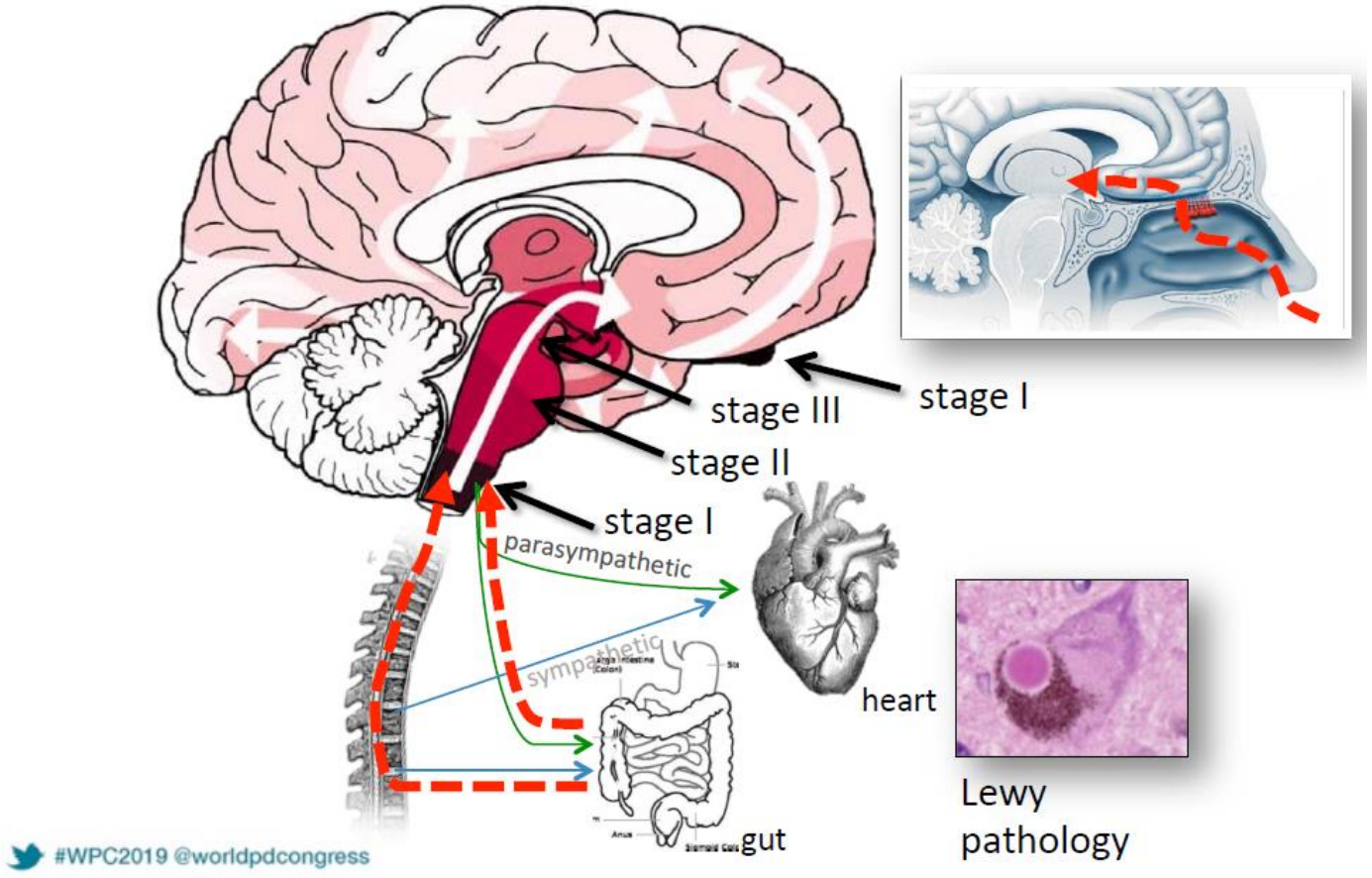
Origins and early stages of Parkinson's

David Melton

Does Parkinson's start outside the brain ?

Per Borghammer Denmark

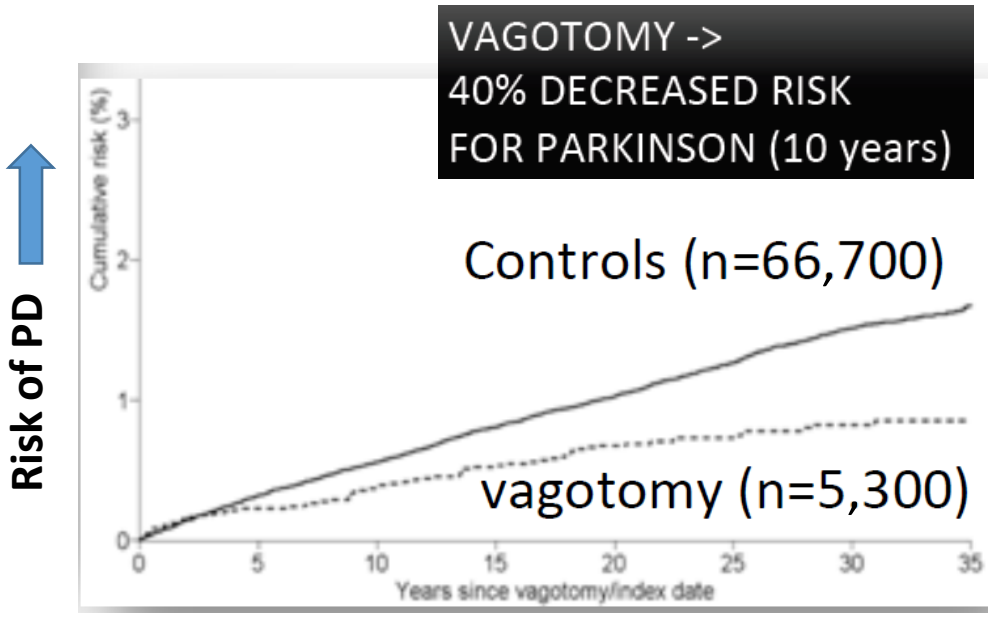
Dual hit hypothesis

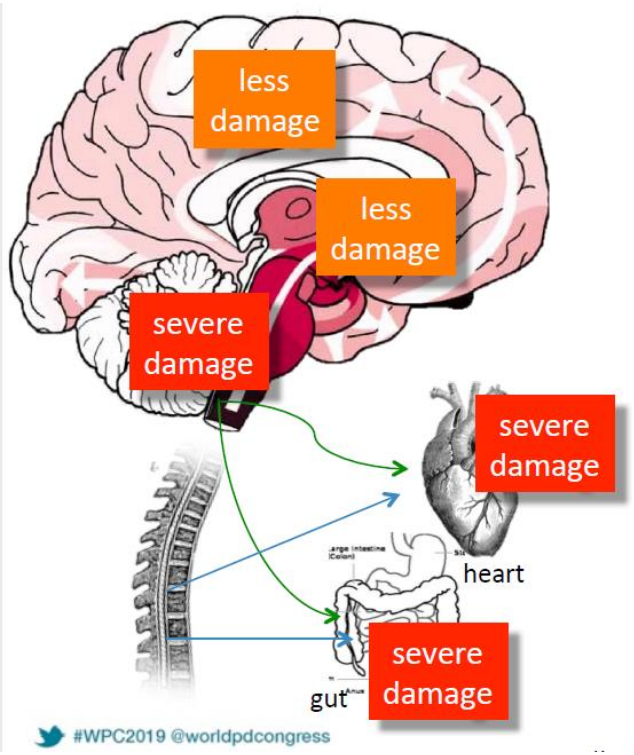


Body first evidence in Parkinson's

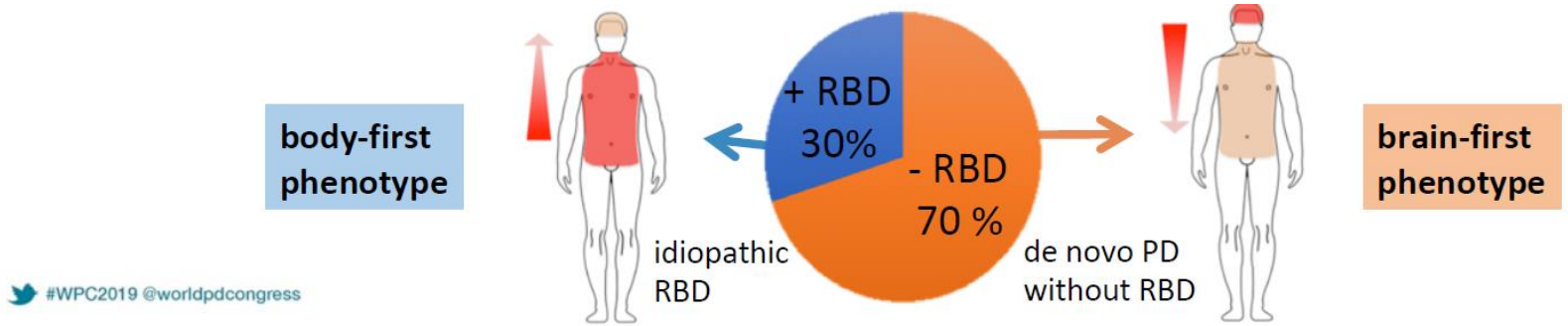
- **Lewy pathology in gut 20 years before diagnosis**
- **vagotomy protects against PD**
- **animal evidence – gut-to-brain spreading**
- **RBD patients have severe autonomic damage but minimal dopaminergic damage**

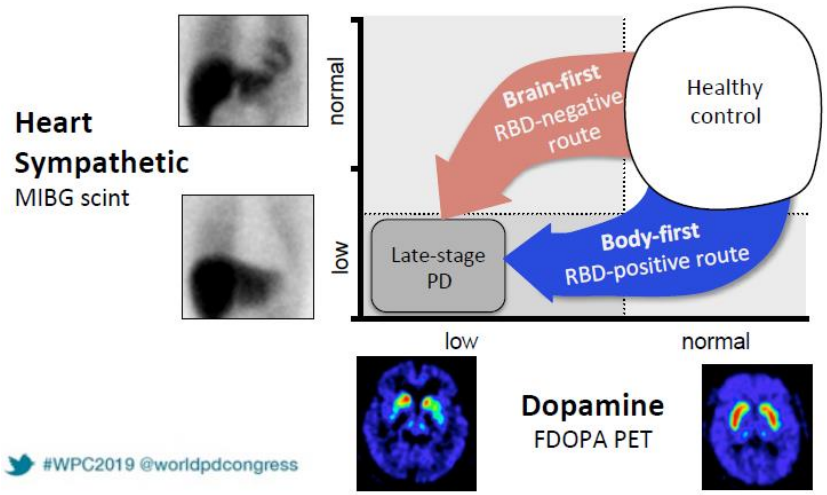
(RBD = Rapid eye movement sleep behaviour disorder)

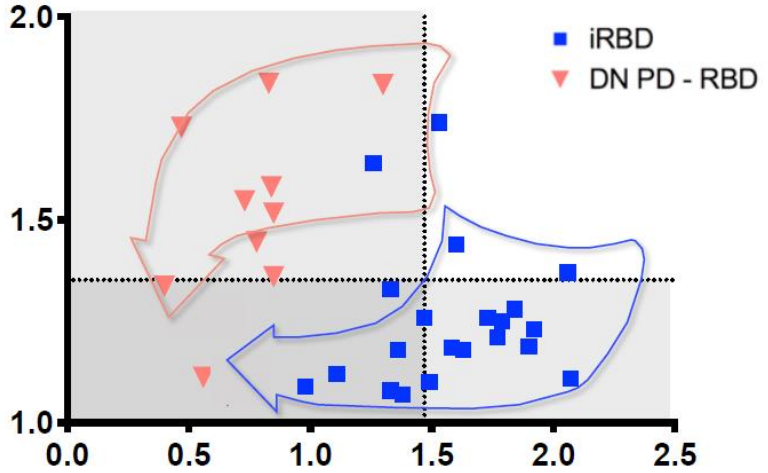




…maybe PD only starts in the gut in some patients ?







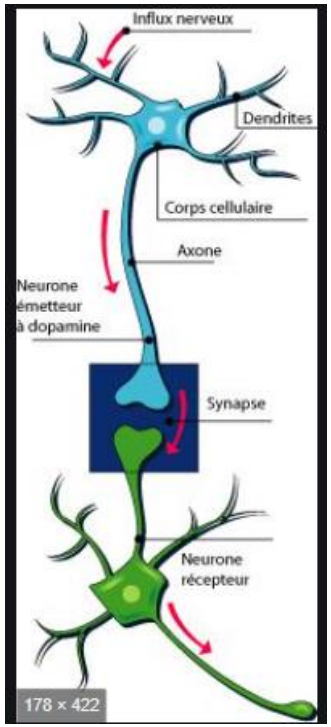
Role of α-synuclein in Parkinson's

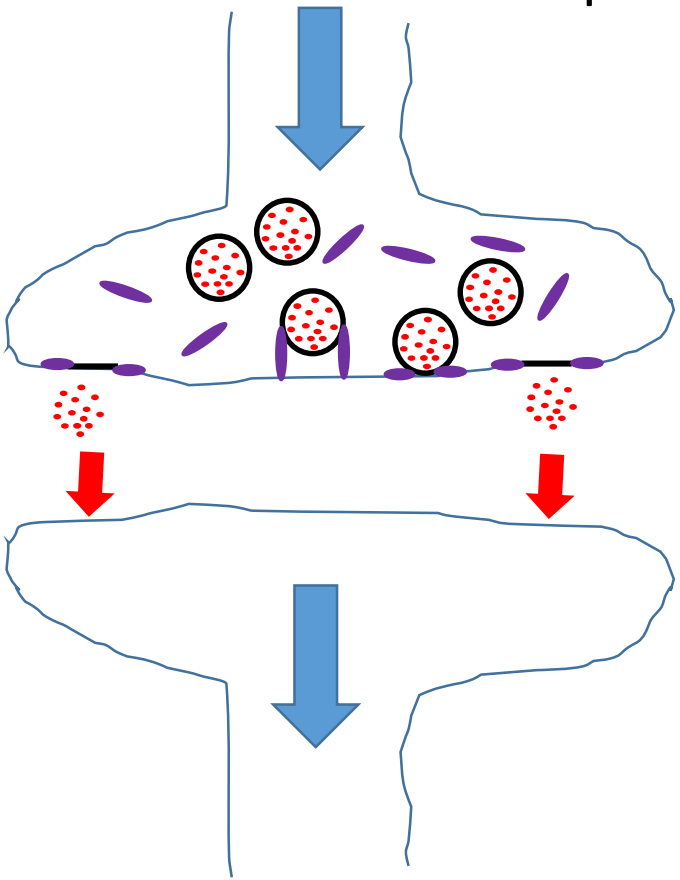
- Normal role of α-Syn
- α-Syn aggregation and disease

- Ronald Melki France

Alpha-synuclein normal function

- Small protein-140 amino acids
- Unusual protein in that it does not have a single distinct folded structure
- Has a key role in neurotransmission at presynaptic terminals



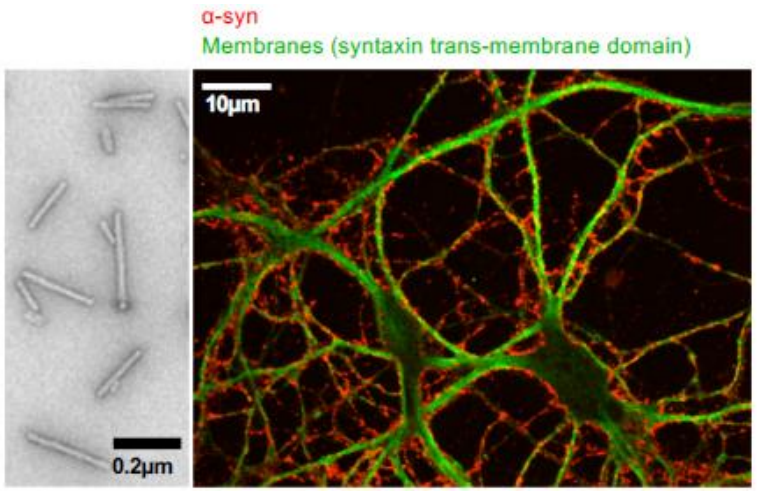


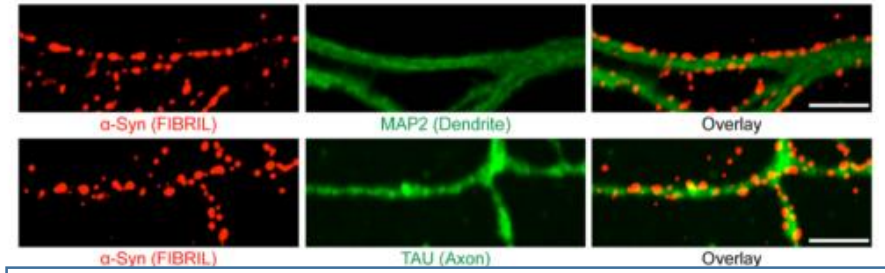
α-Syn

Vesicle with neurotransmitter (e.g. Dopamine)

α-Syn aggregation

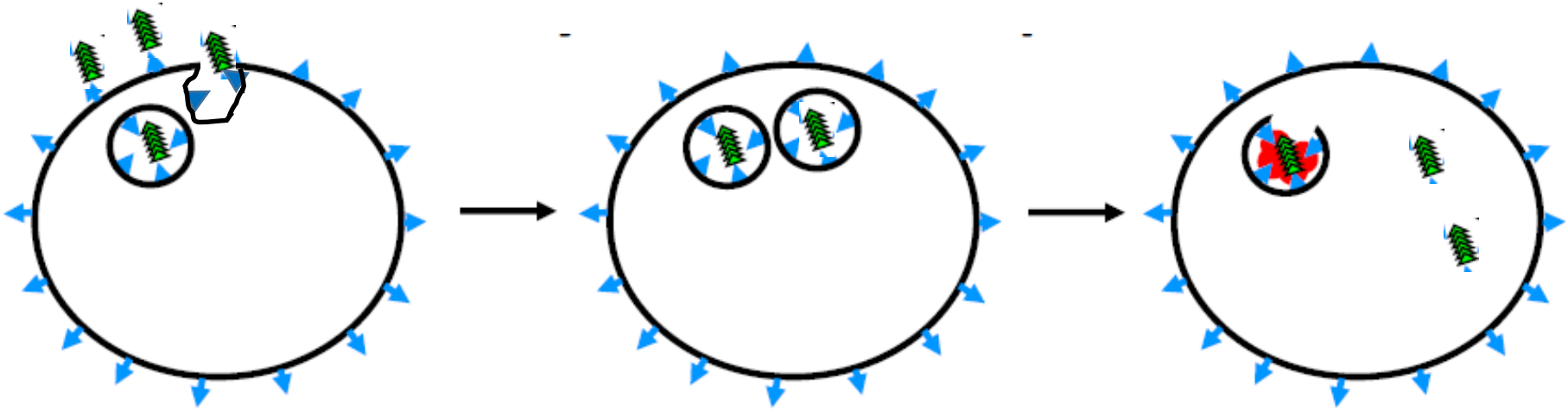
- α-Syn is dynamic, it can adopt different structural forms in our bodies
- Some of these forms can aggregate into larger assemblies that are damaging to neurons (nerve cells)
- Fibrils of α-Syn binding to neurons:



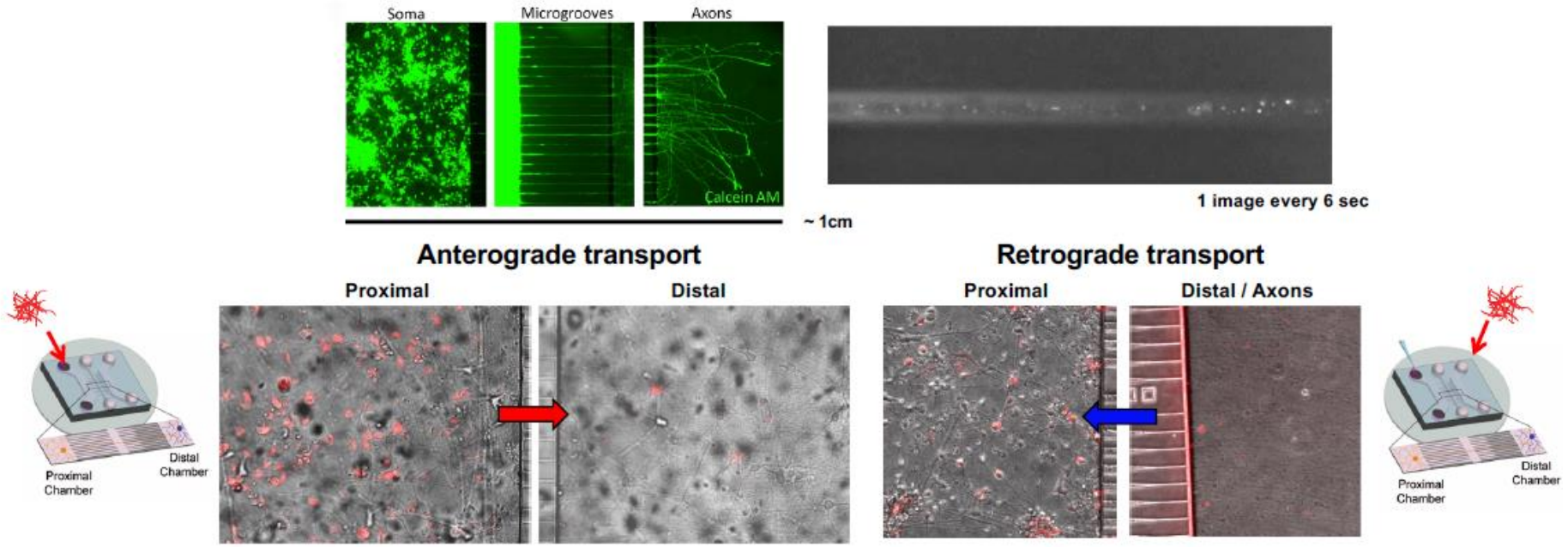


α-Syn fibrils are taken up by neurons in vesicles but then they escape into the interior

- Vesicles are part of an essential intracellular system for breaking down and recycling damaged proteins

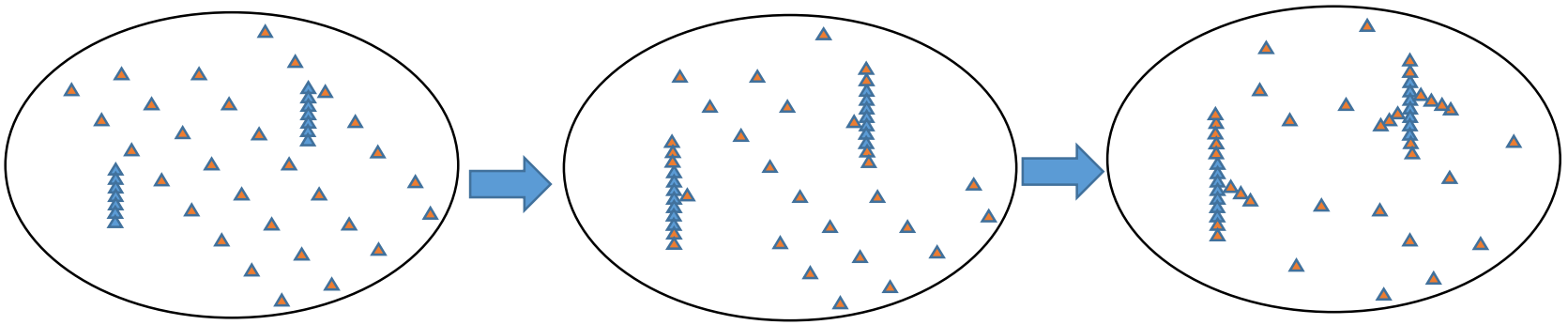


Fibrillar α-Syn is taken up by neurons & transported through axons



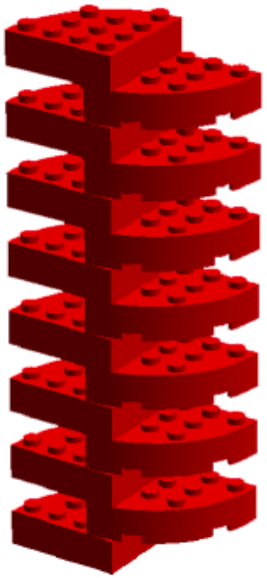
This is pathogenic (bad for us) because:

- The binding of α-Synuclein fibrils damages the cell membrane of neurons and compromises neuron to neuron communication
- α-Synuclein fibrils damage the vital internal neuronal vesicle compartment
- α-Synuclein fibrils seed the aggregation of normal α-Synuclein within neurons and this damages mitochondria- the vital energy generating structures within all cells

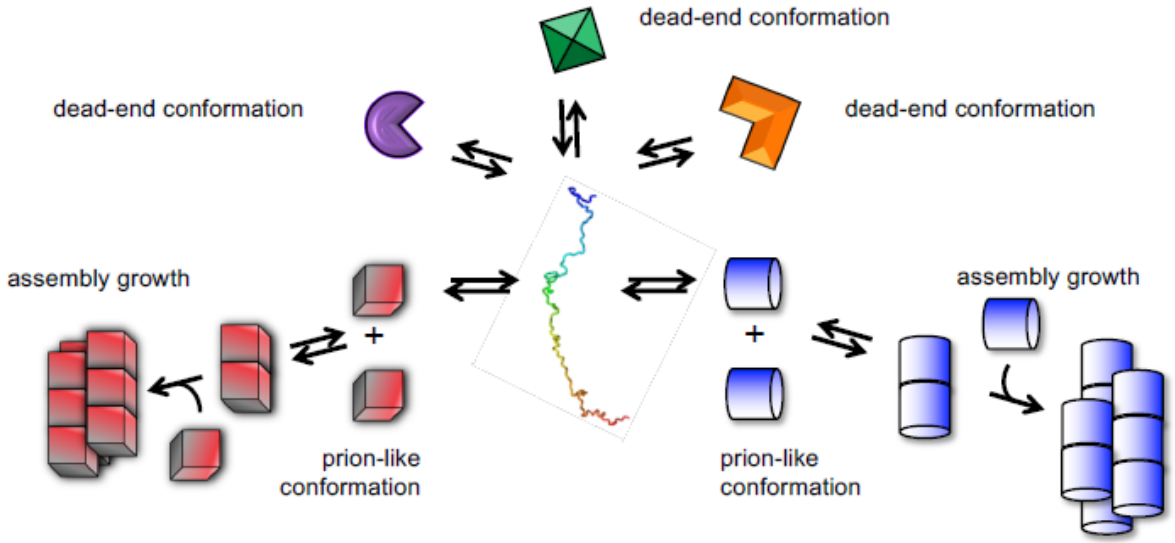


- These effects combine to cause neuron degeneration

How can α-Syn aggregation cause distinct diseases ?

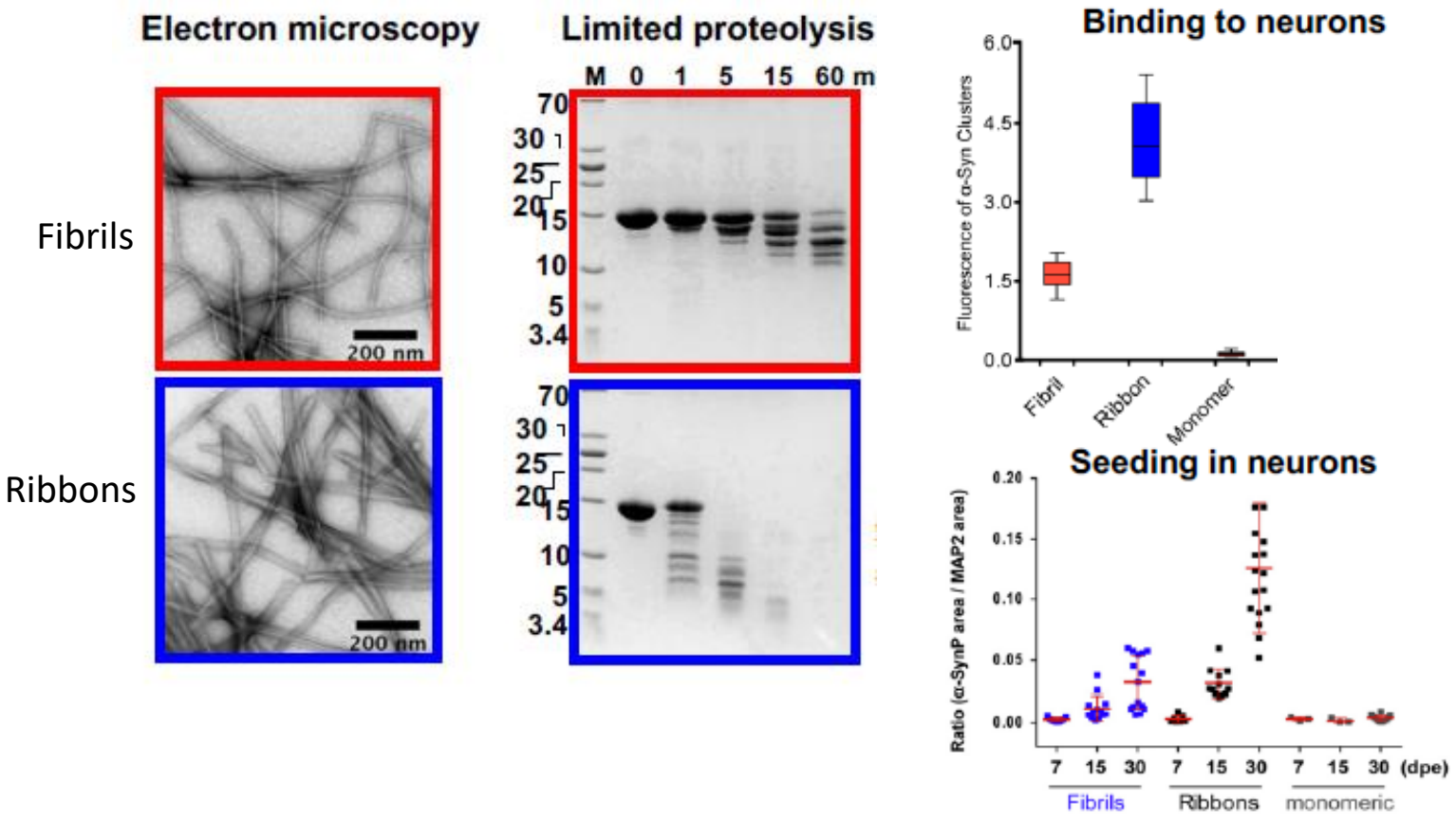


Ribbons



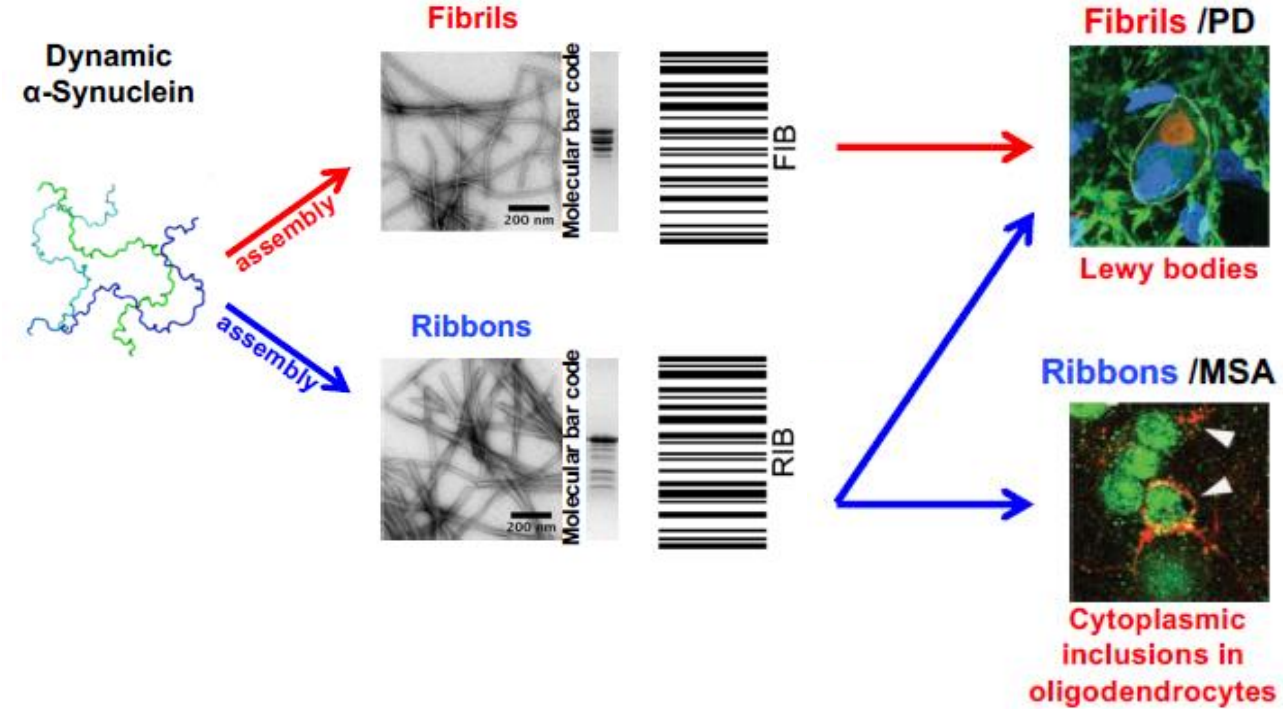
Fibrils

Different α-Syn aggregates have distinct structural characteristics and binding and seeding properties



In animal models α-Syn fibrils and ribbons cause different diseases

- Fibrils cause Parkinson's
- Ribbons cause Parkinson's and MSA-multiple system atrophy - an earlier onset faster progressing condition affecting different parts of brain to PD (L dopa is ineffective) and supporting (glial) cells rather than neurons



The challenge

- α-Synuclein aggregation occurs constantly in **everyone**
- It only becomes harmful if the normal cellular processes that combat aggregation fail to cope
- Combating pathogenic assembly and propagation of α-Synuclein and its many damaging effects on neurons should prevent disease progression