
Prion-like propagation of alpha-synuclein aggregates in the brain of wild-type mice

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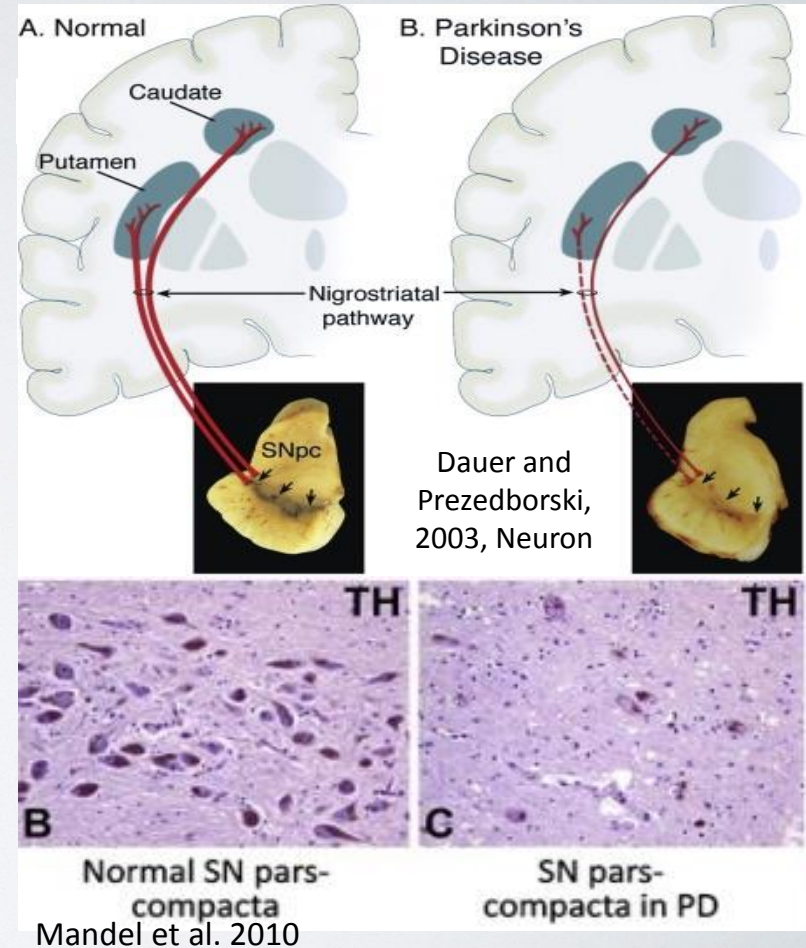


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No conflict of interest to disclose

α - Synuclein and Parkinson's disease

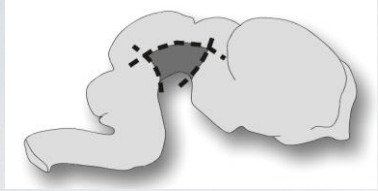
- Lewy bodies (LB) and Lewy neurites, hallmarks of Parkinson's disease
- Misfolded and hyper phosphorylated α -syn
- Death of midbrain dopamine neurons is key to motor symptoms
- Non-motor symptoms are also a major issue



Fetal neuron transplants in Parkinson's disease

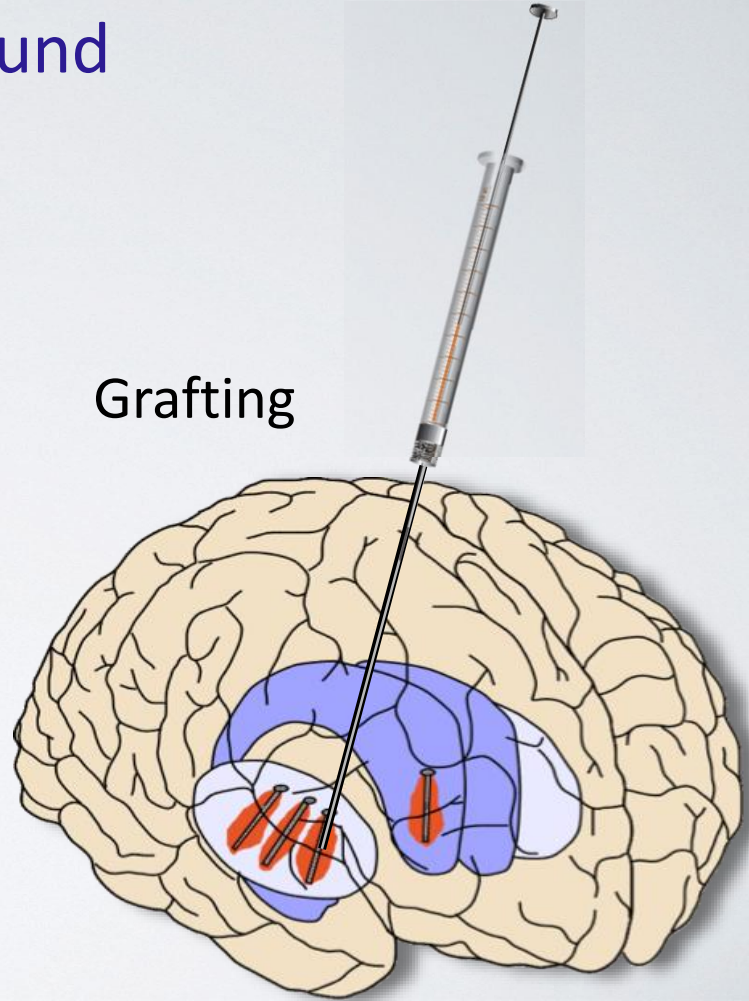
1987-1999 Lund

Fetal DA neurons



Multiple donors for
each brain

Grafting

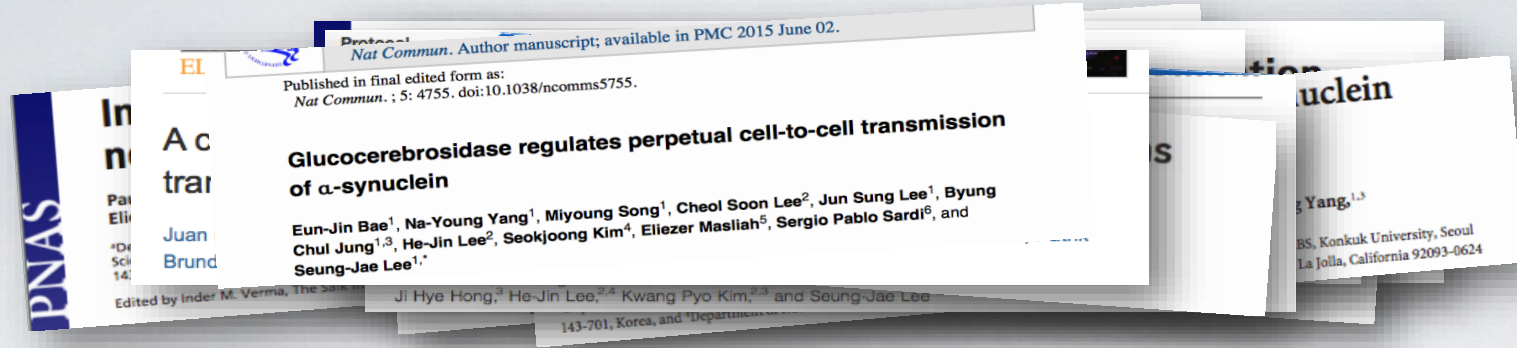


Young transplanted neurons with Lewy bodies



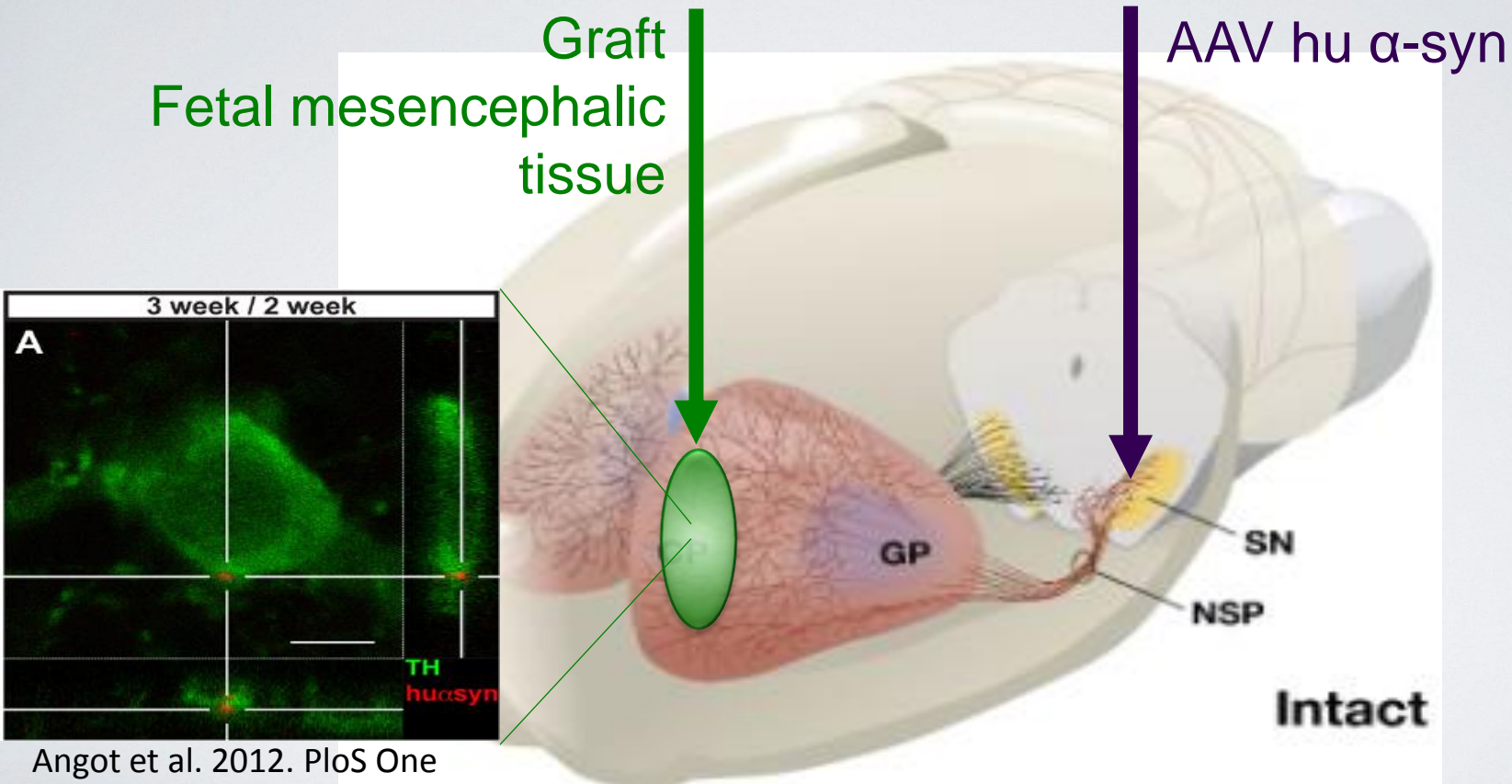
Lewy bodies in grafted neurons in at least
9 cases from 5 different surgical centers

Cell-to-cell transfer: “Prion-like” propagation hypothesis



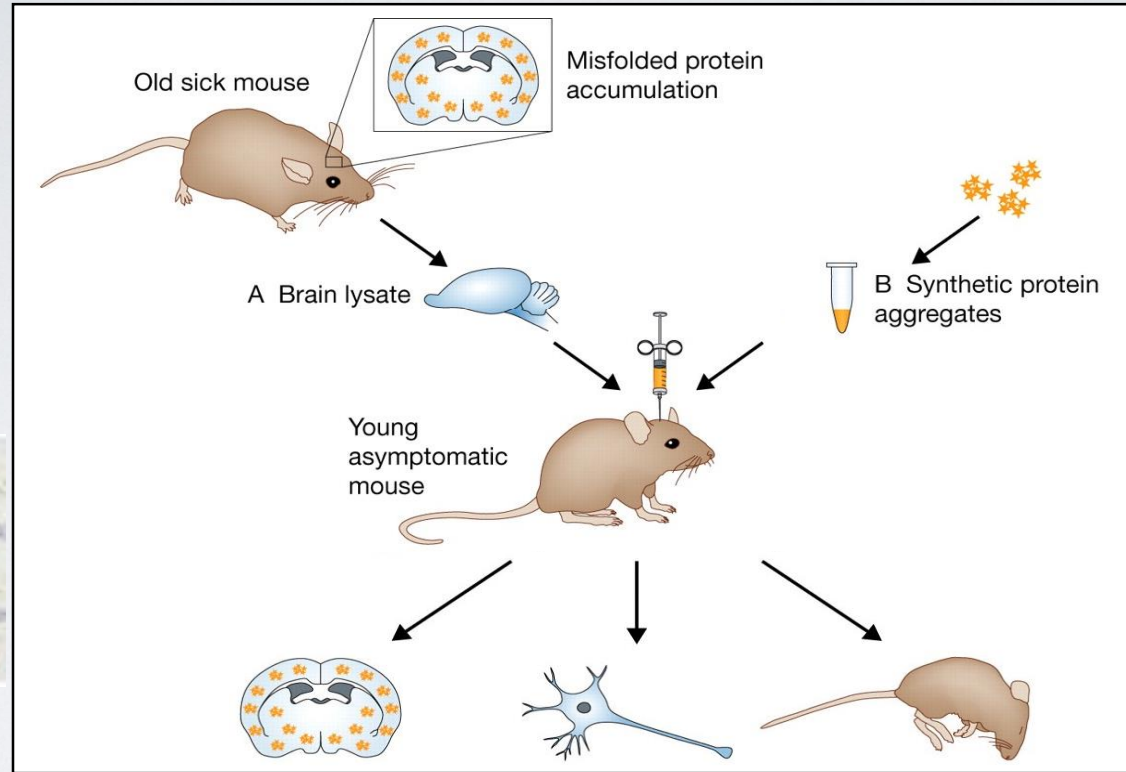
Adapted from Angot et al. 2010

First animal model of cell-to-cell transfer

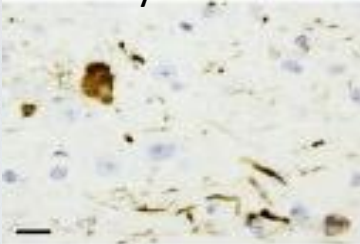


Modified from Kirik et al. 2004, Nat Neurosc

α -Synuclein seeding in vivo, and propagation

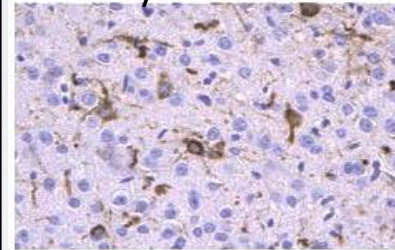


Brain lysate



Mougenot et al. 2012
Neurobiology of Aging

Synthetic PFFs

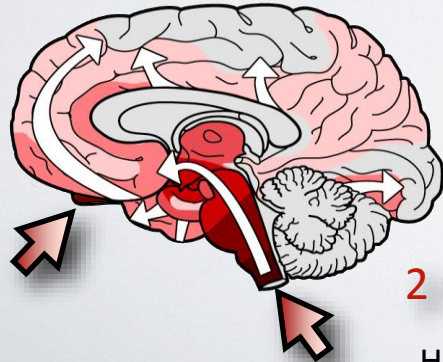
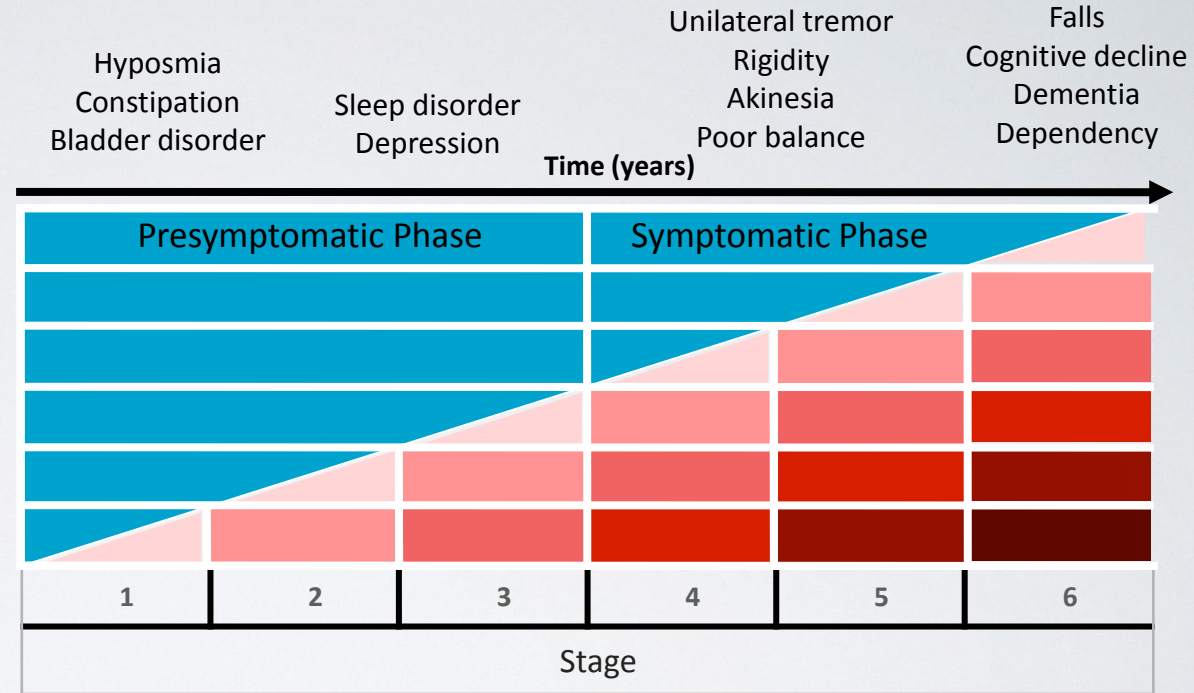


Luk et al. 2012 J
Exp Med

Adapted from Polymenidou and Cleveland, 2012 JEM

Propagation along connections (as suggested in humans) ?

Parkinson's disease staging



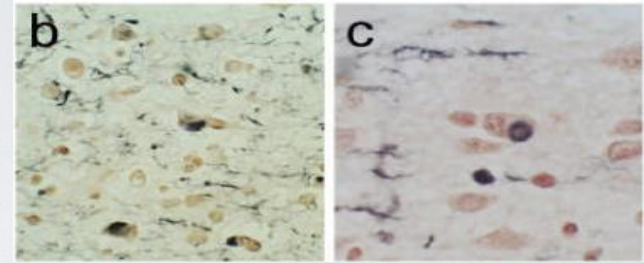
2 routes of progression ?

Hawkes et al.. 2007, 2009, 2010

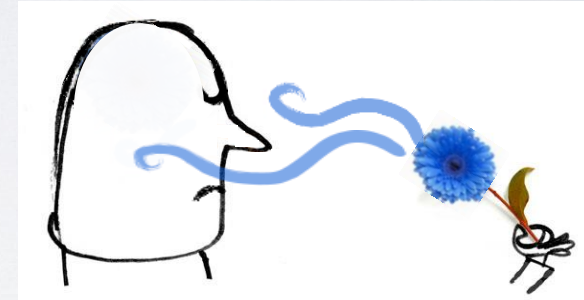
Braak et al. 2002, 2003, 2004

Olfactory system in Parkinson's disease

- α -Syn pathology: first in the olfactory bulb (then in the DMX) (Beach et al. 2009, Braak and Del Tredici 2016)
- Olfactory dysfunction: > 4 years before clinical diagnosis of PD
- Prevalence: 75-96% in patients with PD (Attems et al. 2014 Acta Neuropathologica)



Beach et al. 2009, Acta Neuropathologica

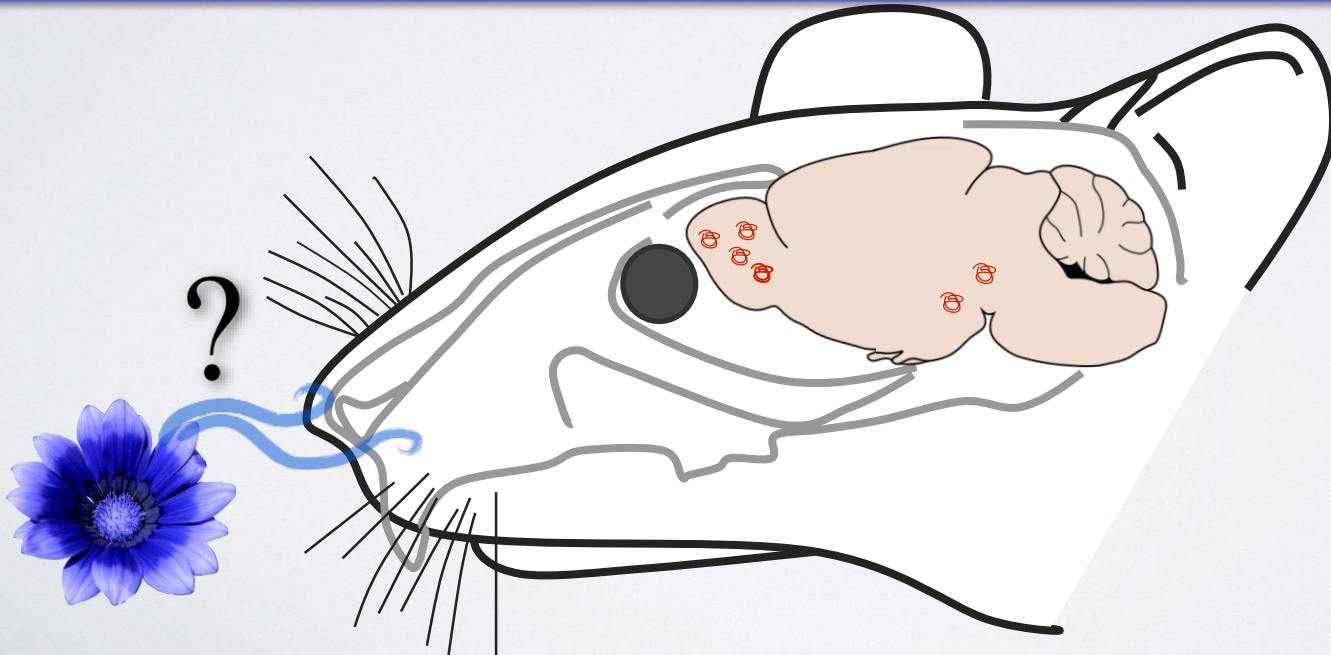


The olfactory system is involved in prodromal Parkinson's disease

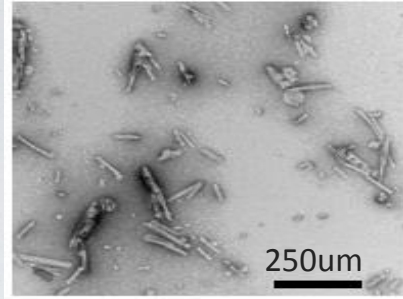
Olfactory bulb pathology model

Cell-to-cell transfer and propagation of α -syn during prodromal PD are potential therapeutic targets

Create a model of progressive α -syn pathology of direct relevance to prodromal PD



Olfactory bulb pathology model

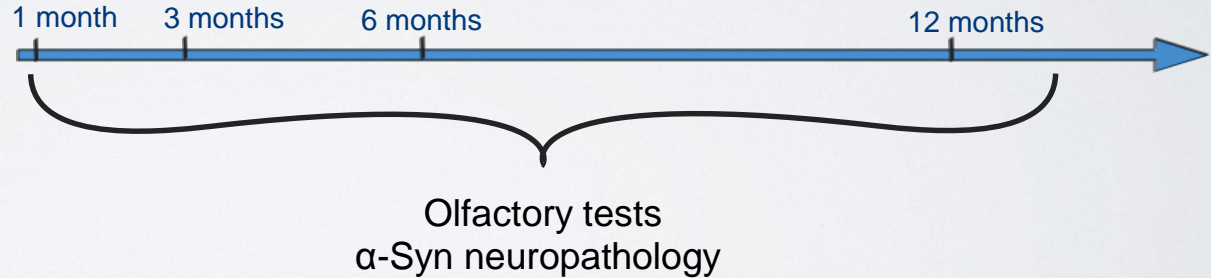
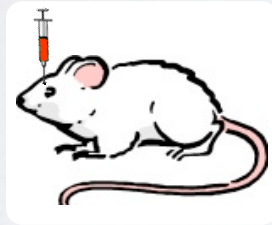


α -Syn fibrils (PFFs)

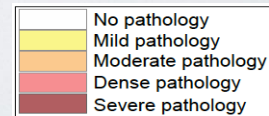
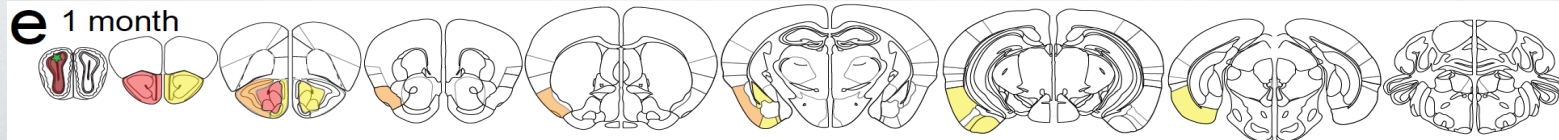
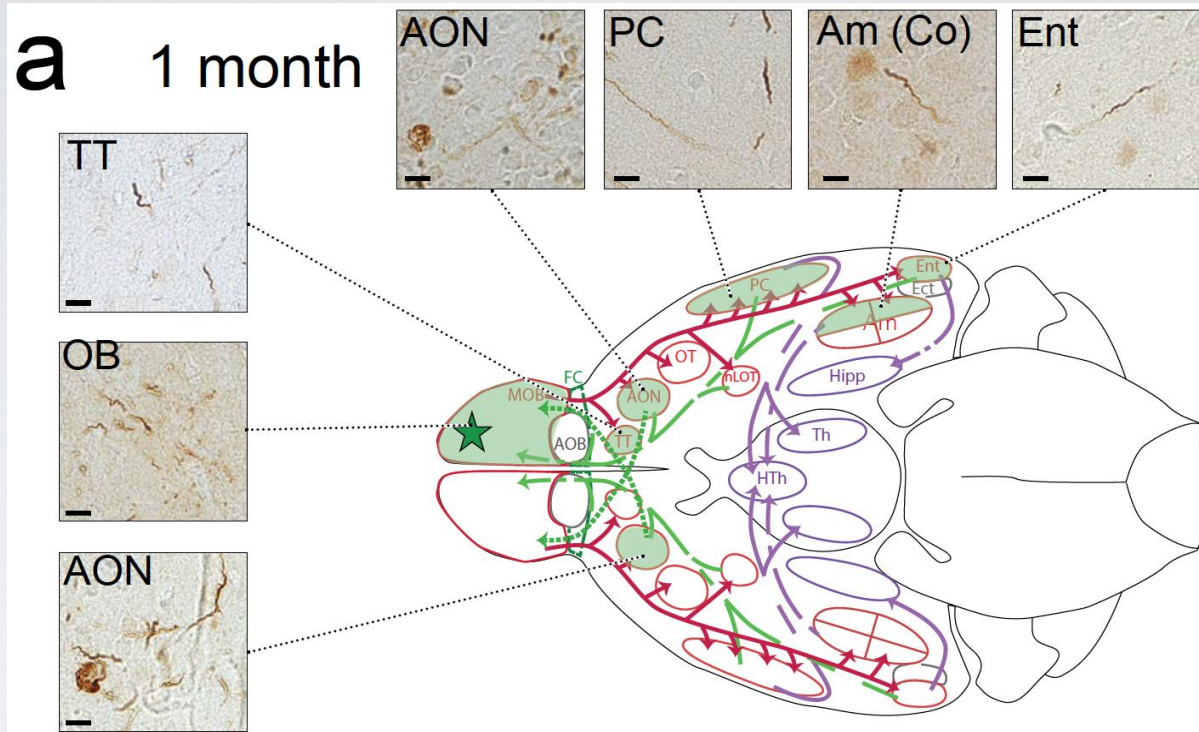
[α -syn monomer and PBS as controls]

Injection into the olfactory bulb

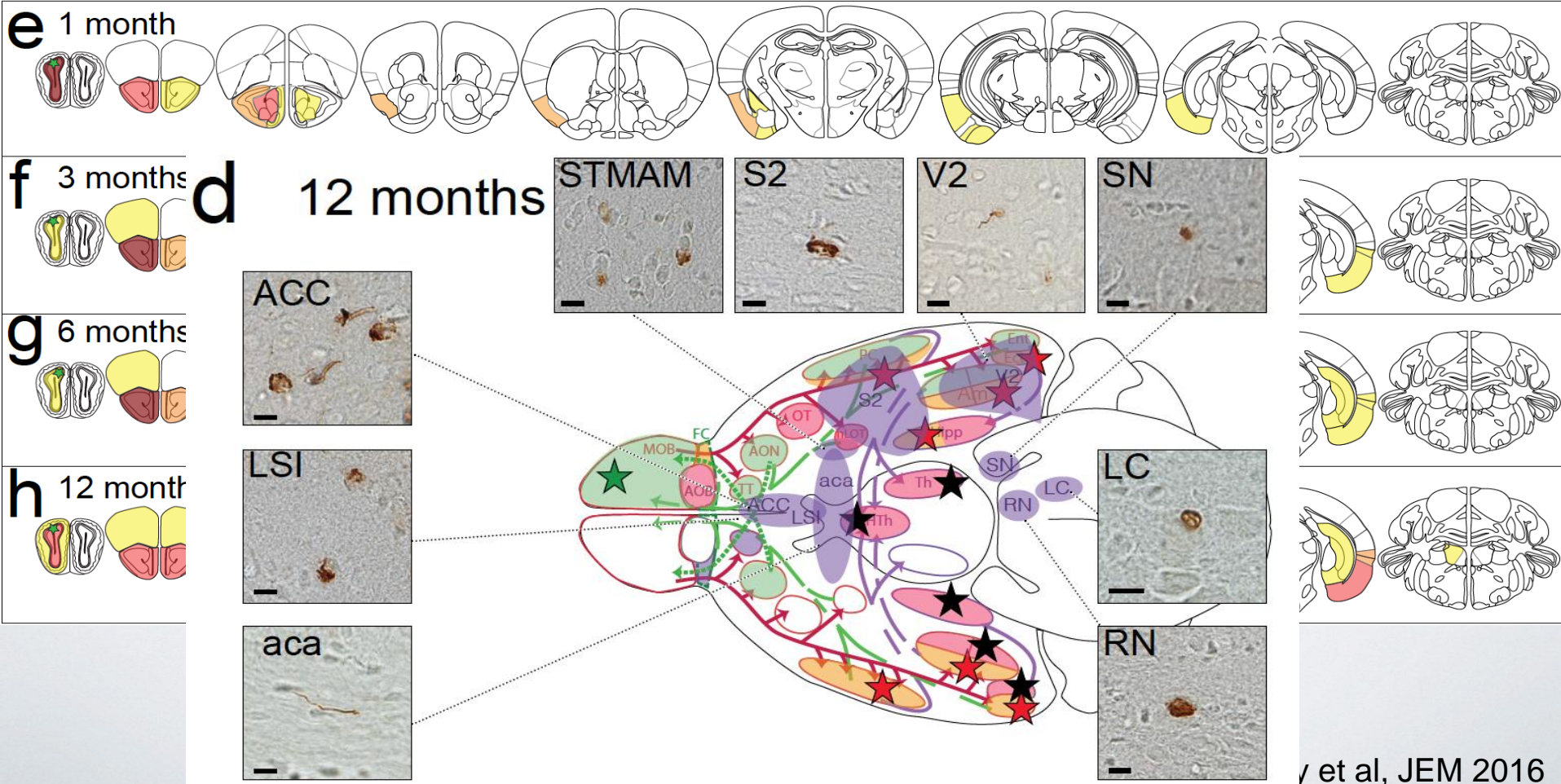
Wild type
mice



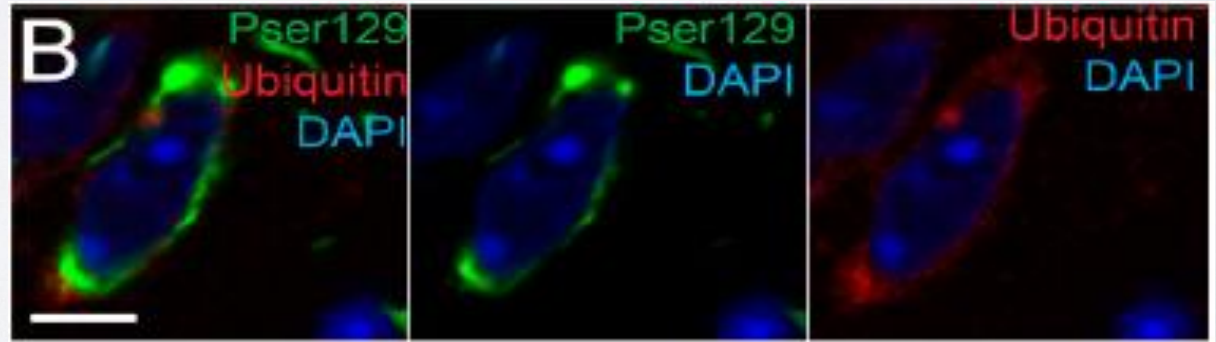
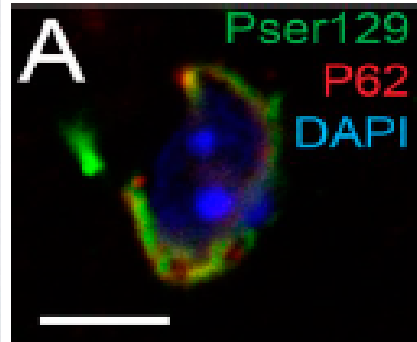
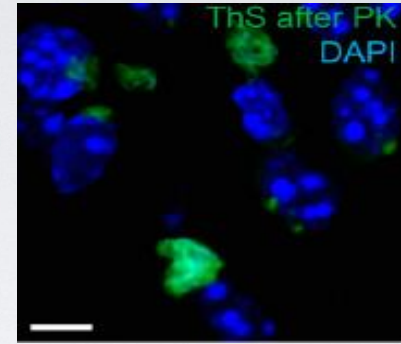
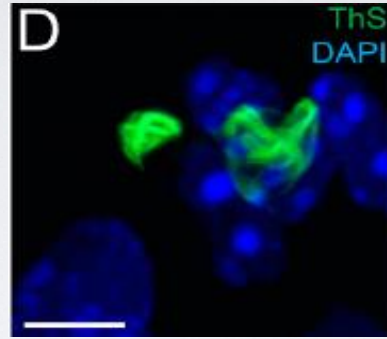
Pser129 α -syn pathology in olfactory structures



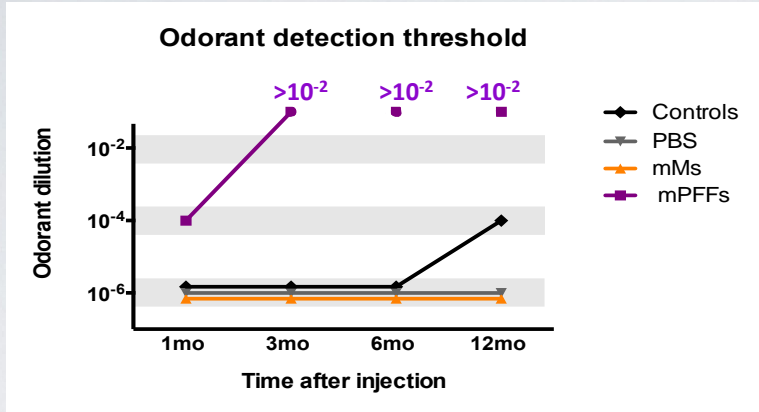
Pser129 pathology α -syn propagation



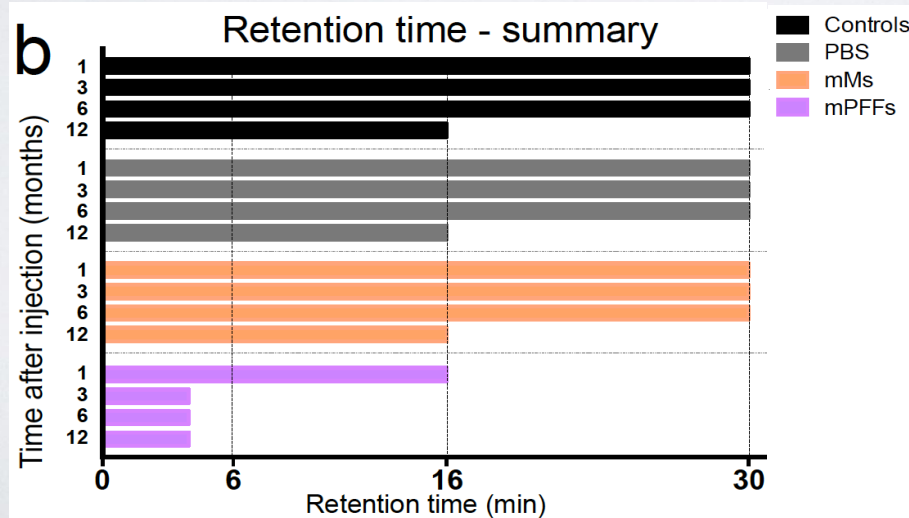
Inclusions positive for markers of Lewy bodies in neurons



Progressive olfactory deficits



- Severe deficit of **odor detection** in PFFs-injected mice



- Severe deficit of **odor retention** in PFFs-injected mice

Concluding remarks

- ✓ Neuron-to-neuron transfer *in vivo*
 - ✓ Seeding *in vivo*
 - ✓ Propagation of pathology between distal brain regions, following neuronal connections
-
- ➡ Mechanisms of initiation of pathology?
 - ➡ Mechanisms of transmission between cells/ distal brain regions?
 - ➡ Non-neuronal cells involved in propagation?

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