Is alpha-synuclein a prion-like protein in Parkinson's disease?

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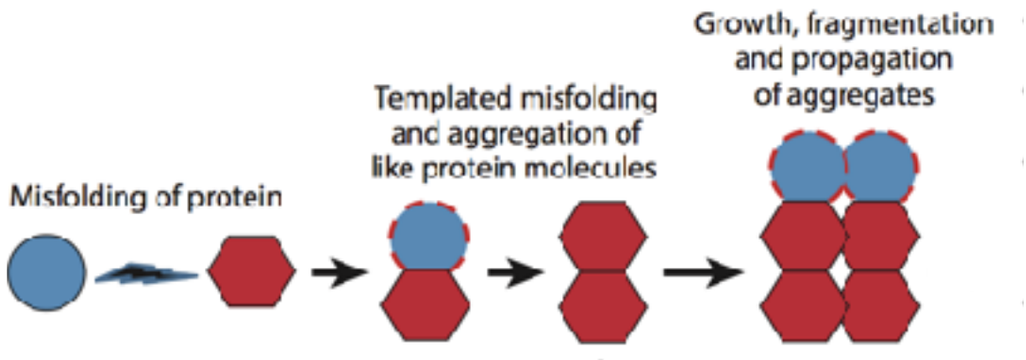
National Medical Research Council of Singapore
Awards Ceremony and Research Symposium
Neurological & Sense Disorder track
March 7, 2017
Singapore

What is a prion?

Prions (‘proteinaceous infectious particles’) are unconventional infectious agents consisting of misfolded prion protein molecules….the molecules aggregate with one another and impose their anomalous structure on benign prion protein molecules



Jucker and Walker, Nature 2013

Themes for today's talk

- Studies in Parkinson's disease
- Experiments modelling the prion-like behavior of α-synuclein
- Two key future questions

Lewy bodies now seen in at least 10 cases from 5 different surgical centers

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]

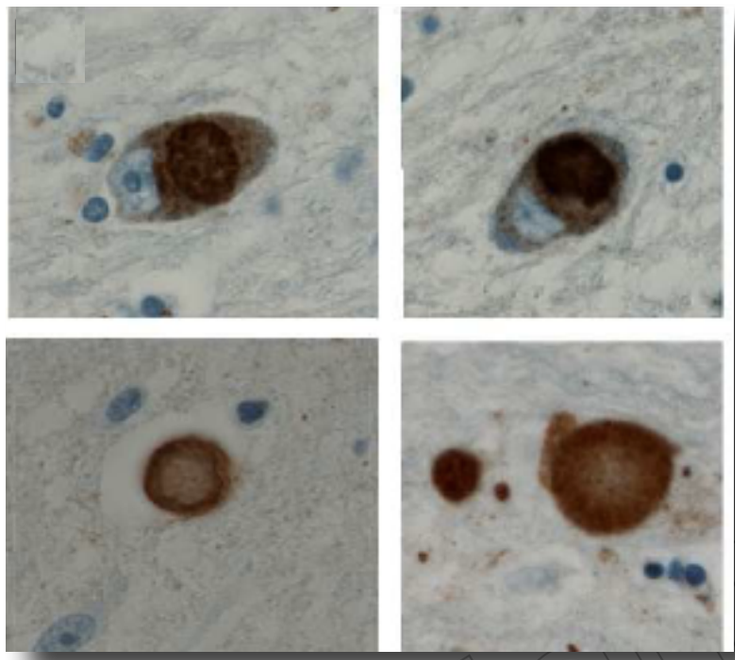
Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

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

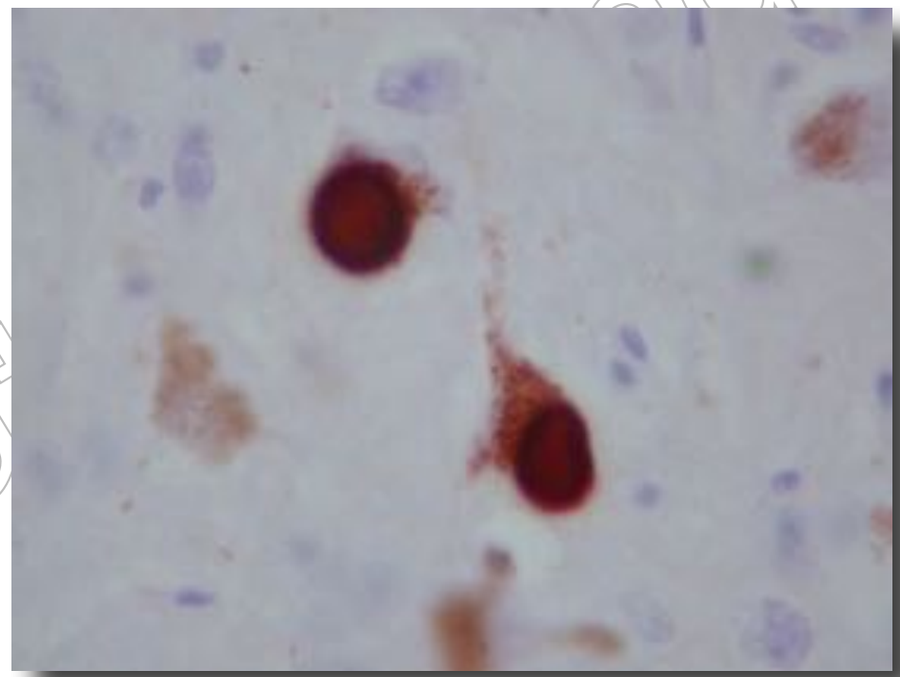
nature medicine

Lewy bodies in neural grafts

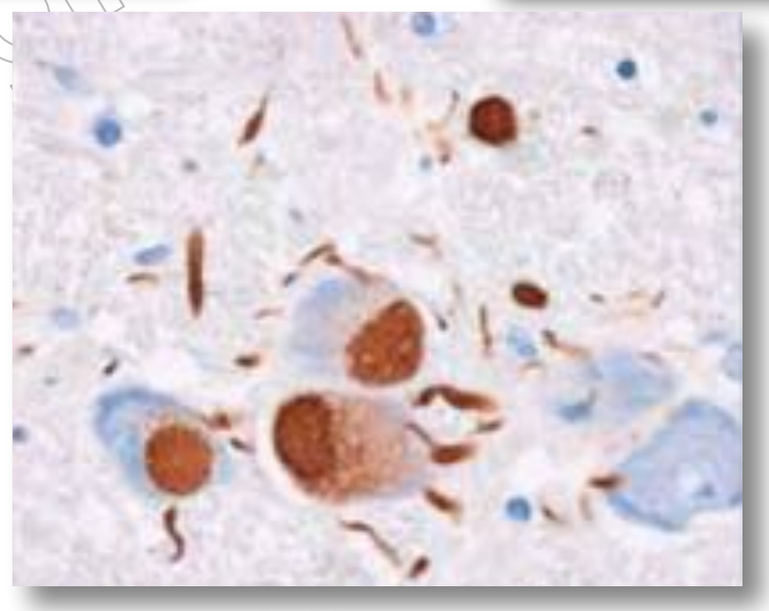
α-synuclein



Graft
(patient 3)



Graft
(patient 8)

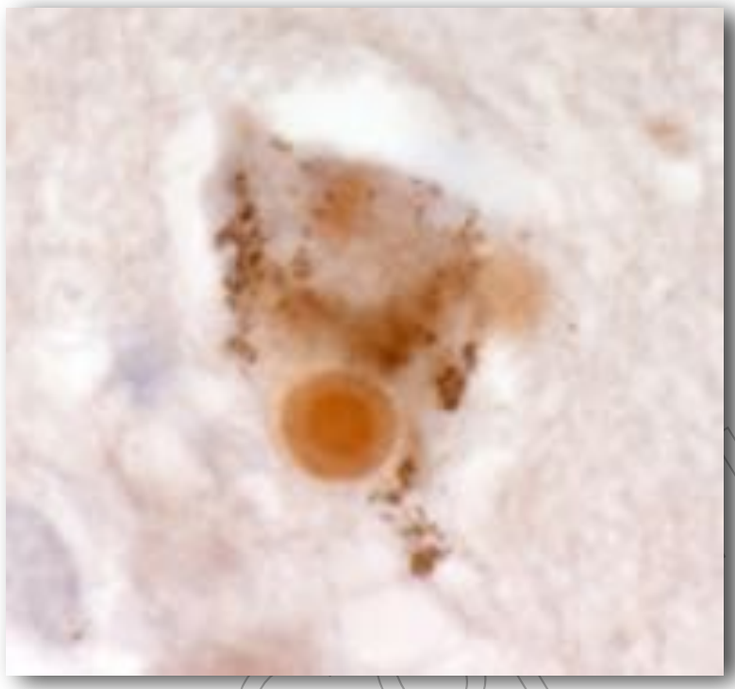


Nigra
(patient 3)

Li et al. 2008 and 2010

All markers consistent with Lewy bodies

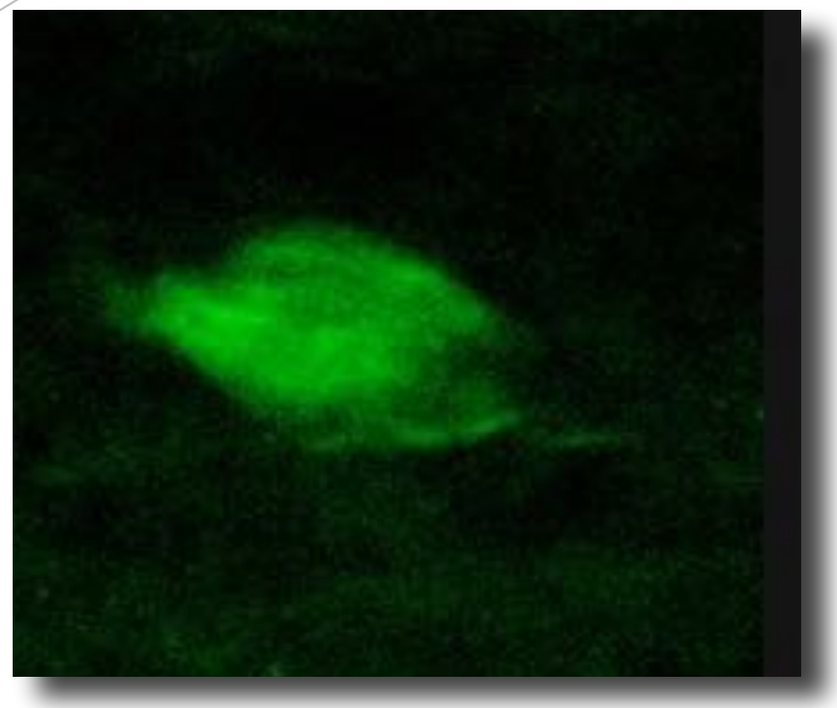
Ubiquitin



Graft
(patient 8)

Phospho-S129-
α-synuclein

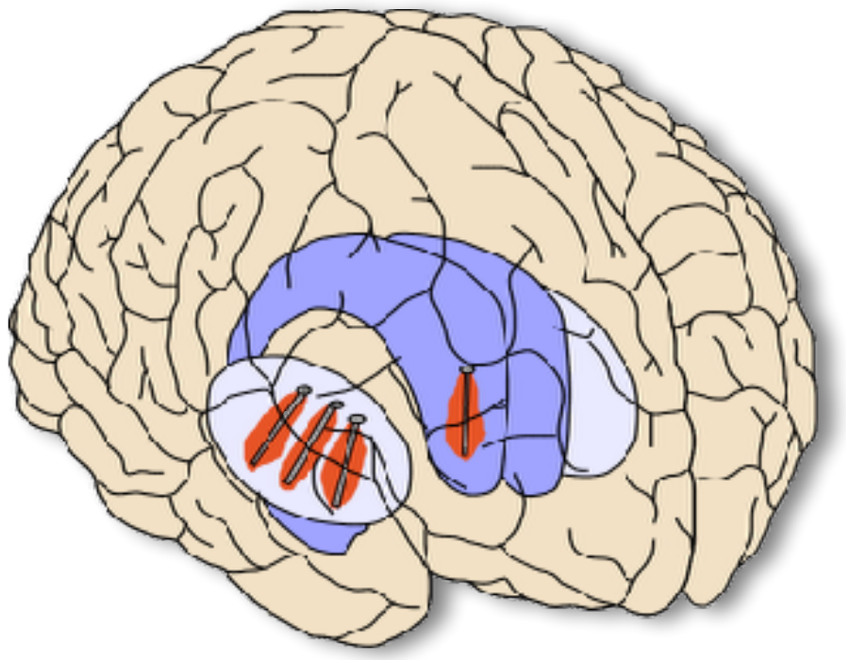
Thioflavin S



Graft
(patient 3)

Li et al. 2008 and 2010

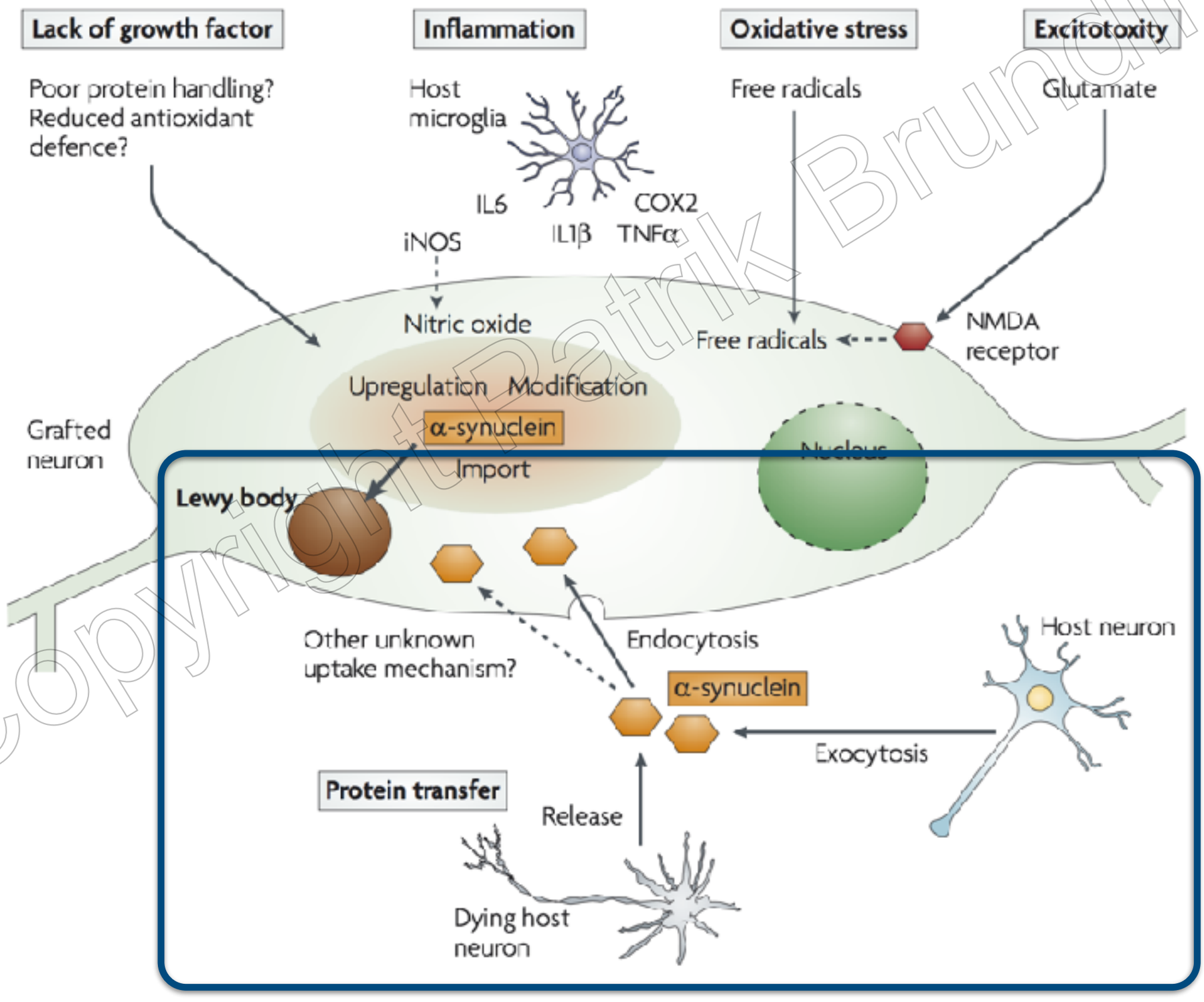
Time-dependent increase in pathology



	12-year-old graft (P3)	16-year-old graft (P3)	24-year-old graft (P4)
Grafted pigmented neurons with Lewy bodies	2%	5%	12%

Li et al. 2008, 2010 and 2016

A prion-like mechanism is possible

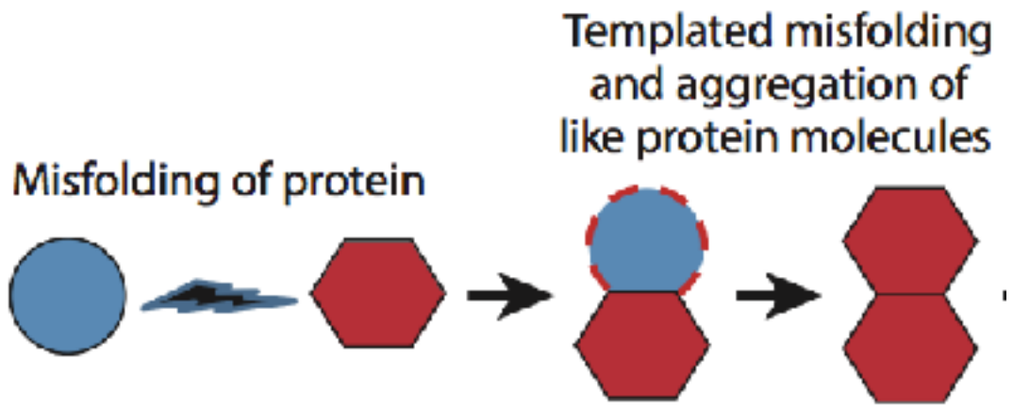


Brundin et al. 2008

Expanding the prion concept

*….we suggest that "prion" should be defined broadly as a "<u>proteinaceous **nucleating** particle</u>" (rather than a "proteinaceous infectious particle").*

This expanded and refined definition could <u>help to obviate unnecessary confusion and concern about the communicability of noninfectious proteopathies</u> and speed acceptance of this important paradigm within the biomedical community.



Adapted from Walker and Jucker, Annu Rev Neurosci 2015

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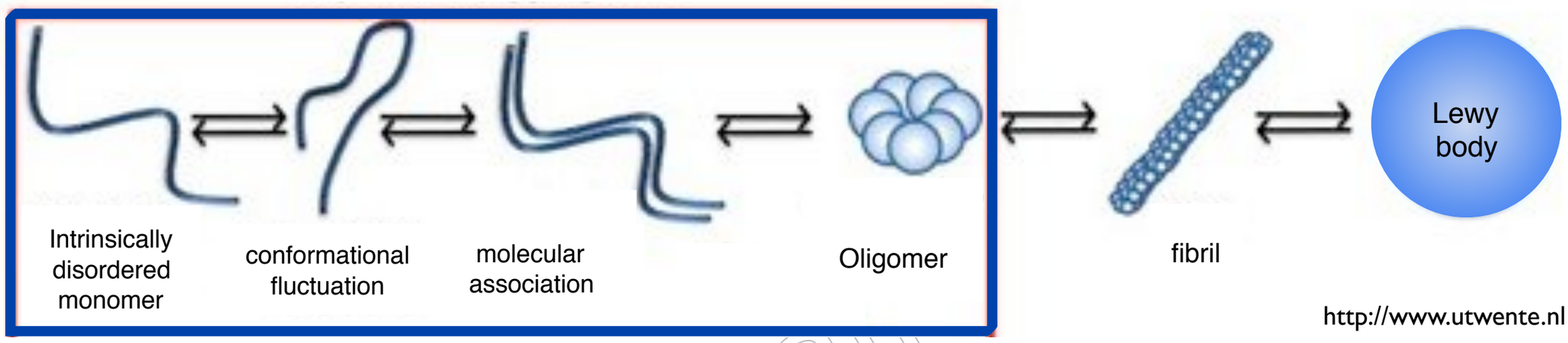
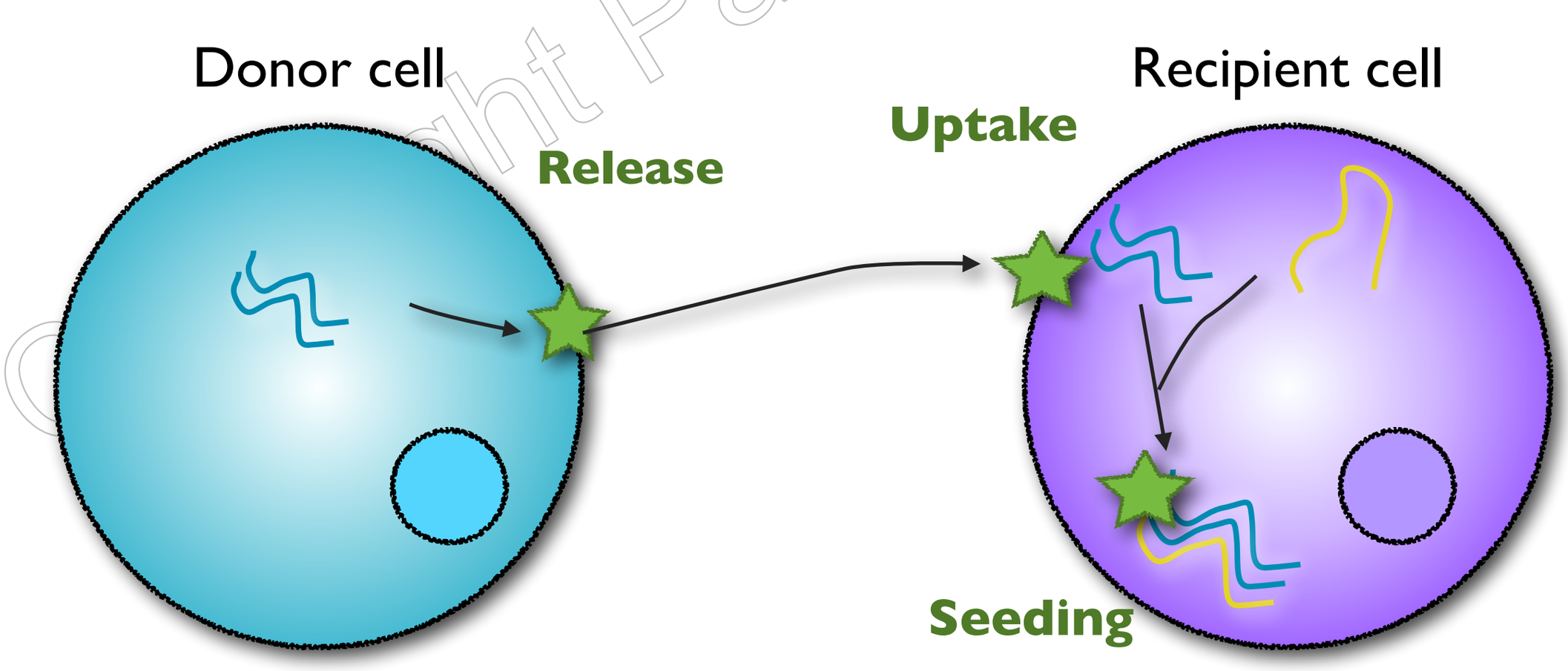
- Experiments modelling the prion-like behavior of α-synuclein
- Two key future questions

α-Syn seeding and prion-like spreading

α-synuclein aggregation

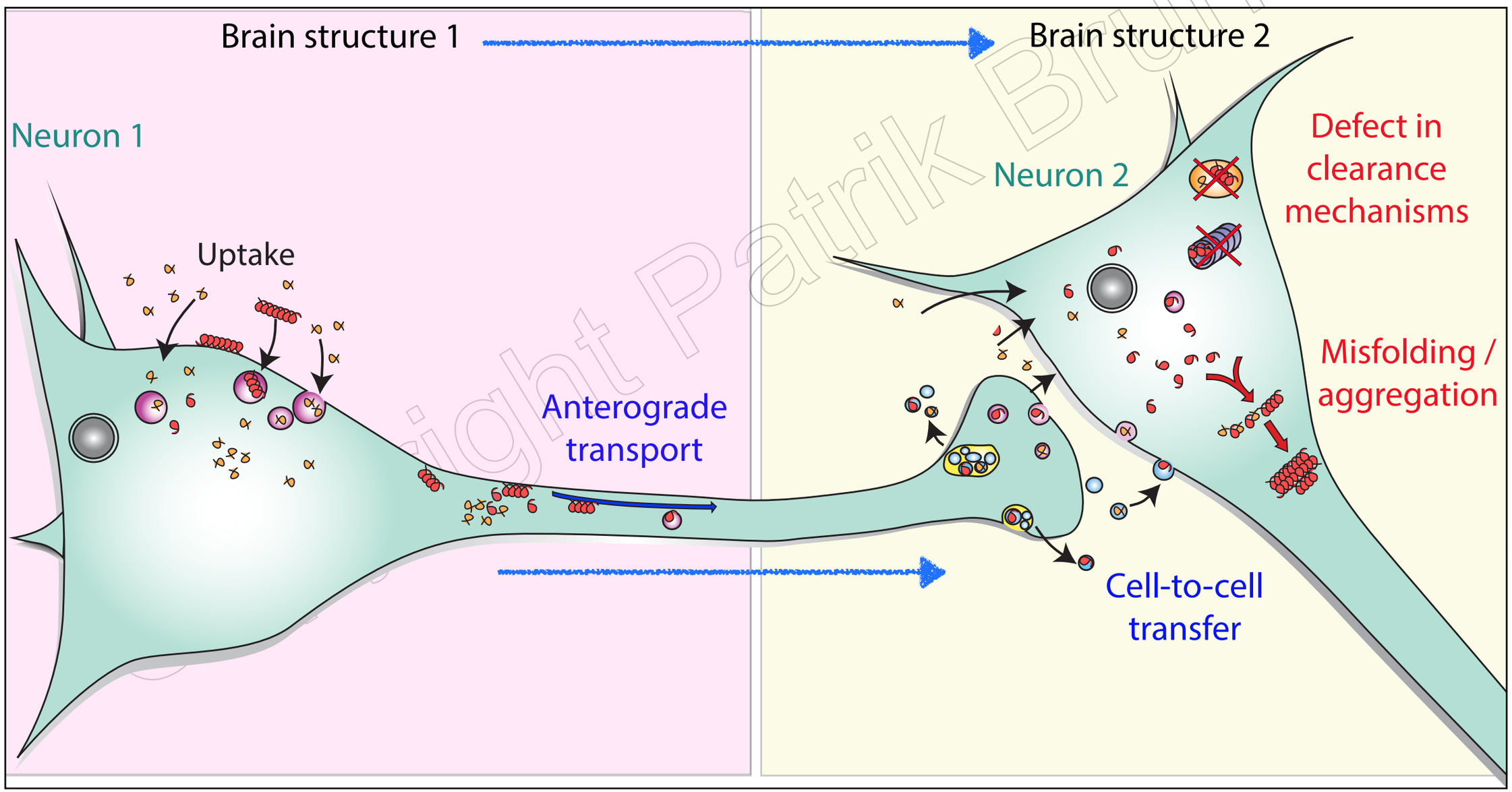


http://www.utwente.nl



Adapted from Angot et al. 2010

Animal models offer additional dimensions



Braak staging - progression of α-synuclein pathology

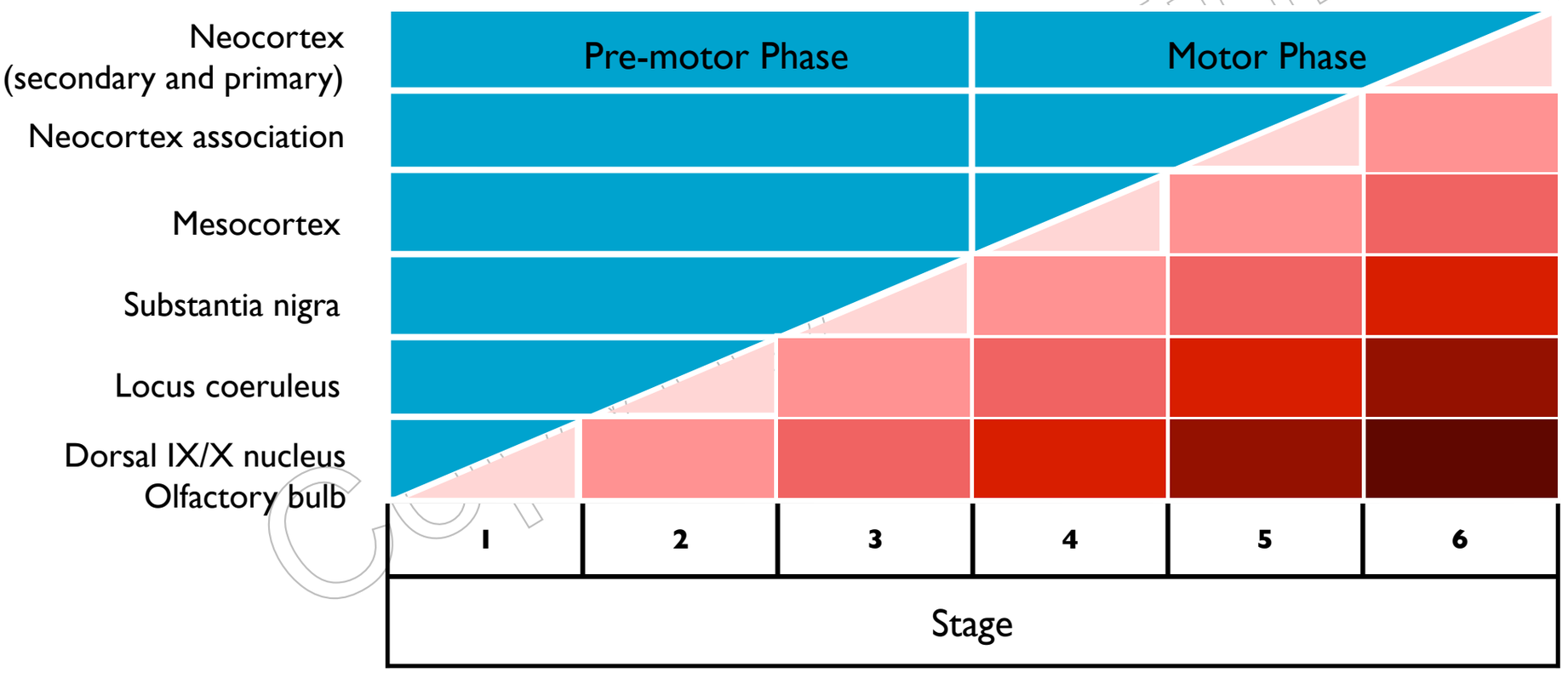
Hyposmia
Constipation
Bladder disorder

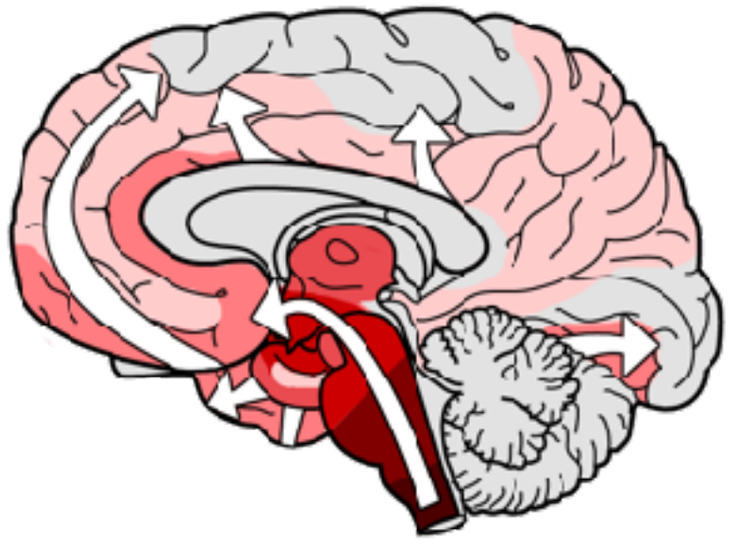
Sleep disorder
Depression

Unilateral tremor
Rigidity
Akinesia
Bilateral disease
Poor balance

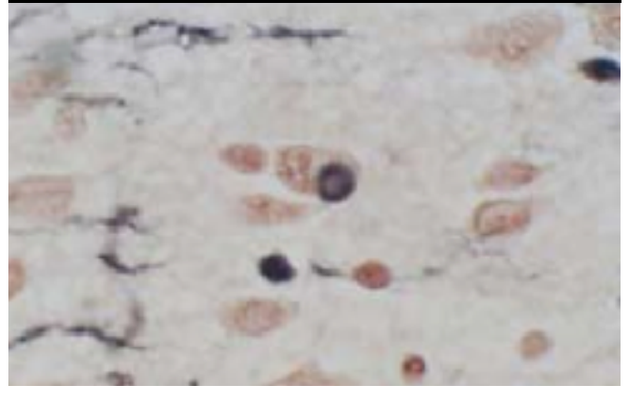
Falls
Dependency
Cognitive decline
Chair/bed bound
Dementia

Time (years)





Anterior olfactory nucleus



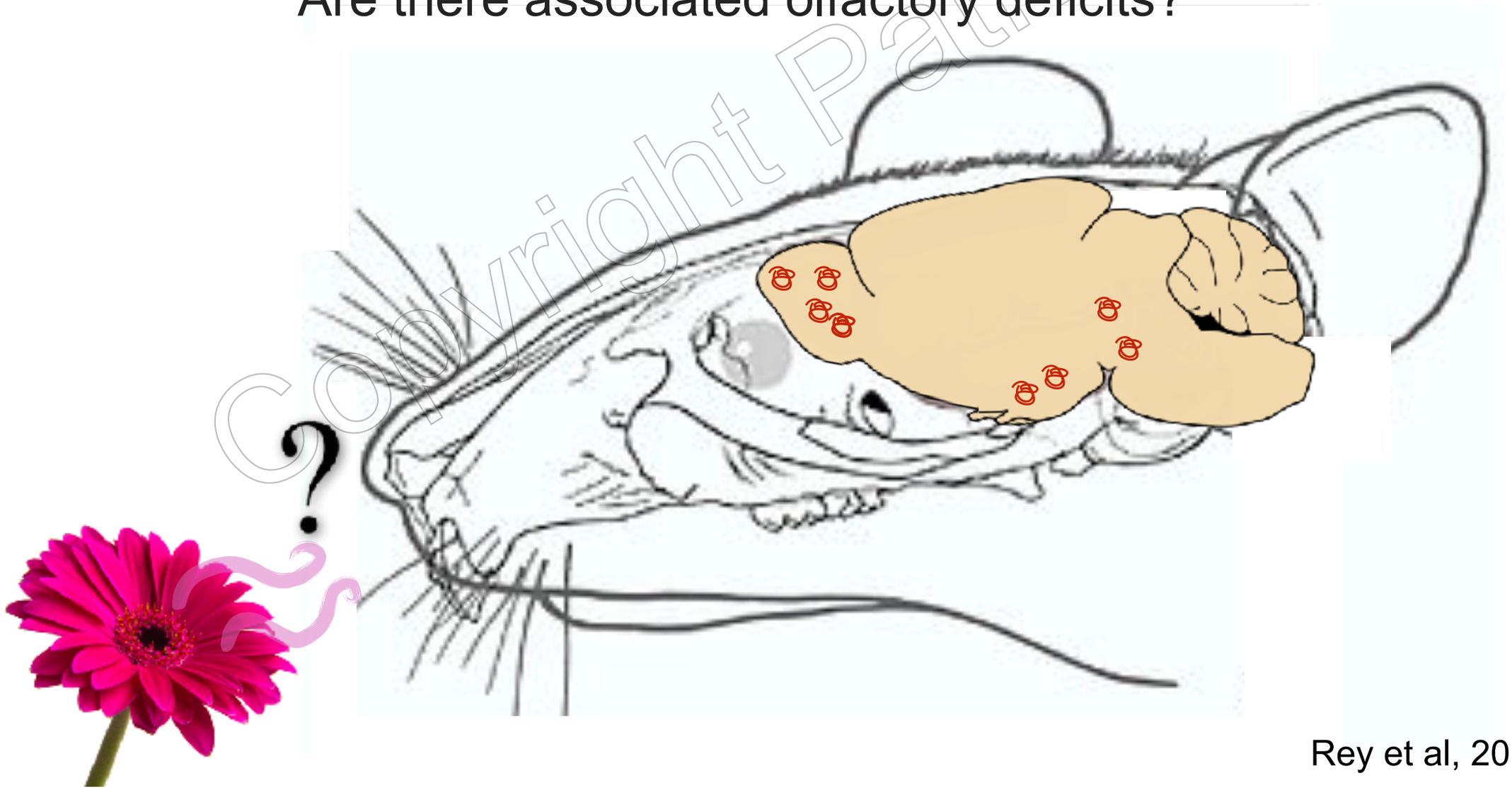
Beach et al. 2008.

Olfactory bulb pathology model

Create a model of progressive pathology of direct relevance to the “Braak model”

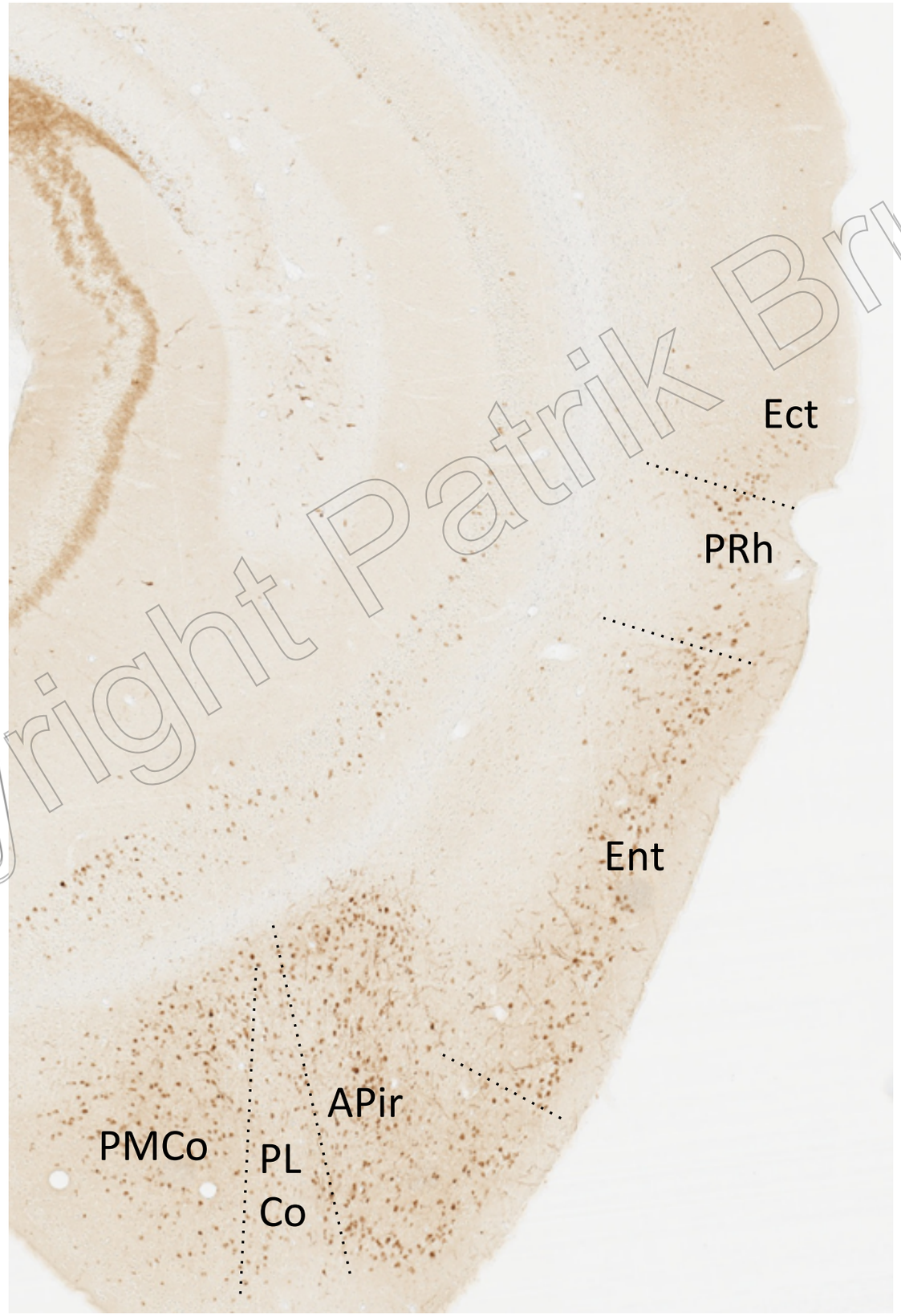
Can preformed α-synuclein fibrils induce spread of pathology in the olfactory system?

Are there associated olfactory deficits?

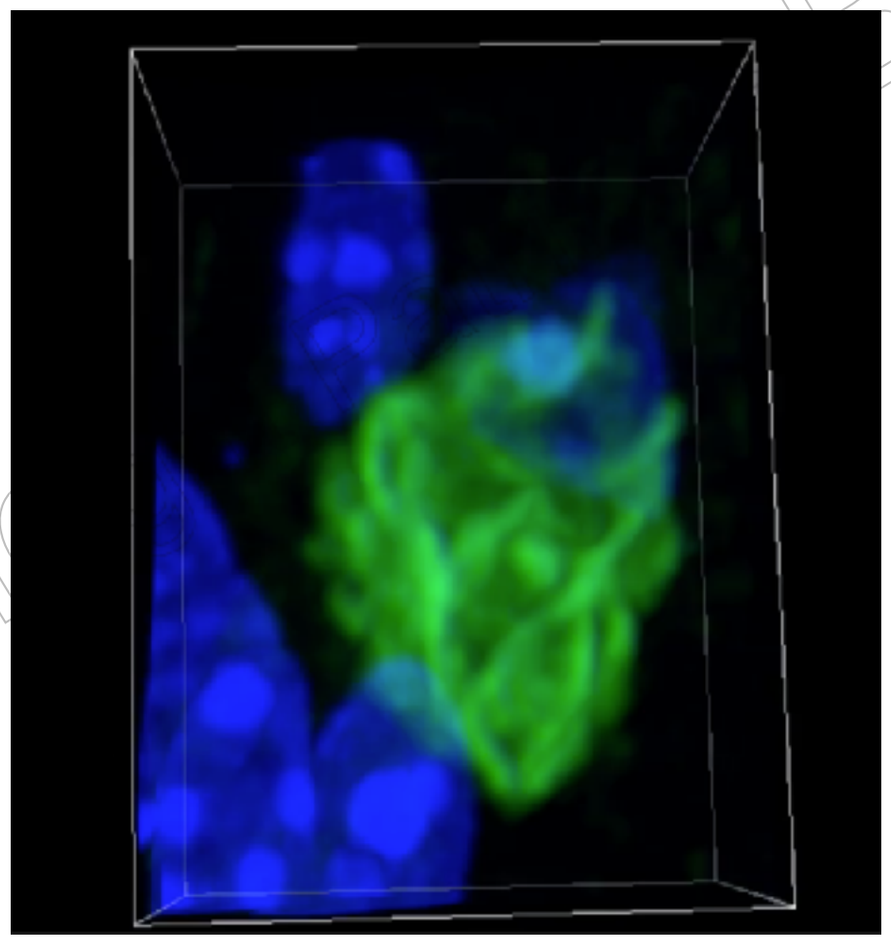


Rey et al, 2013 and 2016

Spreading of Pser129 α-syn in brain

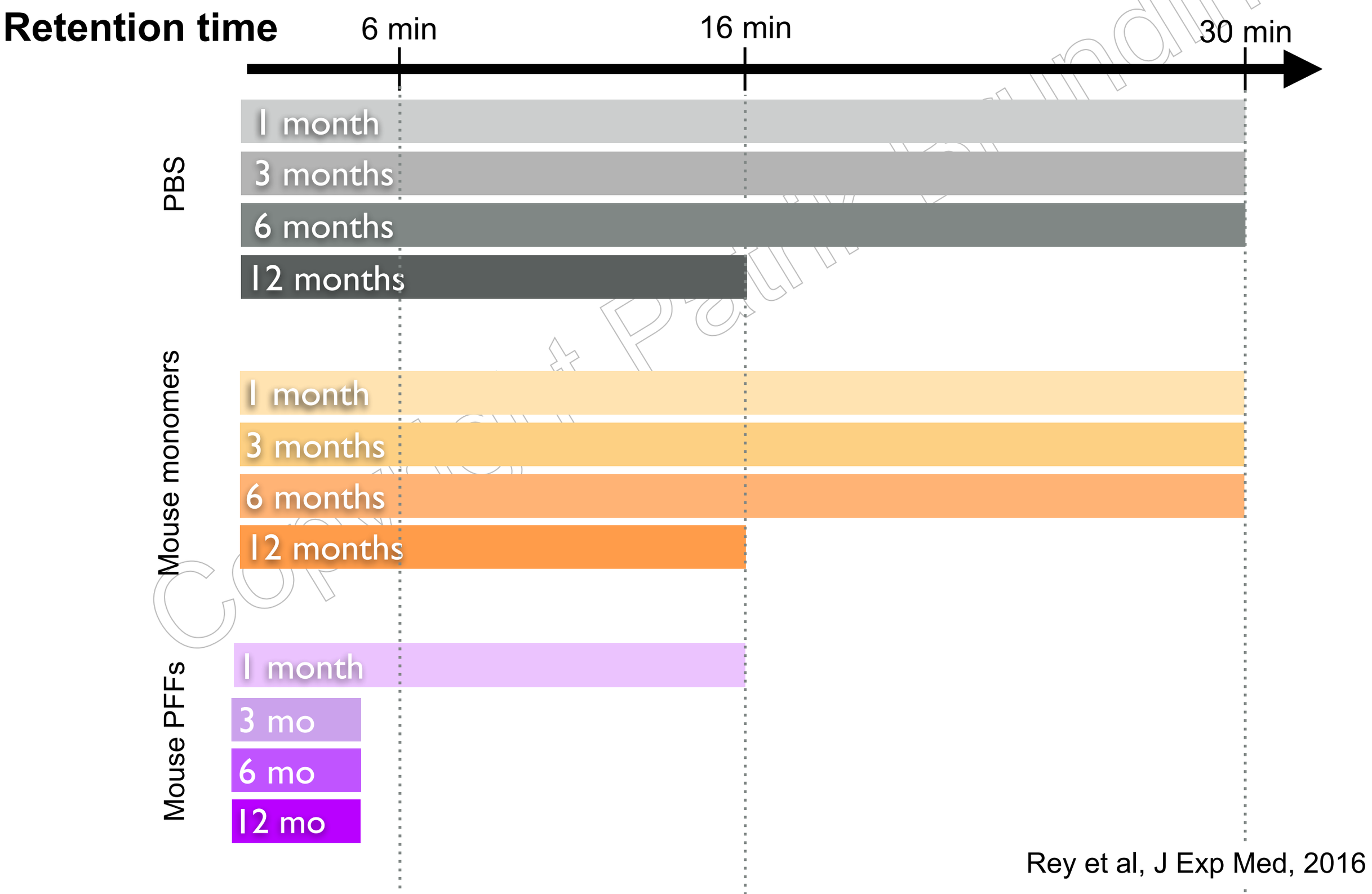


The aggregates are also thioflavin S-positive



Olfactory dysfunction

Progressive deficit in odor retention



Rey et al, J Exp Med, 2016

Future of olfactory bulb model of "prodromal" Parkinson's disease

- Understand triggers
- Define if cell death or protein aggregates drive the functional deficits
- Identify features of the α-synuclein fibril structure that determine pathology

Themes for today's talk

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- Two key future questions

1. Do different “strains” of α-synuclein aggregates exist?

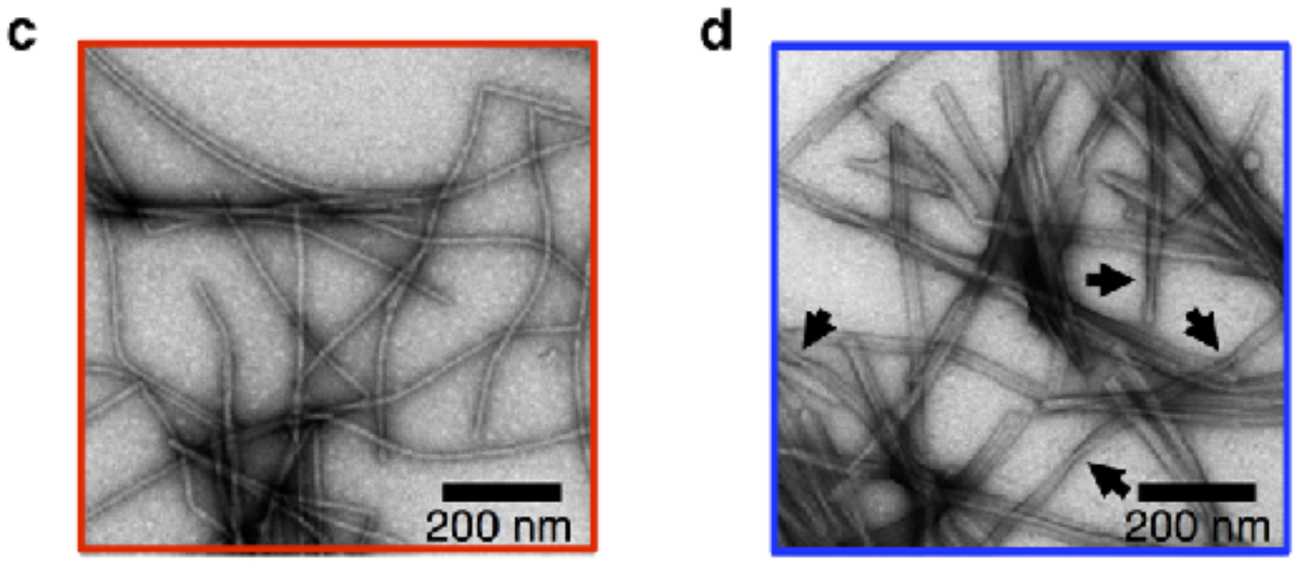
ARTICLE

Received 22 Mar 2013 | Accepted 9 Sep 2013 | Published 10 Oct 2013

DOI: 10.1038/ncomms3575 OPEN

Structural and functional characterization of two alpha-synuclein strains

Luc Bousset[1], Laura Pieri[1], Gemma Ruiz-Arlandis[1], Julia Gath[2], Poul Henning Jensen[3], Birgit Habenstein[4], Karine Madiona[1], Vincent Olieric[5], Anja Böckmann[4], Beat H. Meier[2] & Ronald Melki[1]



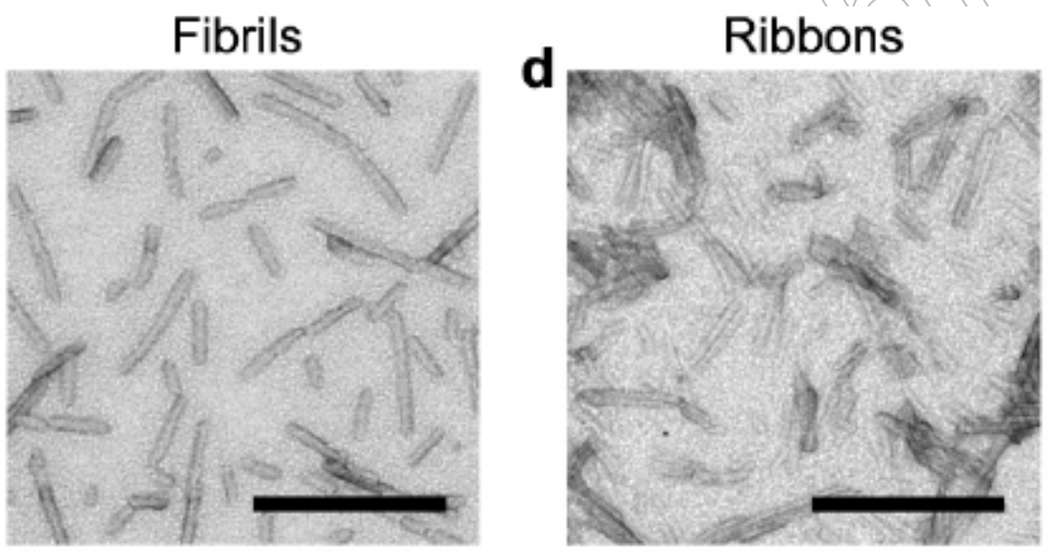
two polymorphs of α-synuclein. We present evidence that the two forms indeed fulfil the molecular criteria to be identified as two strains of α-synuclein. Specifically, we show that the two strains have different structures, levels of toxicity, and *in vitro* and *in vivo* seeding and propagation properties. Such strain differences may account for differences in disease progression in different individuals/cell types and/or types of synucleinopathies.

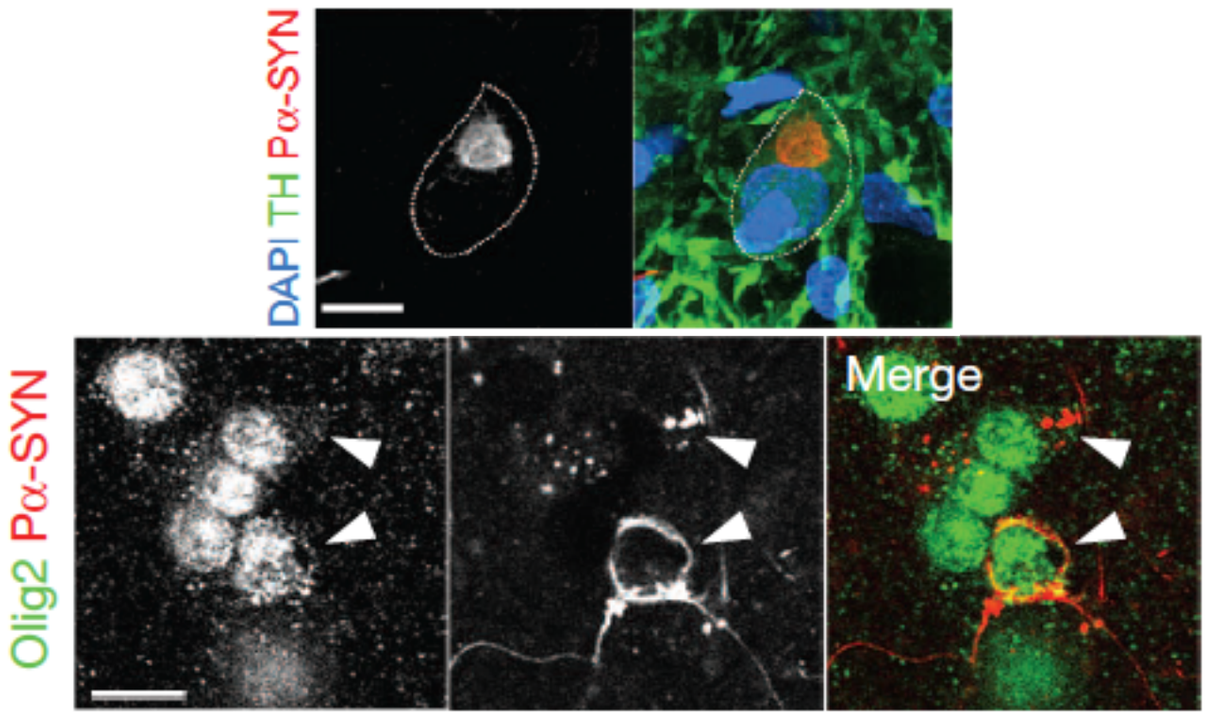
α–Synuclein strains cause distinct synucleinopathies after local and systemic administration

W. Peelaerts[1], L. Bousset[2], A. Van der Perren[1], A. Moskalyuk[3], R. Pulizzi[3], M. Giugliano[3,4,5,6], C. Van den Haute[1,7], R. Melki[2] & V. Baekelandt[1]

| NATURE | 2015

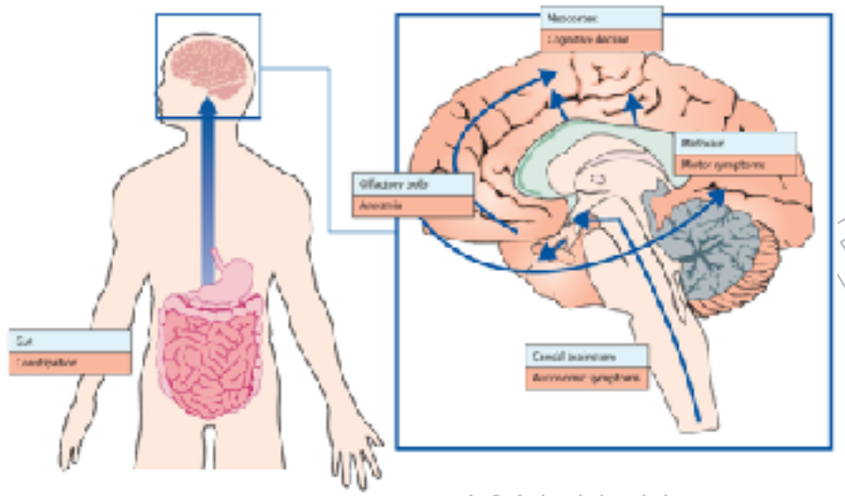
Different strains of α-synuclein aggregates, causing different pathologies





2. What is the initial trigger of formation and progression of α-synuclein aggregation?

2. What is the initial trigger?



- No evidence (yet) of communicability
- Inflammation might be a key trigger
- Environmental (toxin or infectious) insults are possible
- Genetic susceptibility (‘trigger facilitators’ or ‘poor defence’) can play a role
- Trigger site might differ between patients

The olfactory bulb as the entry site for prion-like propagation in neurodegenerative diseases

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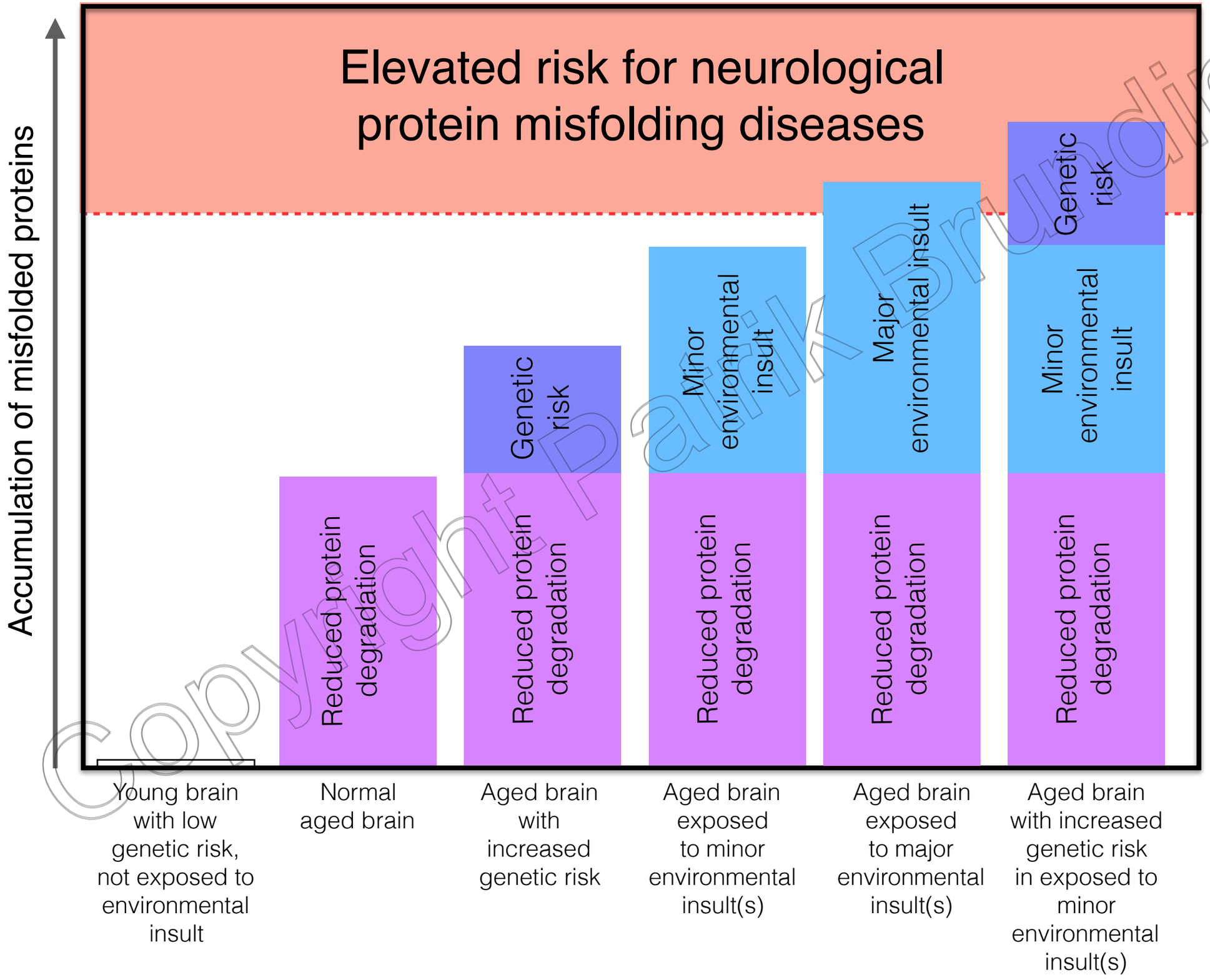
Neurobiology of Disease

Article history:
Received 7 October 2016
Revised 13 December 2016
Accepted 15 December 2016
Available online xxxx

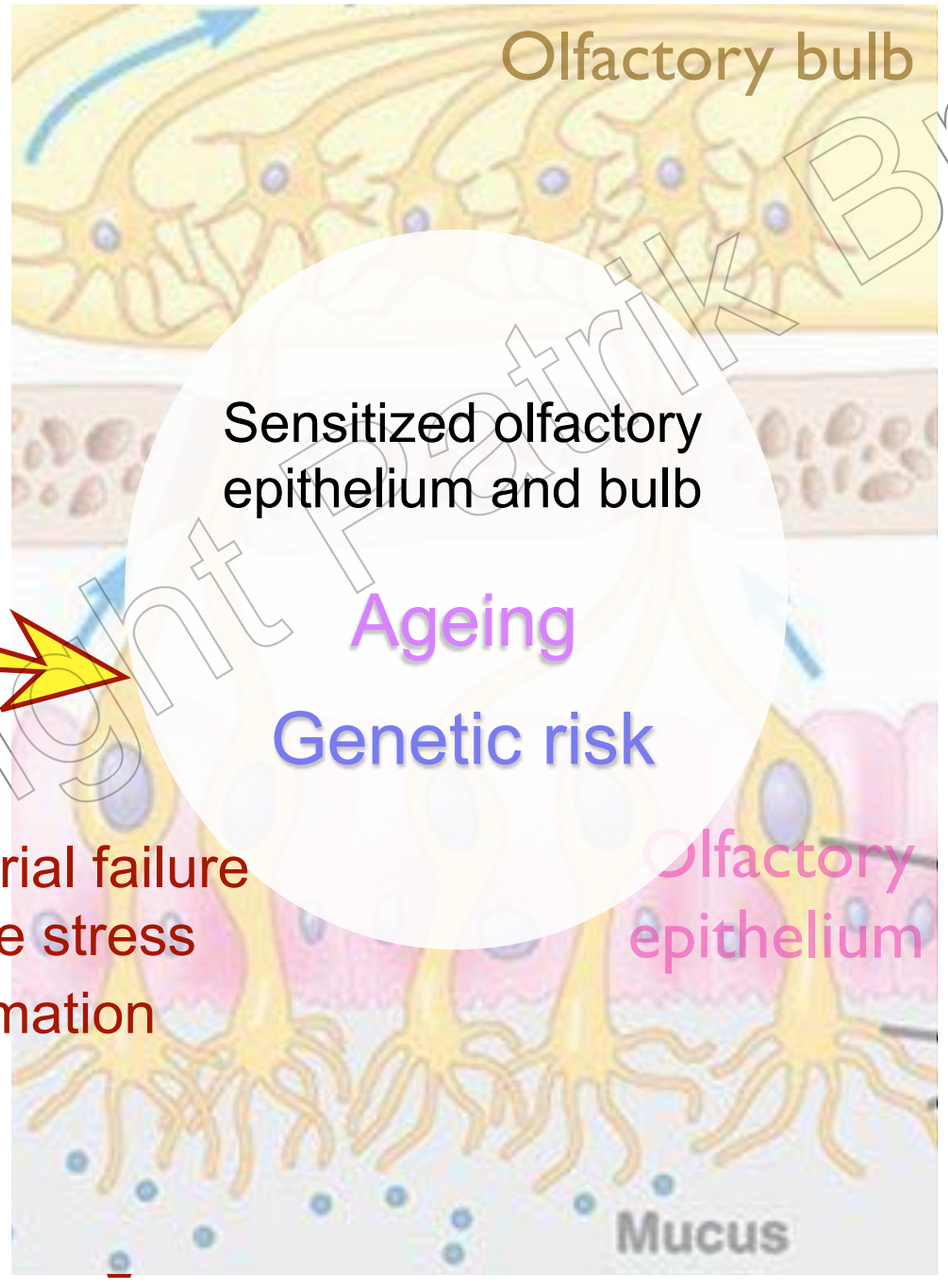
A B S T R A C T

Olfactory deficits are present in numerous neurodegenerative disorders and are accompanied by pathology in related brain regions. In several of these disorders, olfactory disturbances appear early and are considered as prodromal symptoms of the disease. In addition, pathological protein aggregates affect olfactory regions prior to other regions, suggesting that the olfactory system might be particularly vulnerable to neurodegenerative diseases. Exposed to the external environment, the olfactory epithelium and olfactory bulb allow pathogen and toxin penetration into the brain, a process that has been proposed to play a role in neurodegenerative diseases.



George and Brundin 2017

The olfactory bulb as a trigger site



Environmental factors

Toxins
Viruses
Nanoparticles
Pollutants
Pesticides
Metals

Sensitized olfactory epithelium and bulb

Ageing

Genetic risk

Mitochondrial failure
Oxidative stress
Inflammation

α-Synuclein aggregation

Prion-like propagation

Concluding remarks

- α-Synuclein can behave like a prion
- Animal models help identify underlying mechanisms
- Extracellular α-synuclein is a novel therapeutic target, also in “prodromal” Parkinson’s disease

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Trevor Tyson

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NIH National Institute of Neurological Disorders and Stroke
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
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