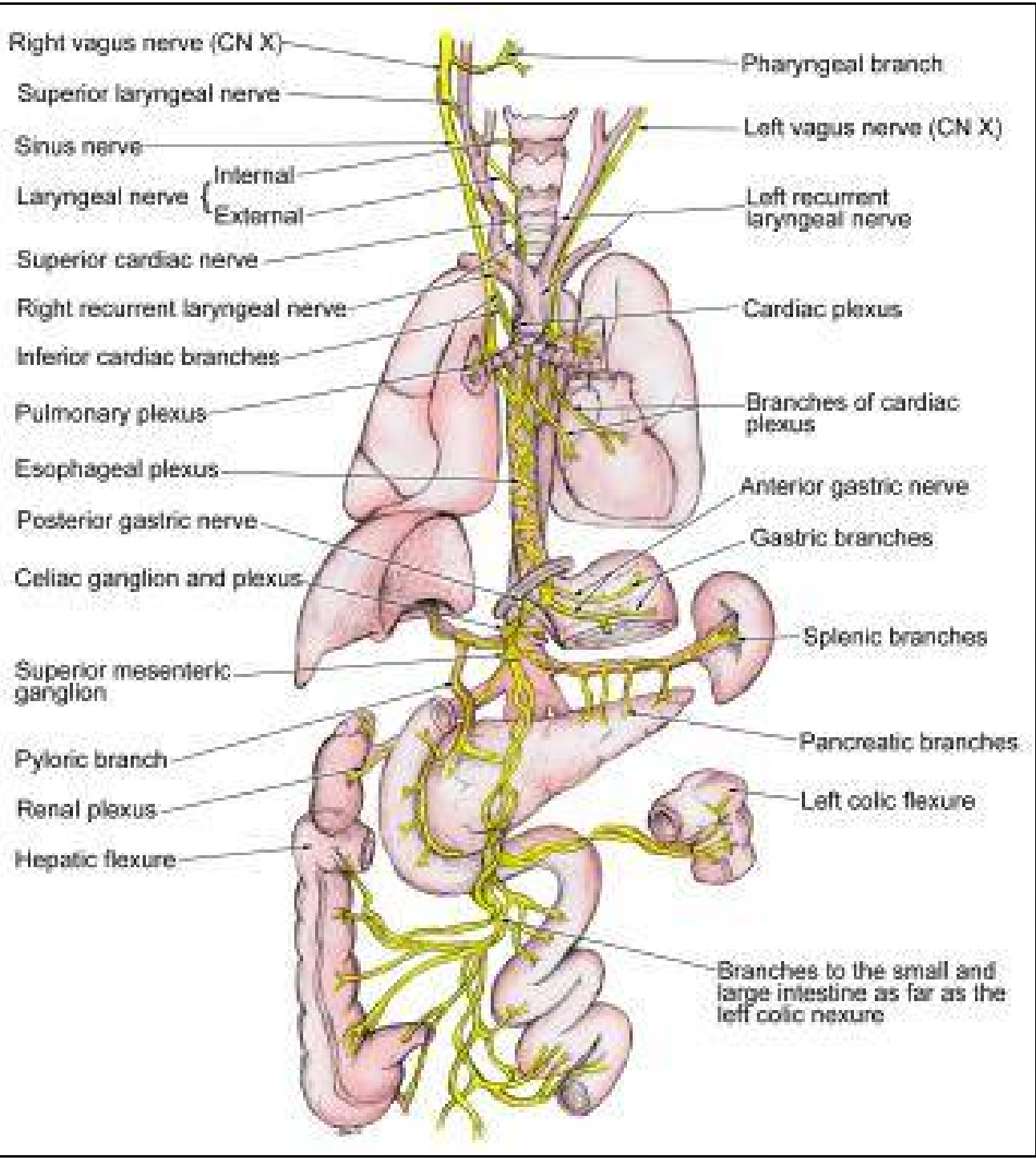
PLoS one

Colonic Biopsies to Assess the Neuropathology of Parkinson's Disease and Its Relationship with Symptoms

Thibaud Lebouvier[1,2,3,4]*, Michel Neunlist[1,4,6]*, Stanislas Bruley des Varannes[1,2,3,6], Emmanuel Coron[1,2,3,6], Anne Drouard[2], Jean-Michel N'Guyen[7], Tanguy Chaumette[1,4], Maddalena Tasselli[1,4], Sébastien Paillusson[1,4], Mathurin Flamand[1,2,3,6], Jean-Paul Galmiche[1,2,3,6], Philippe Damier[2,3,5]¶, Pascal Derkinderen[1,2,3,5,6]*¶

1 UMR 913, Inserm, Nantes, France, 2 CIC-04, Inserm, Nantes, France, 3 UFR Médecine, Université de Nantes, Nantes, France, 4 UFR Sciences et Techniques, Université de Nantes, Nantes, France, 5 Service de Neurologie, CHU Nantes, Nantes, France, 6 Institut des Maladies de l'Appareil Digestif (IMAD), CHU Nantes, Nantes, France, 7 Pôle d'Information Médicale, Évaluation et Santé Publique (PIMESP), CHU Nantes, Nantes, France

- 29 PD, 10 controls:
  - 80% vs 10% chronic constipation
  - 72% vs 0% had Lewy neurites on biopsy


Right vagus nerve (CN X)
Superior laryngeal nerve
Sinus nerve
Laryngeal nerve
Internal
External
Superior cardiac nerve
Right recurrent laryngeal nerve
Inferior cardiac branches
Pulmonary plexus
Esophageal plexus
Posterior gastric nerve
Celiac ganglion and plexus
Superior mesenteric ganglion
Pyloric branch
Renal plexus
Hepatic flexure
Pharyngeal branch
Left vagus nerve (CN X)
Left recurrent laryngeal nerve
Cardiac plexus
Branches of cardiac plexus
Anterior gastric nerve
Gastric branches
Splenic branches
Pancreatic branches
Left colic flexure
Branches to the small and large intestine as far as the left colic flexure

Vagus nerve transmission

- Animal models showing ASN tx from gut to brain
  - Does not occur if vagus nerve cut

Vagotomy

- Previously common treatment for peptic ulcers
  - H2 blockers (ranitidine and cimetidine)
  - Proton pump inhibitors (omeprazole etc)
  - H pylori hypothesis
- Vagotomy
  - Truncal
  - Super-selective (only branches to stomach cut)

Vagotomy hypothesis

- Risk of PD reduced after truncal but not super-selective vagotomy
- Denmark study (2015)
  - All vagotomies between 1977-1995
  - Age matched controls (up to 10 for every V patient)
  - Linked to subsequent diagnoses of PD

Results

- 14 883 vagotomies
  - 5339 TV >5 yrs follow up (66 711 controls)
  - 5870 SSV >5 yrs follow up (60 500 control)

- Lower risk of PD in TV vs SSV
- Lower risk of PD in TV vs controls
- Slightly higher risk of PD in SSV vs controls

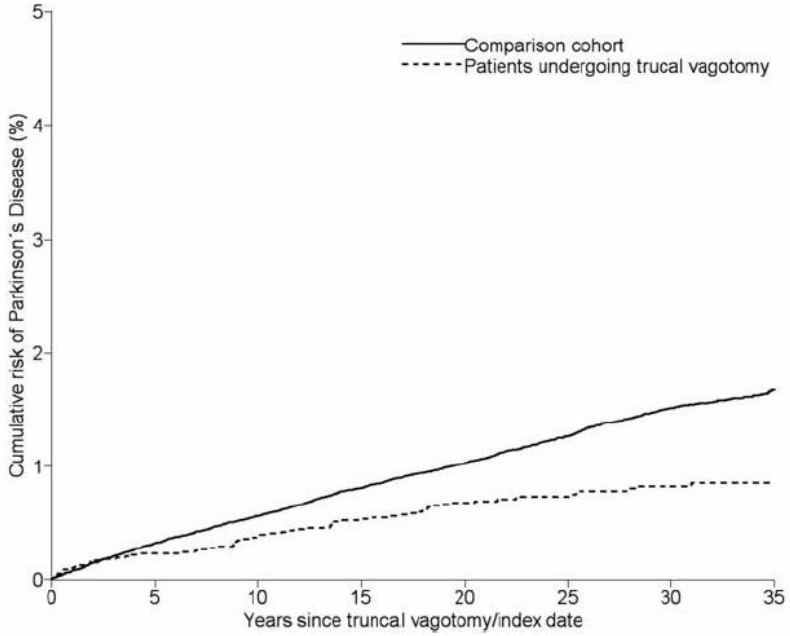


FIGURE 1: Cumulative incidence curves of Parkinson's disease for patients who underwent truncal vagotomy compared to a matched general population cohort.

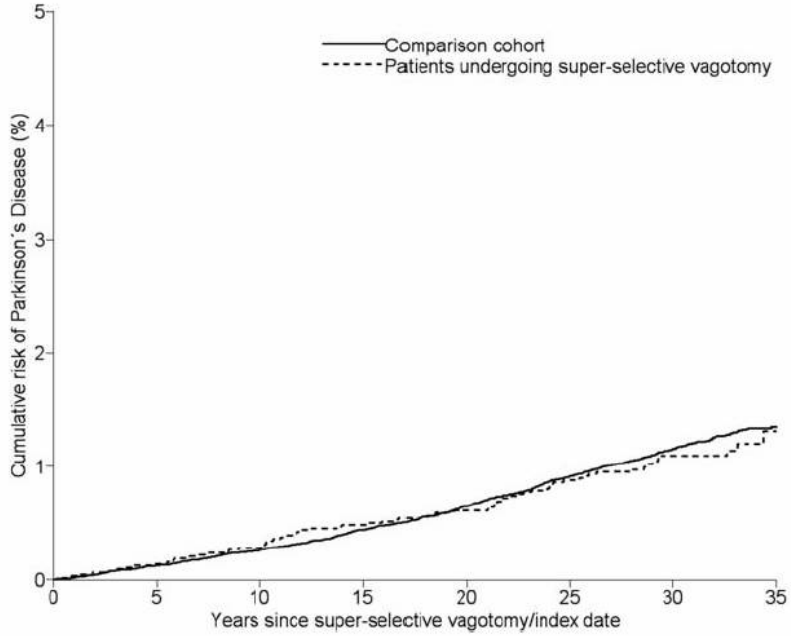


FIGURE 2: Cumulative incidence curves of Parkinson's disease for patients undergoing superselective vagotomy compared to a matched general population cohort.

So….

- Having intact vagus nerve associated with ↑ risk PD
- Why do some still get PD after TV?
  - Transfer occurred before TV
  - Alternative access (nose)
- But……..

Conclusions?

- None really possible….
- ….hypothesis generating….
- The search continues
  - Cause
  - Treatment