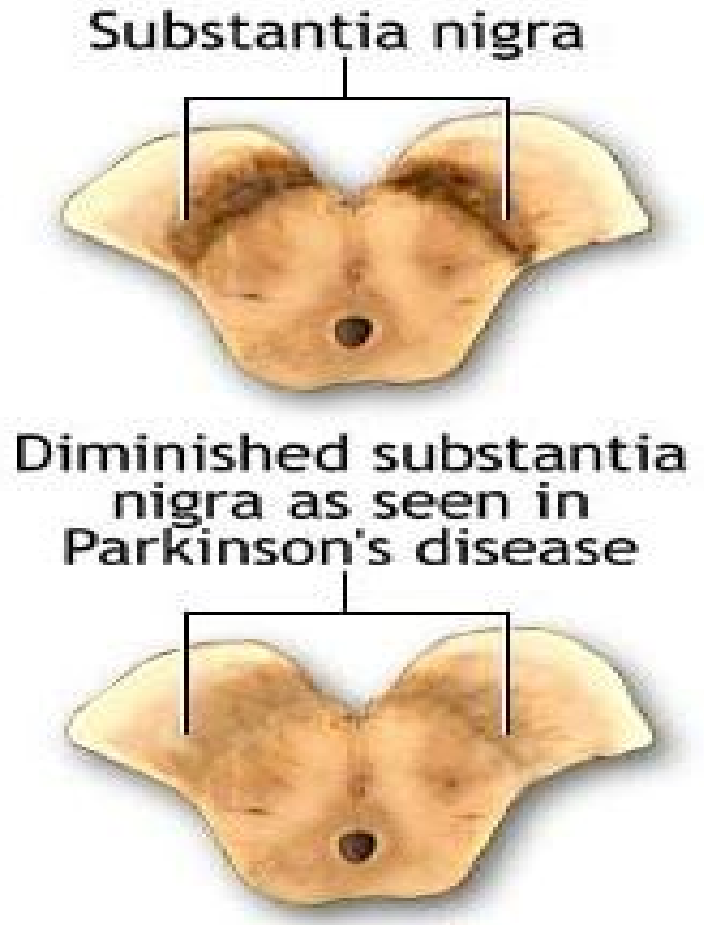
α-Synuclein misfolding and axon degeneration as key pathogenic events in Parkinson's Disease

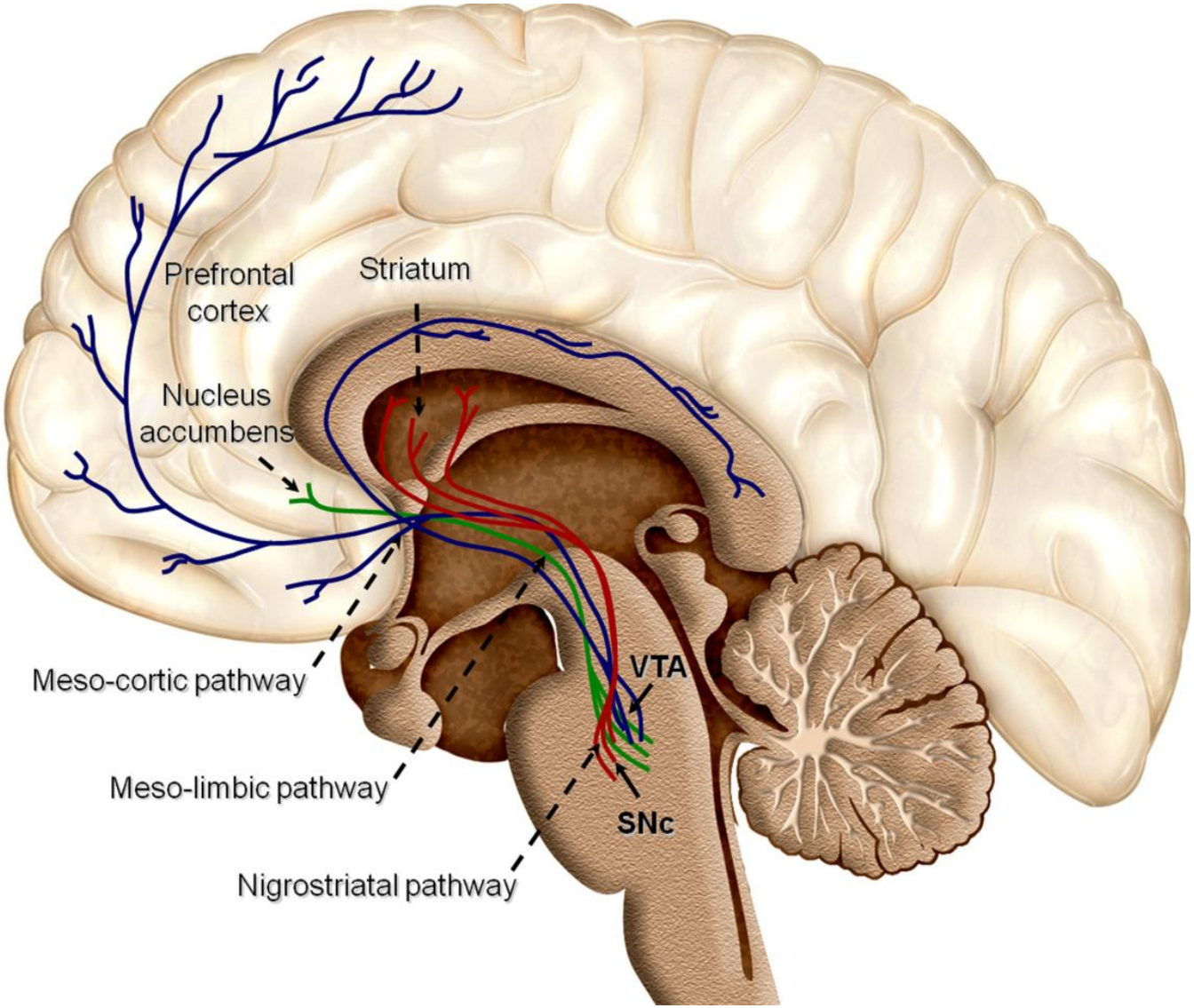
Fella Hammachi
Scottish Centre for Regenerative medicine

Typical Pathology

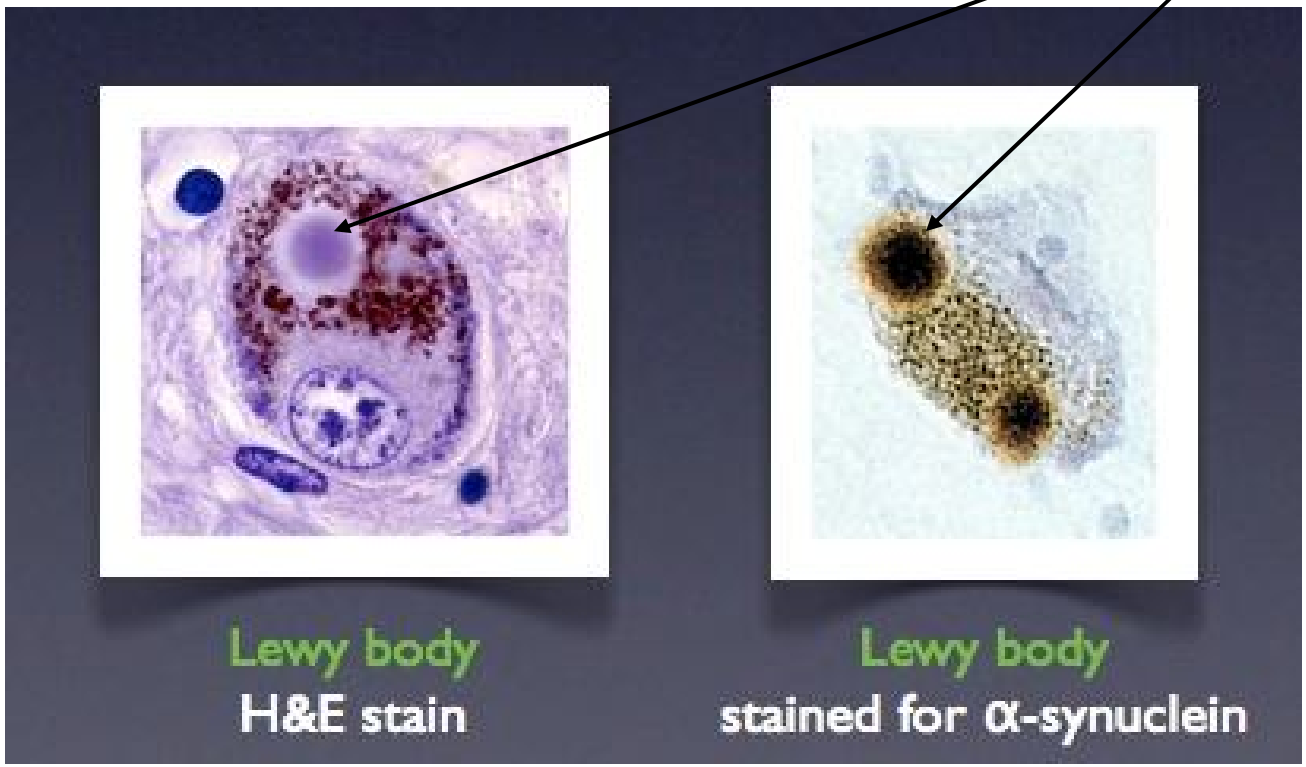
-Loss of dopaminergic neurons in substantia nigra



Substantia nigra (SNc) neurons innervate putamen and caudate of striatum



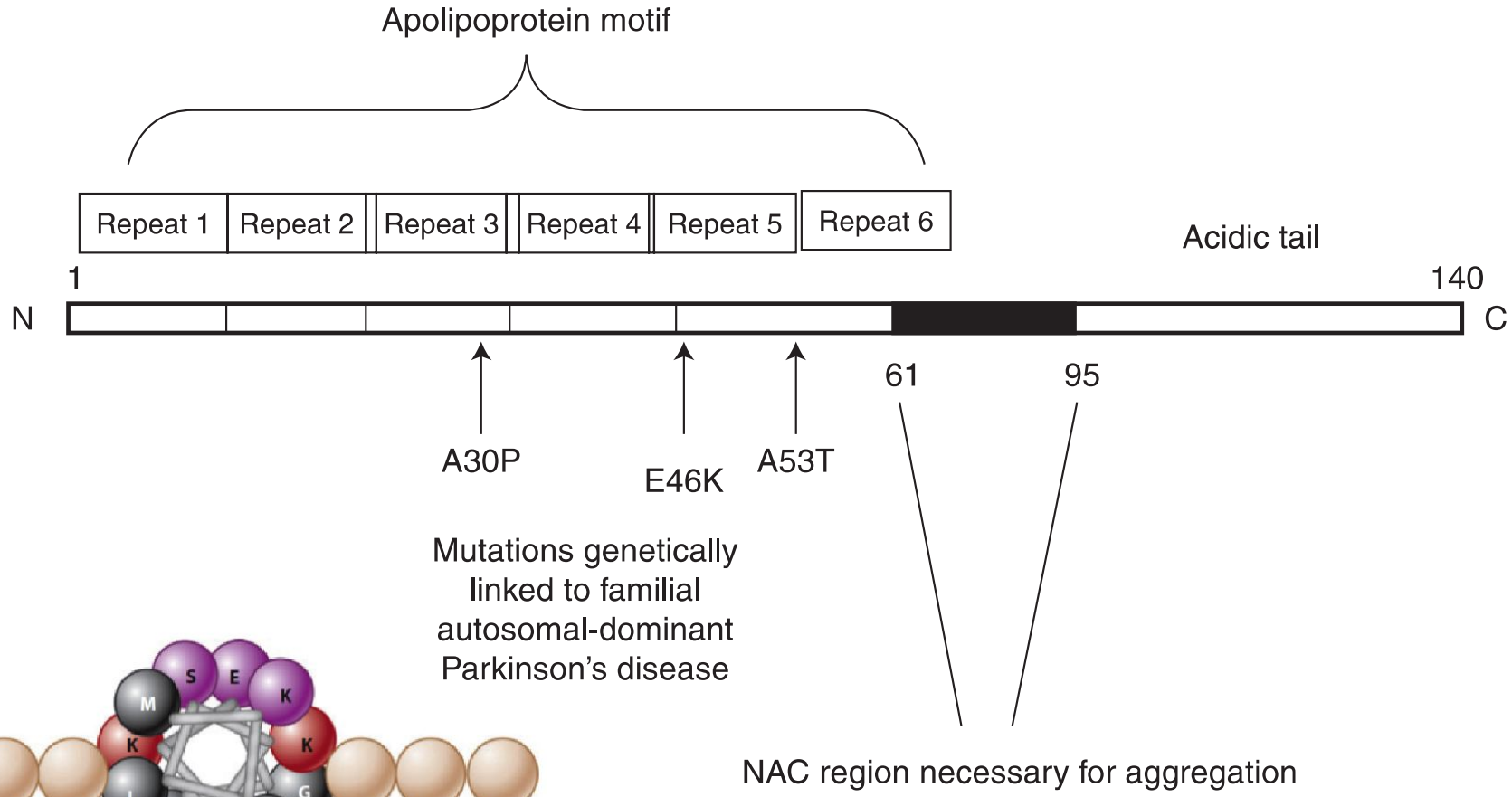
Pathological hallmark of Parkinson's, the Lewy body, contains α-synuclein

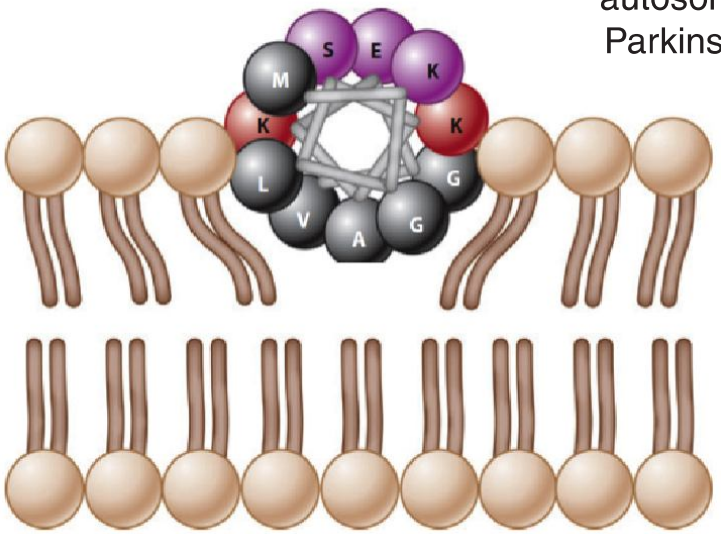


(Pigmented midbrain dopaminergic neurons)

(Spillantini, Nature, 1997)

α-Synuclein misfolding and aggregation in Parkinson's disease

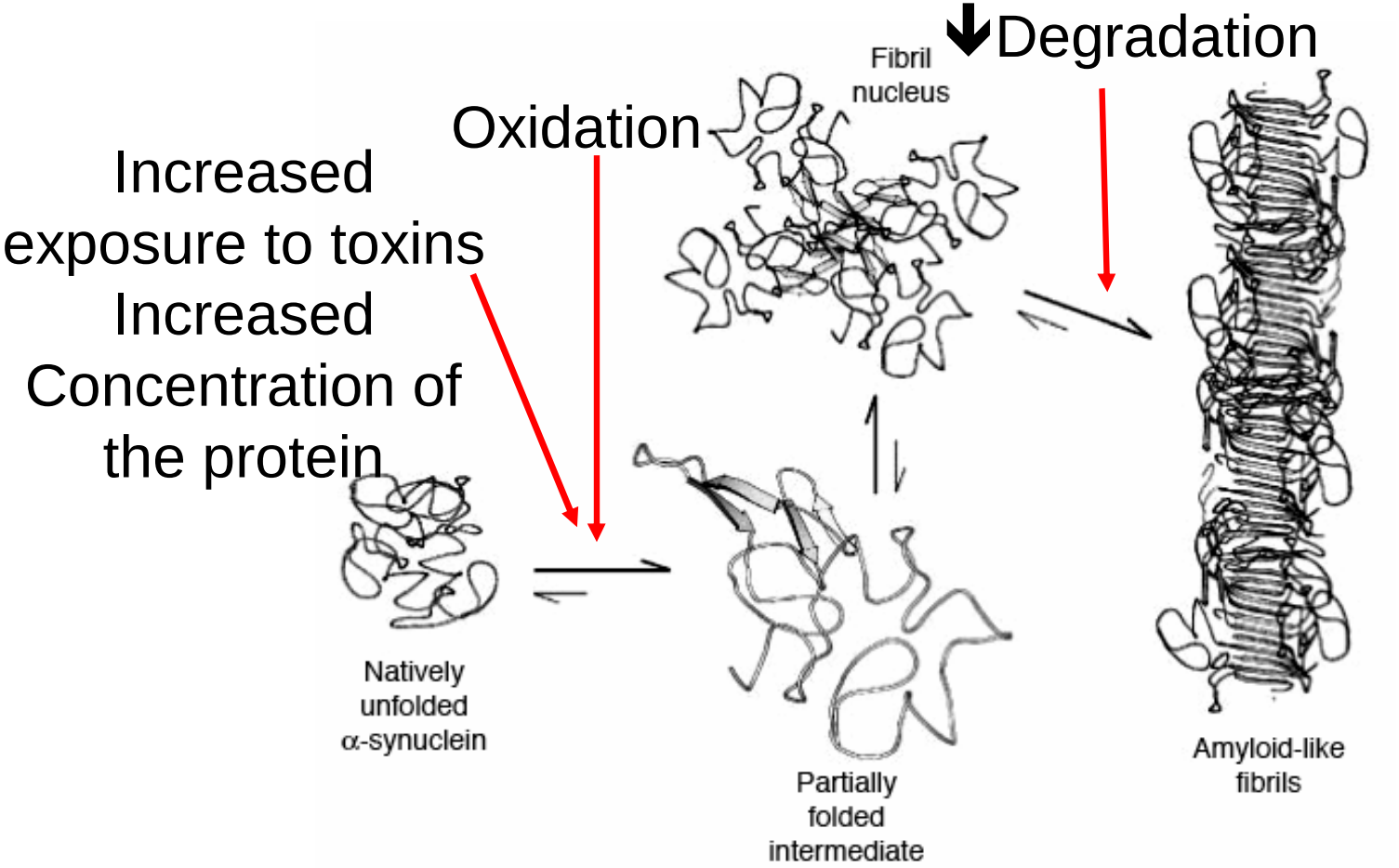




(Stefanis, Cold Spring Harb Perspect Med 2012)

Normal function
(synaptic vesicle release)

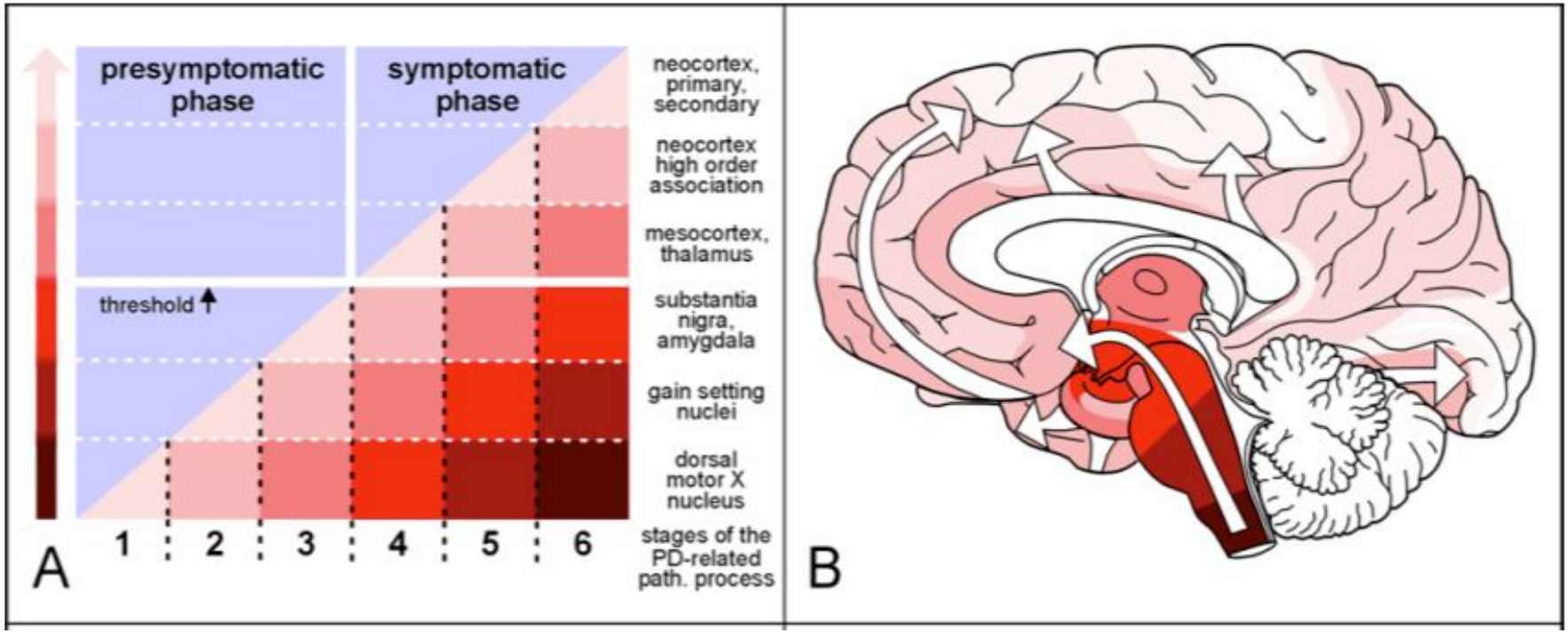
consequences of α-Synuclein misfolding and aggregation in Parkinson's disease



Pathogenic versions found in synucleinopathies

PD is progressive
α-Synuclein species ‘move’ through the brain in a predictable manner

Prion-like transmission ?



Loss of smell

Constipation

Motor

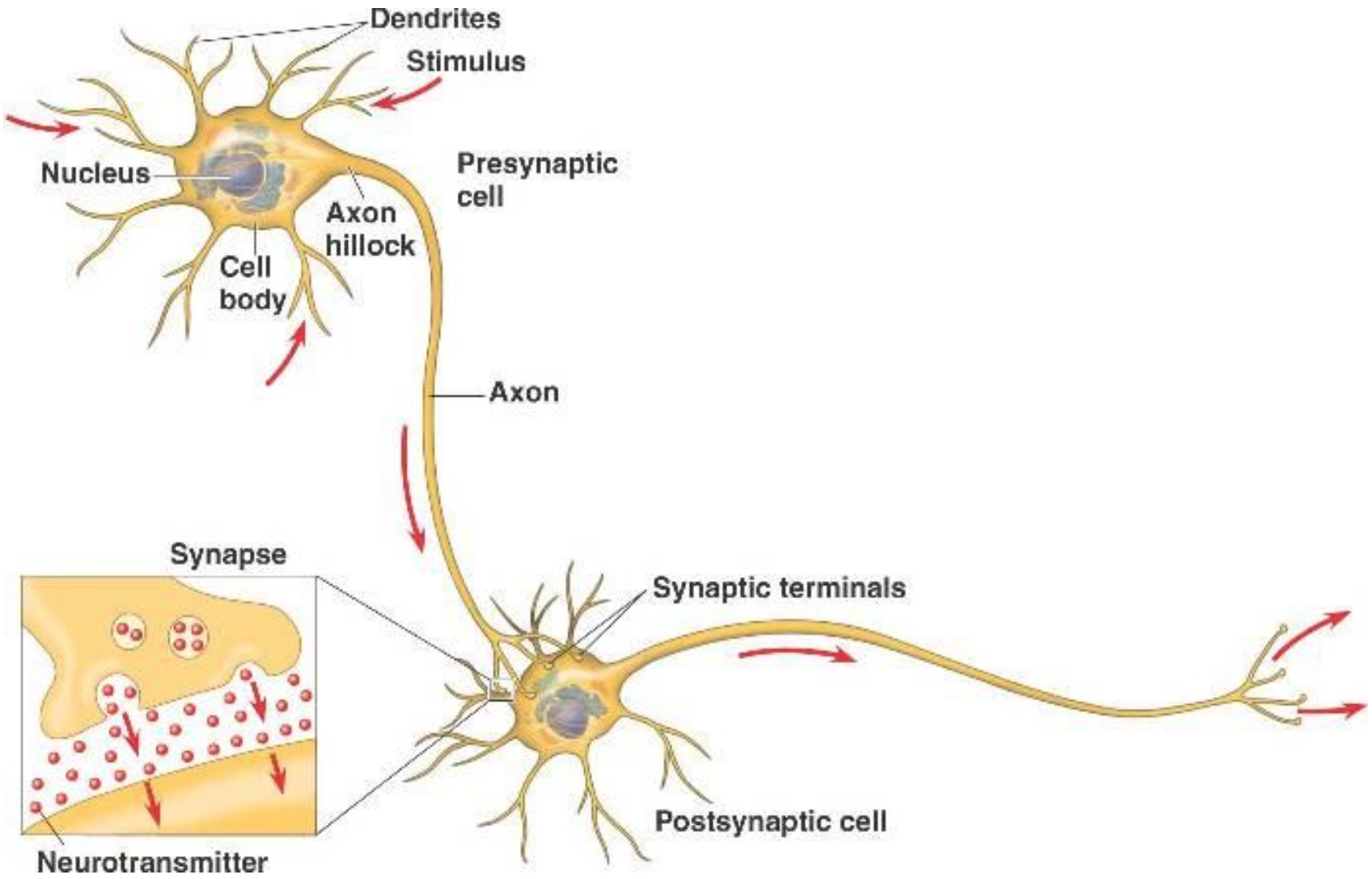
Dementia

Depression

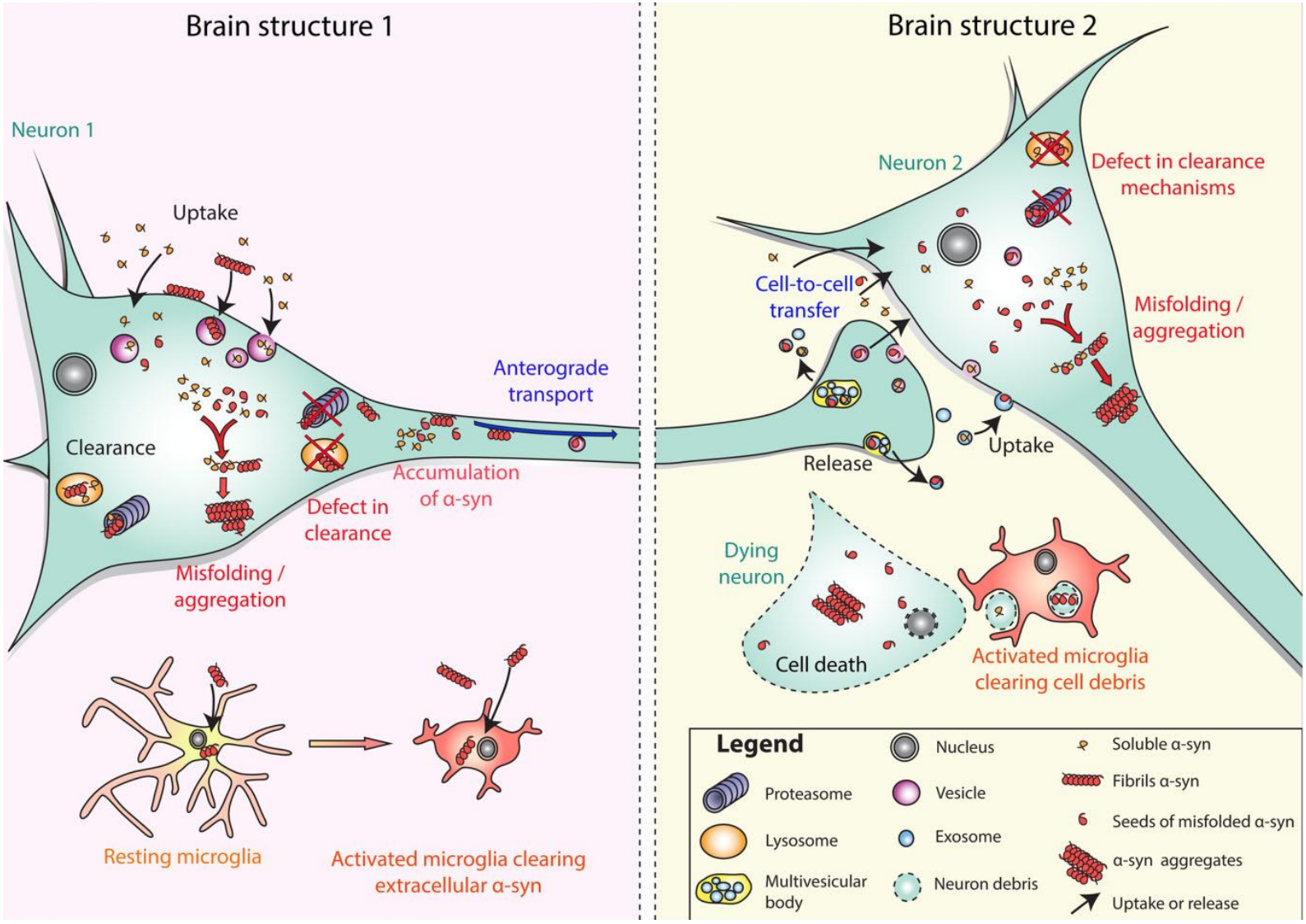
(Braak et al. 2004)

What is/are mechanism(s) underlying the spread of synuclein pathology in Parkinson's disease ?

The structure of a Neuron



Possible mechanisms underlying the spread of synuclein pathology and α-syn aggregation in Parkinson's disease

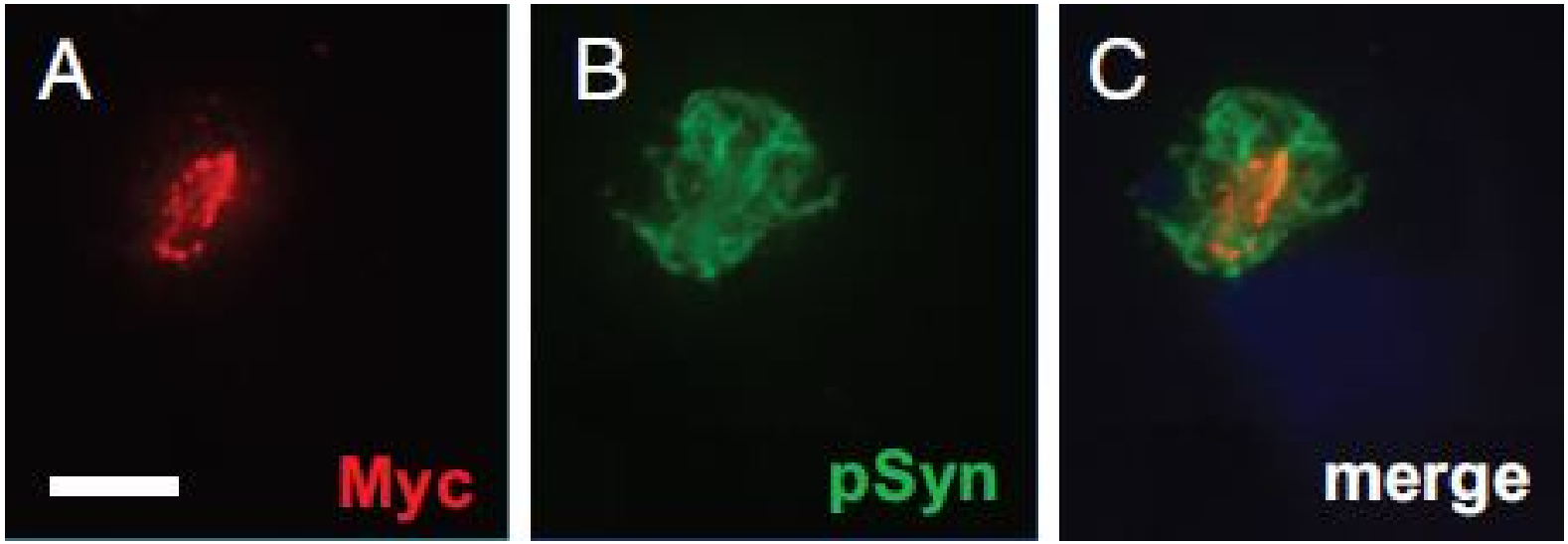


“Seeding” α-Synuclein pathology in human cells

αSyn-Myc fibrils (exogenous)

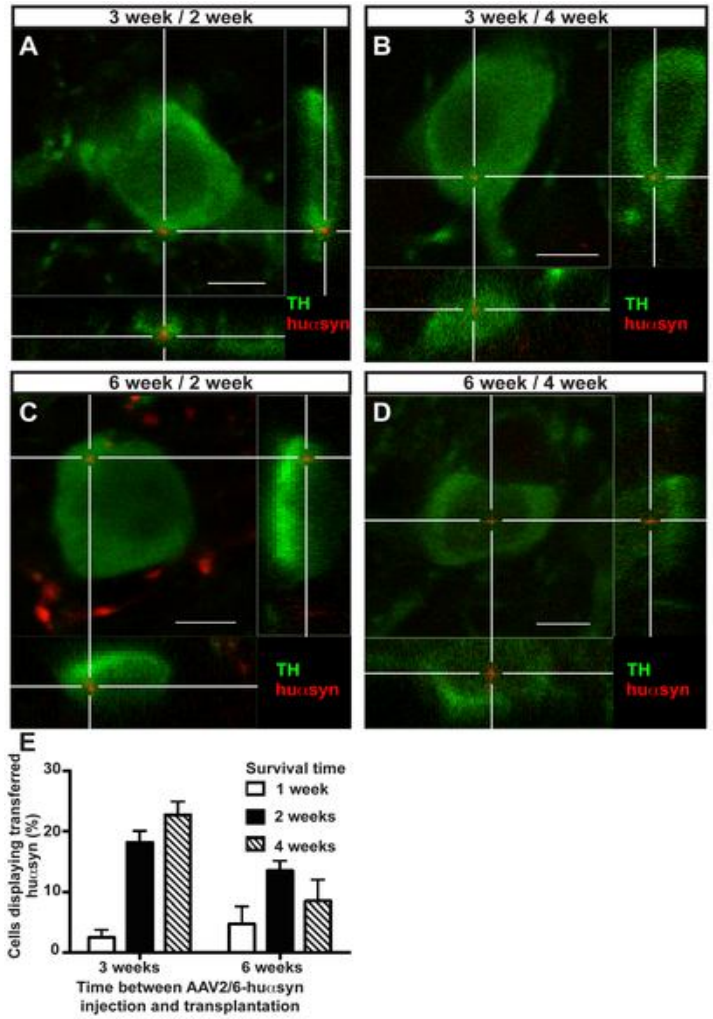
αSyn (endogenous)

‘Lewy body’



Luk et al. Virginia Lee(2009). PNAS

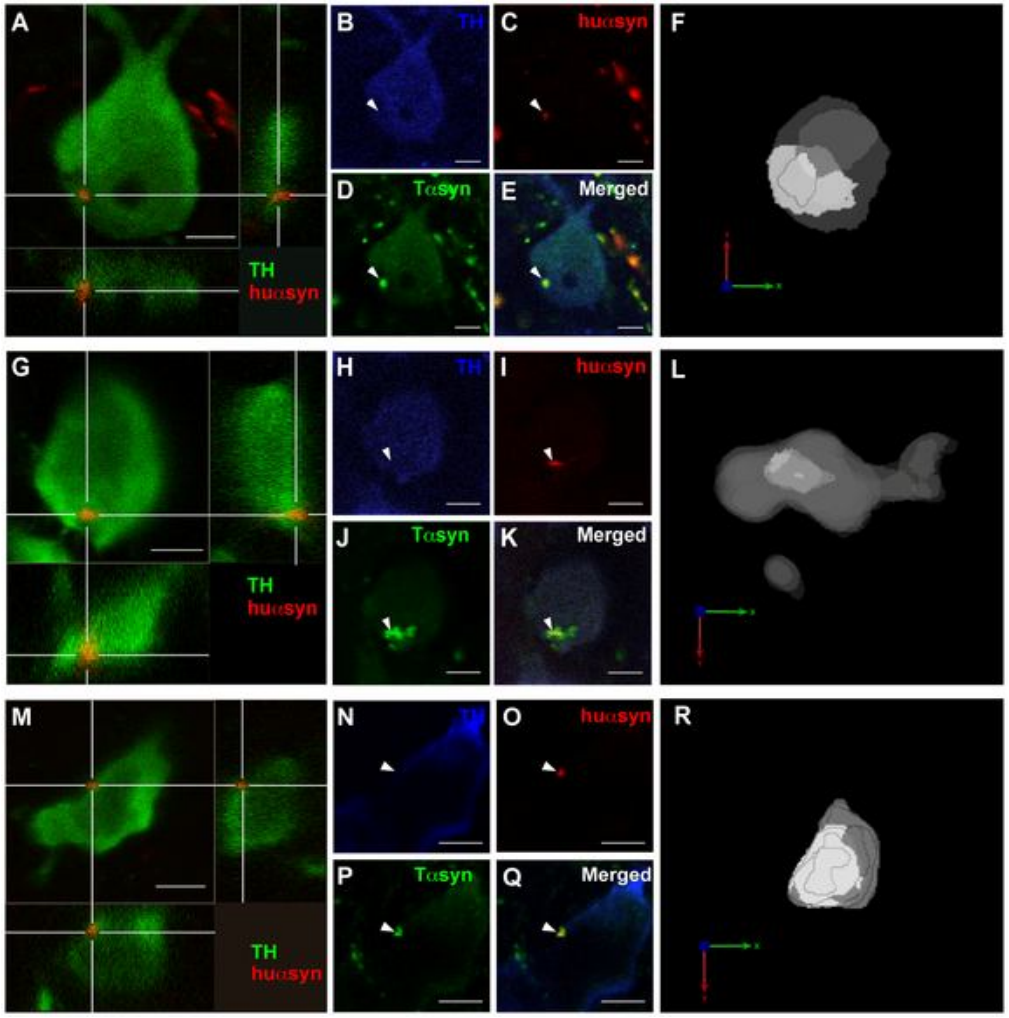
The propagation of human α-synuclein from host tissue to transplanted dopaminergic neurons



frequent transfer of α-synuclein from a rat brain engineered to overexpress human α-synuclein to grafted dopaminergic neurons

Angot E, Steiner JA, Lema Tomé CM, Ekström P, et al. (2012) Alpha-Synuclein Cell-to-Cell Transfer and Seeding in Grafted Dopaminergic Neurons In Vivo. PLoS ONE 7(6): e39465. doi:10.1371/journal.pone.0039465

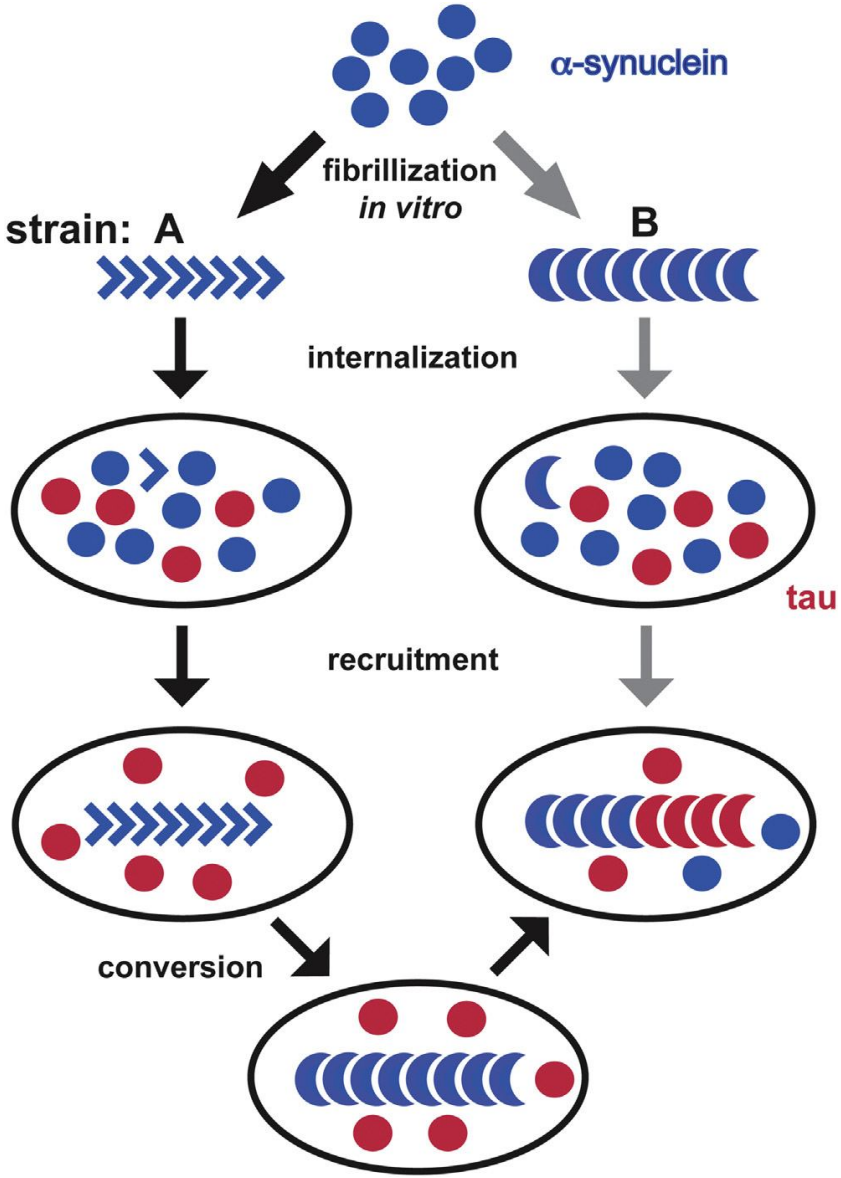
Transferred human α-synuclein seeds the aggregation of rat α-synuclein in the recipient cell.



Seeding of aggregation of endogenous a-synuclein in the recipient neuron by the transferred a-synuclein.

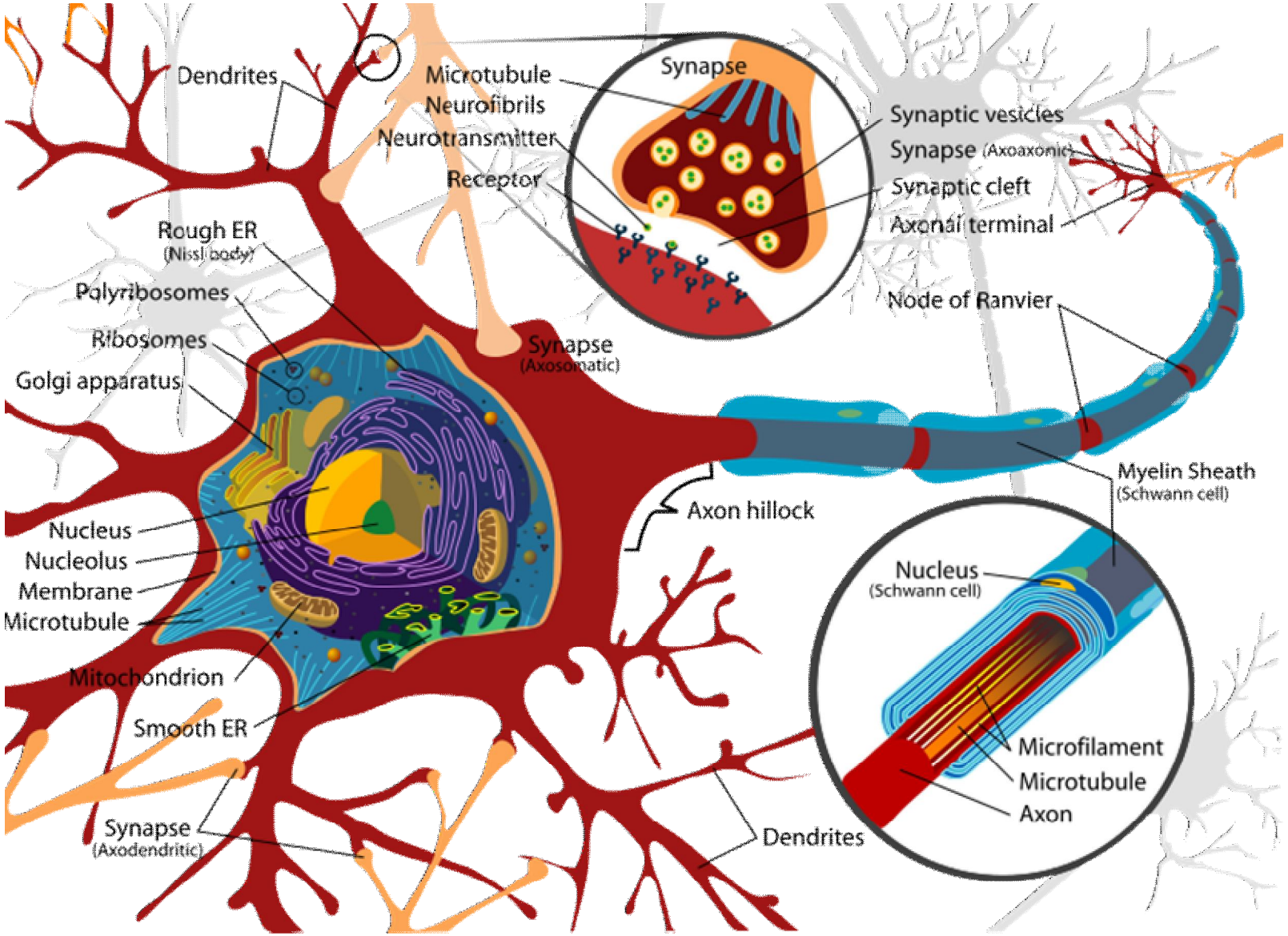
Angot E, Steiner JA, Lema Tomé CM, Ekström P, et al. (2012) Alpha-Synuclein Cell-to-Cell Transfer and Seeding in Grafted Dopaminergic Neurons In Vivo. PLoS ONE 7(6): e39465. doi:10.1371/journal.pone.0039465

α-Synuclein exhibits Prion strain-like properties

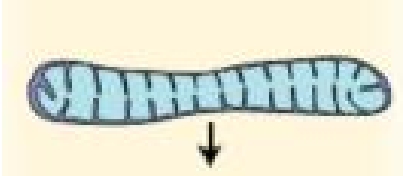


What is/are mechanism(s) underlying the death of neurons in Parkinson's disease ?

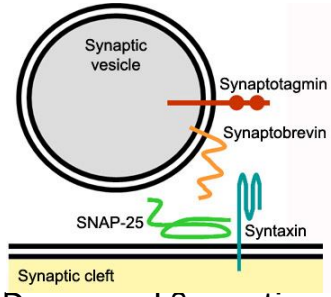
The subcellular structure of the neuron



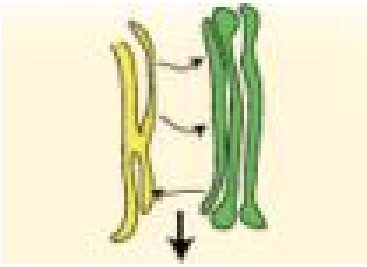
α-synuclein : multiple sites of toxicity



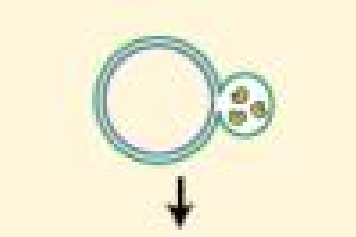
Mitochondria toxicity
Impaired energy production
Apoptosis induction



Decreased Synaptic vesicle release

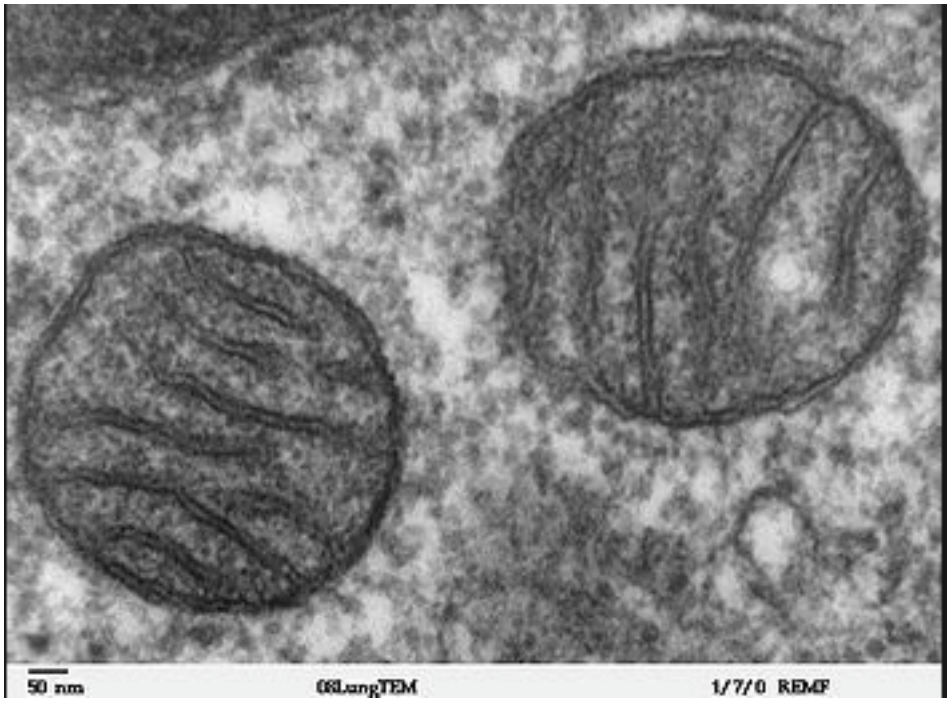


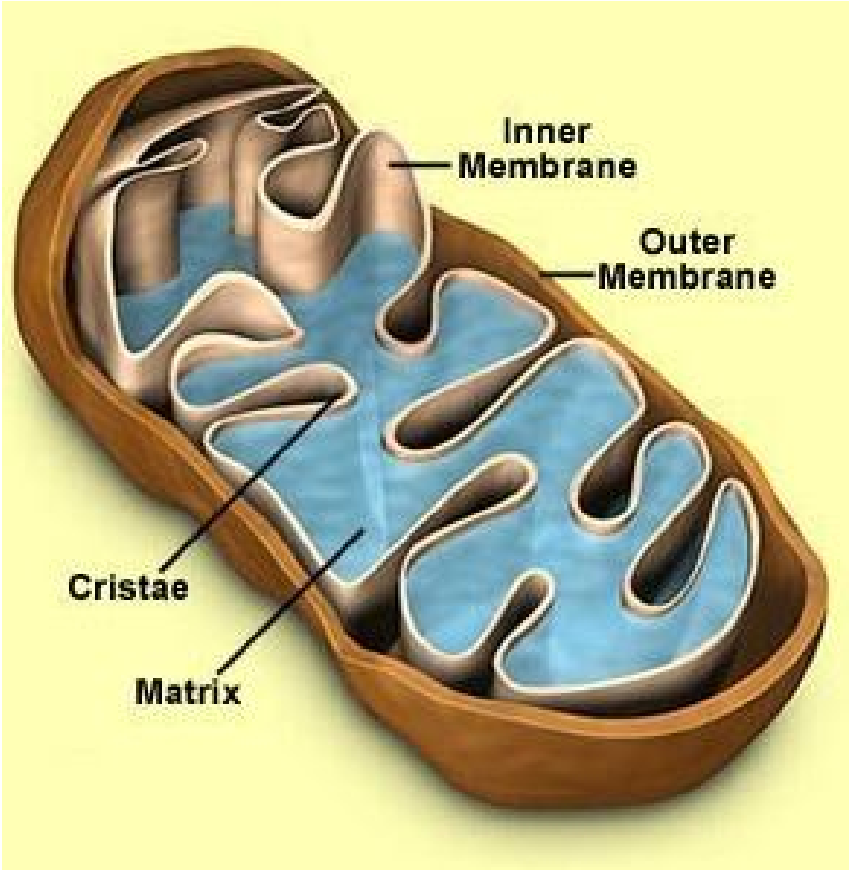
Blocked ER-Golgi transport
ER stress and Golgi fragmentation



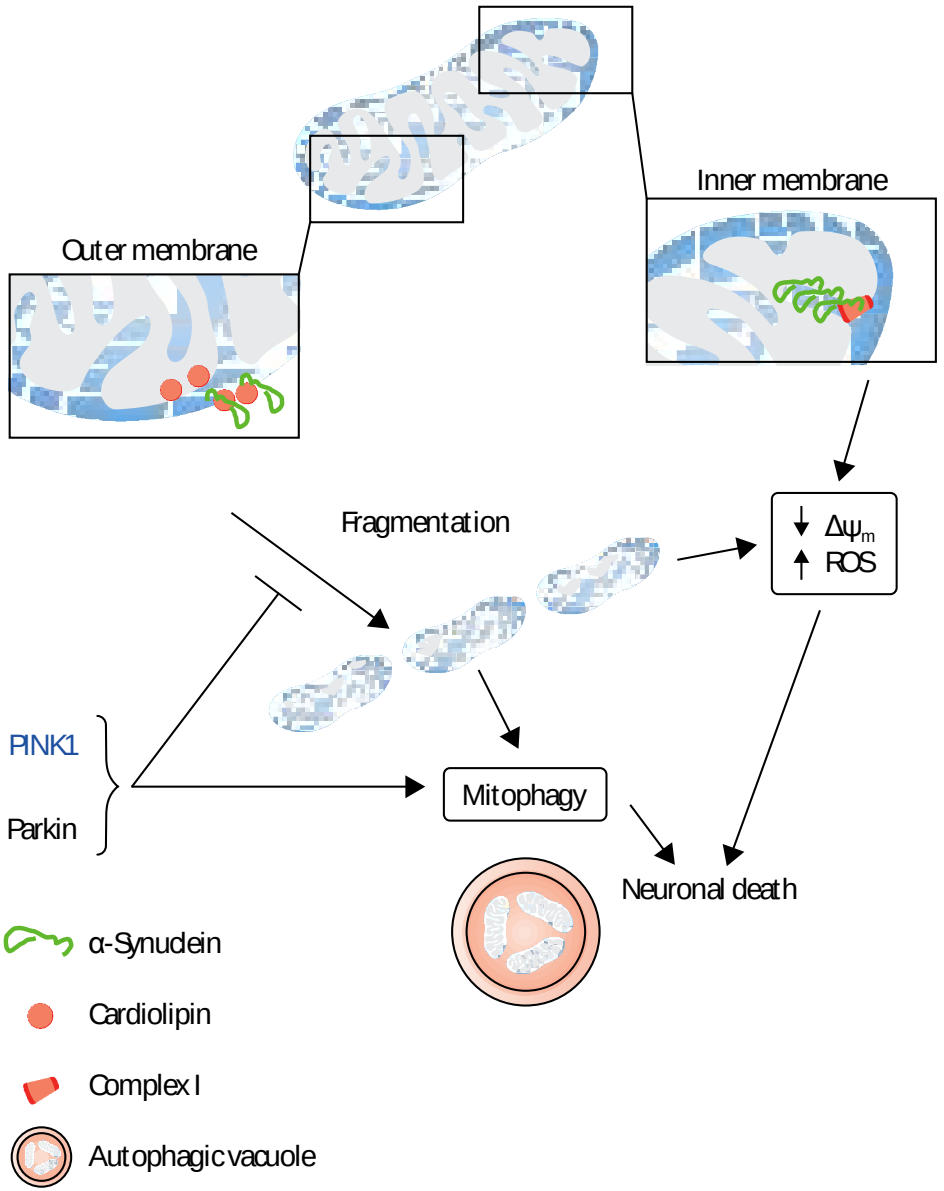
Accumulation of CMA substrates?
Proteasome impairment

The mitochondria

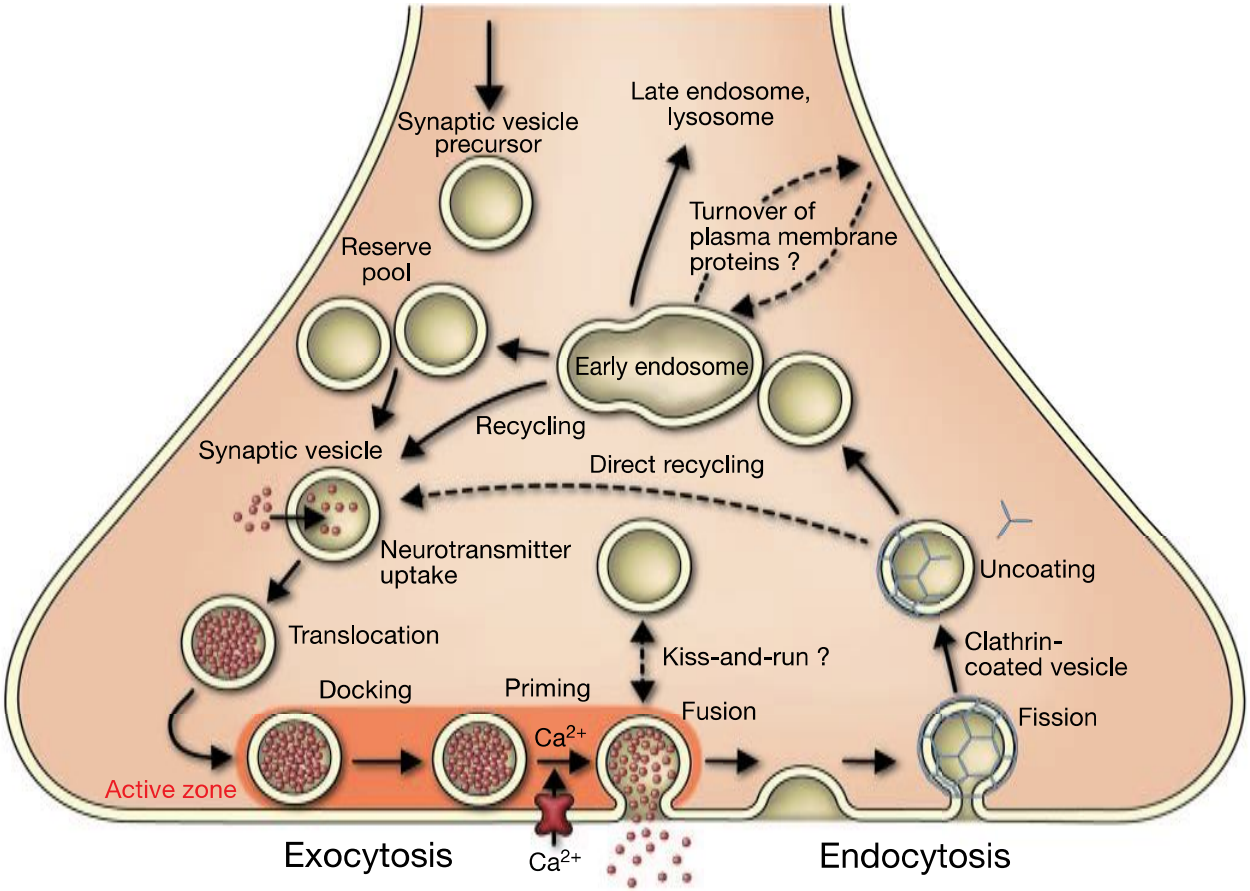




Effects of α-synuclein on mitochondria

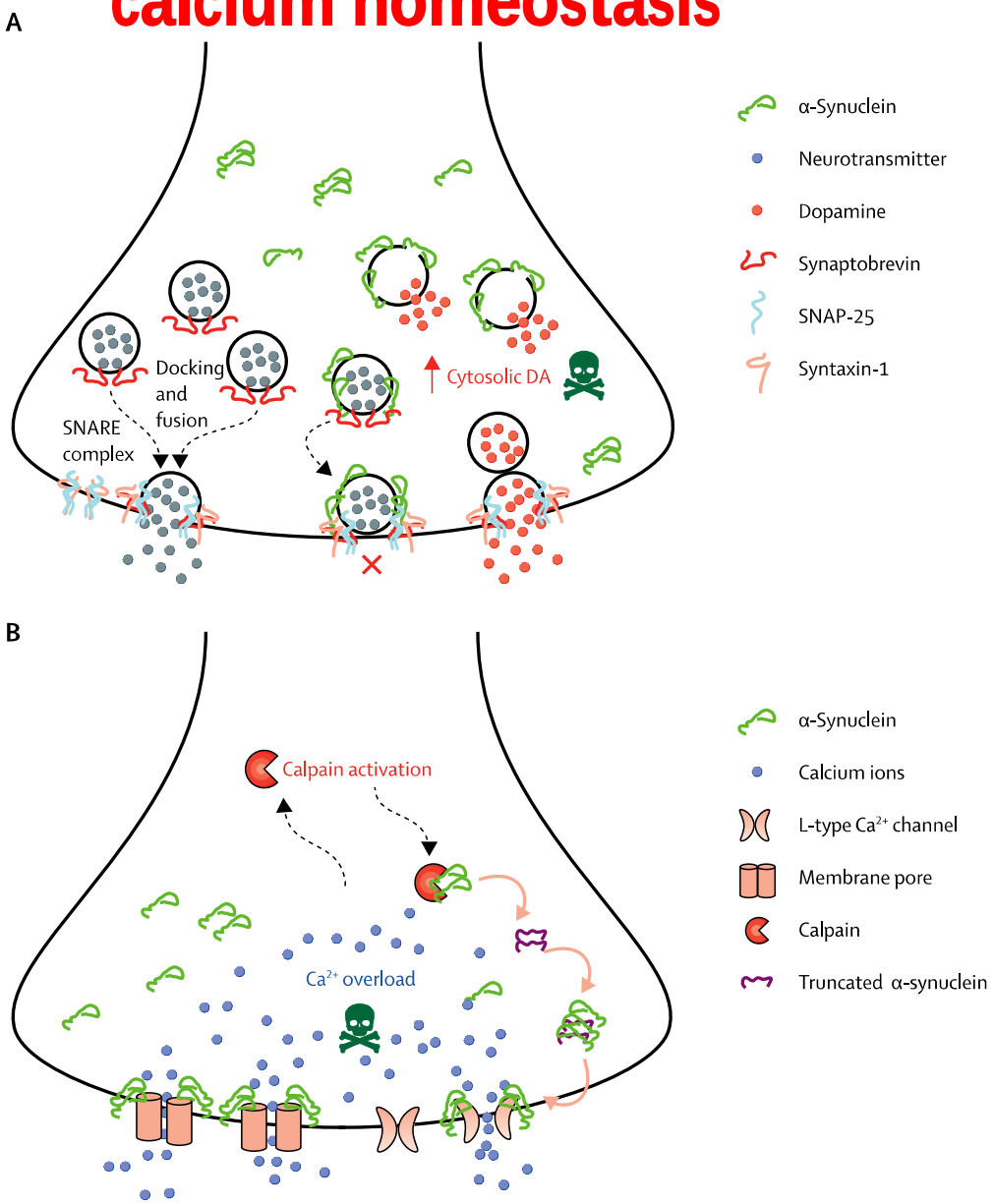


The synapse



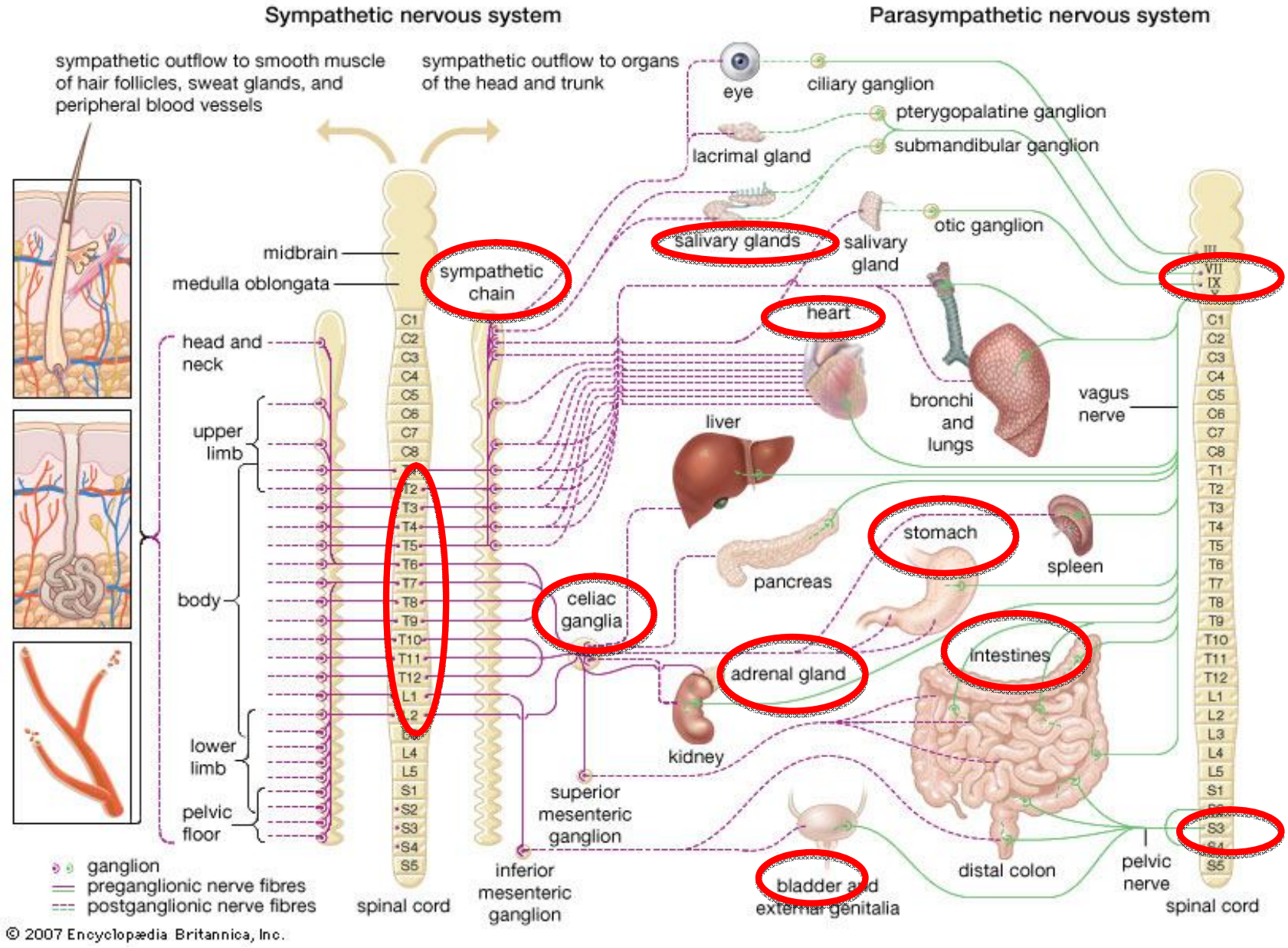
Trafficking pathways in the nerve terminal. Synaptic vesicles are filled with neurotransmitter and stored in the cytoplasm. Active vesicles are translocated to release sites in the active zone where they dock. Priming involves all steps required to acquire release readiness of the exocytotic complex. Although usually assumed to occur after docking, priming and even triggering may precede docking during sustained activity, resulting in immediate fusion of an arriving vesicle. After exocytosis, the vesicle proteins probably remain clustered and are then retrieved by endocytosis. Despite some lingering controversies, consensus is emerging that retrieval is generally mediated by clathrin-mediated endocytosis. After clathrin uncoating, synaptic vesicles are regenerated within the nerve terminal, probably involving passage through an endosomal intermediate. Actively recycling vesicles are in slow exchange with the reserve pool.

Effects of α-synuclein on synapse integrity and calcium homeostasis

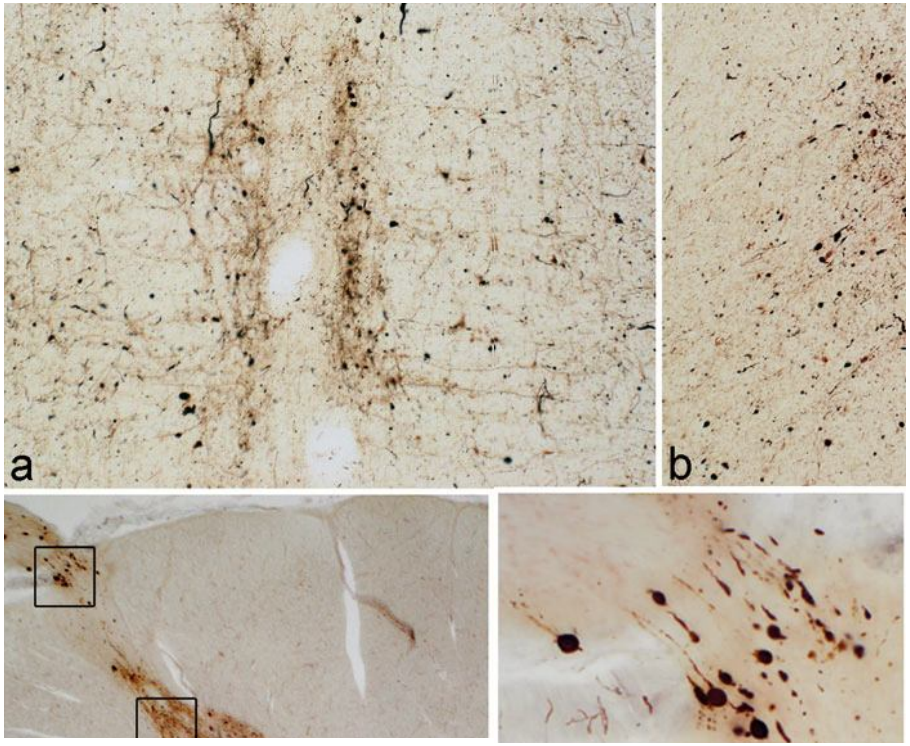


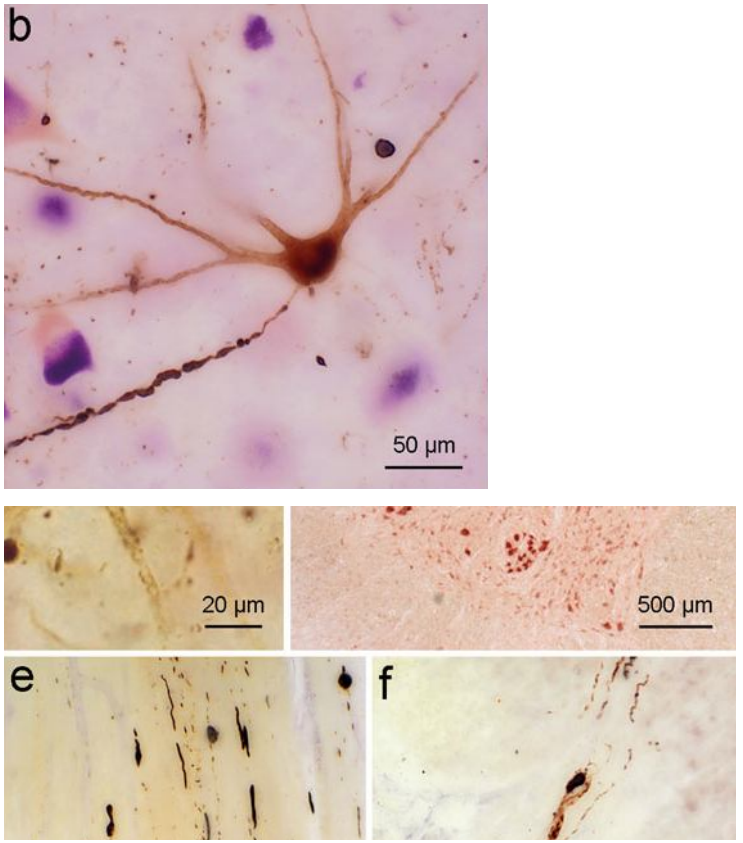
What is the sequence of the pathogenic events leading to the death of neurons in Parkinson's disease ?

Pathological evidence for axonapathy in PD



Spinal cord axonopathy in PD



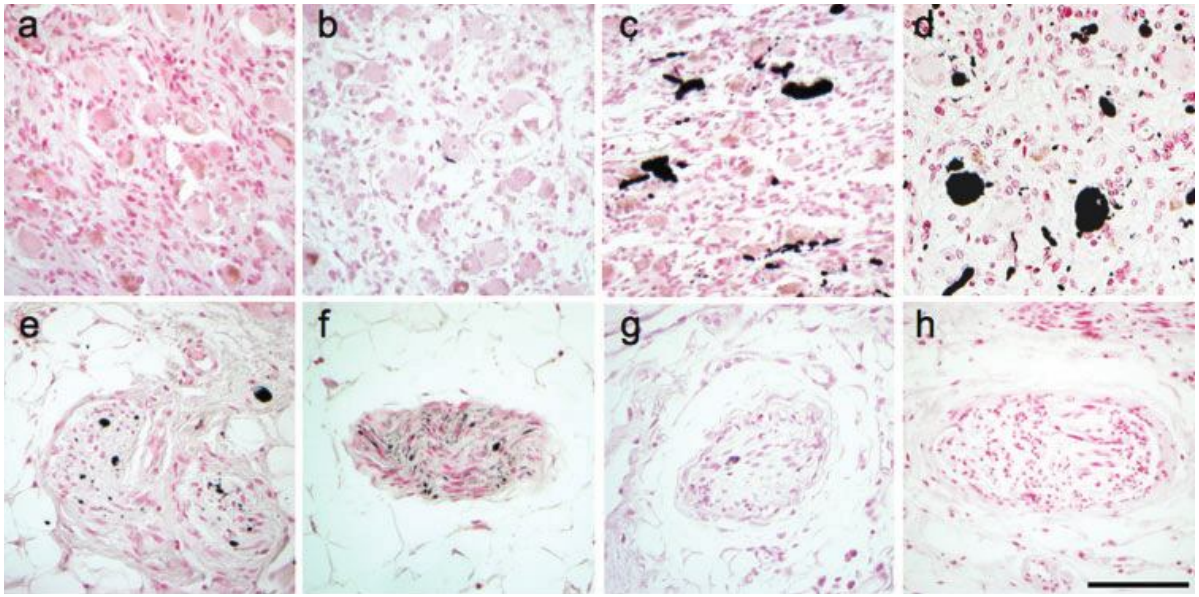


Del Tredici and Braak H Acta Neuropathol 2012;12:643-664

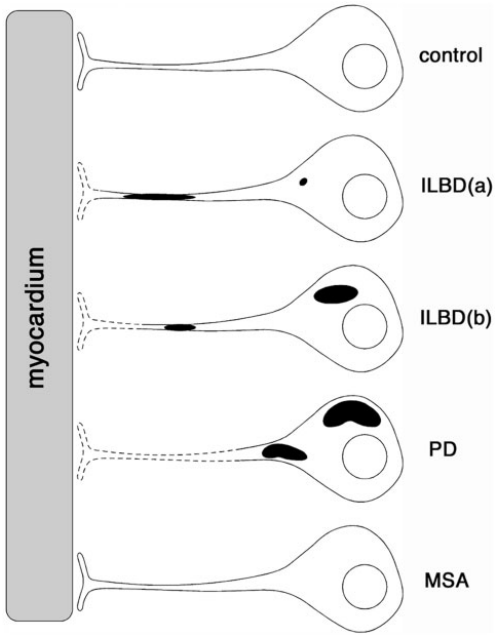
Cardiac axonopathy in PD

Stellate ganglia

Epicardial nerve fibers



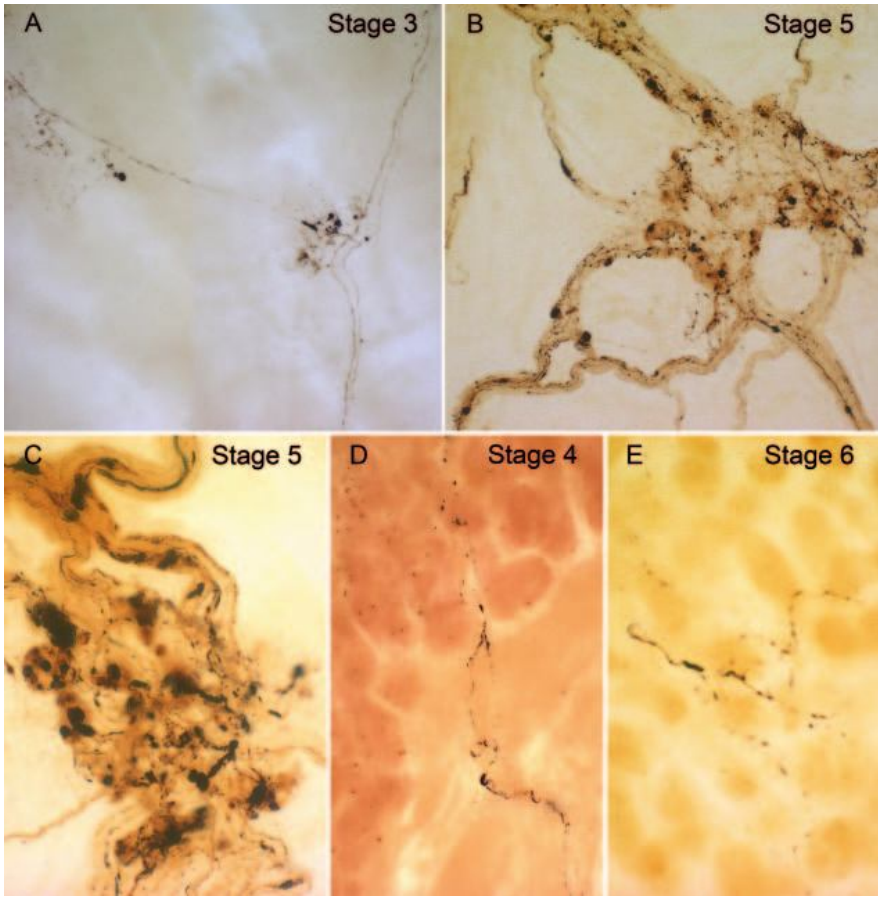
Abnormal asynuclein detected in axons of epicardial nerve fibers before cell bodies of stellate ganglia suggesting a centripetal disease process.



OrimoS, et al. Brain 2008;131:642-650

Intestinal axonopathy in PD

Parasympathetic ganglia of esophagus and stomach have Lewy-related pathology in PD

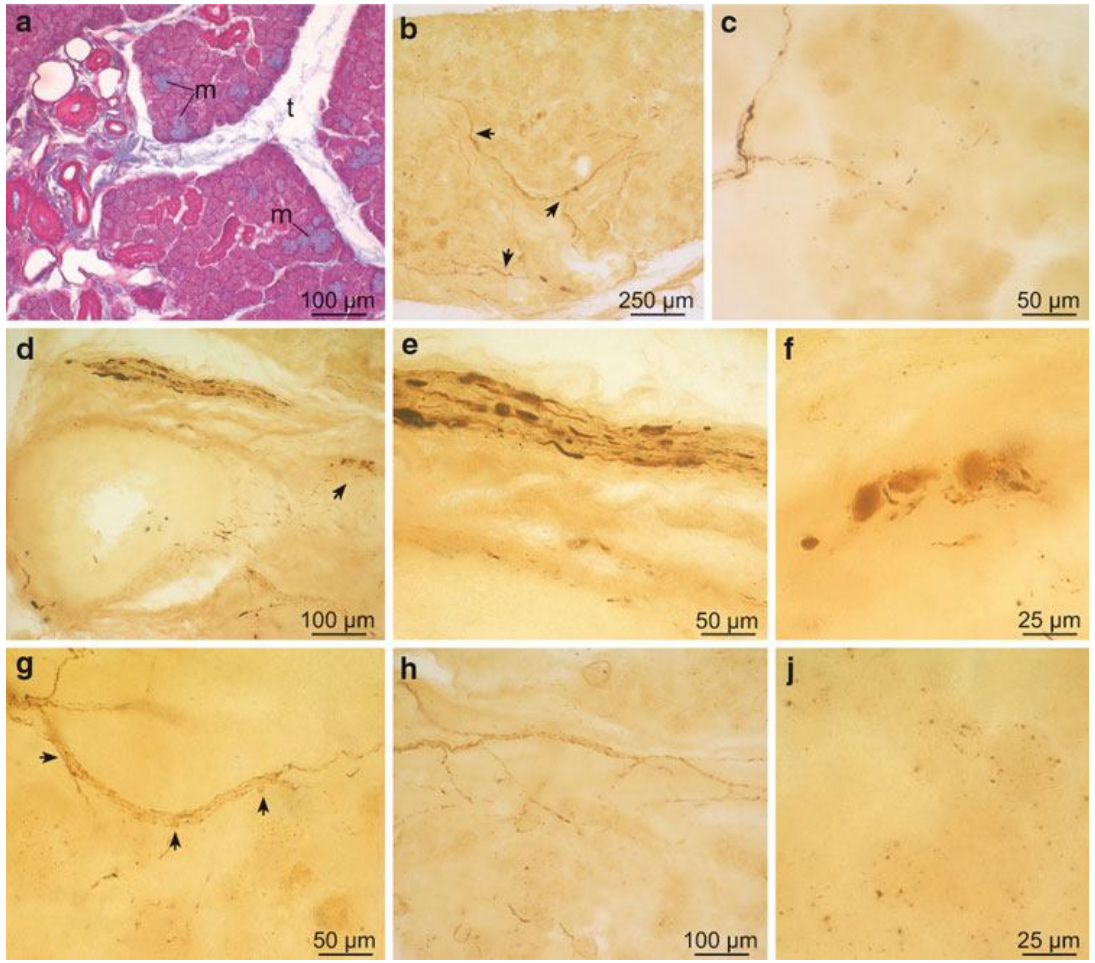


Braak H and Del Tredici K 2008

Wakabayashi K et al. Acta Neuropathol 1988;76:217-221
Bloch A et al. Neuropathol Appl Neurobiol. 2006;32:284-295
Braak H and Del Tredici K. Neurology 2008;70:1916-1925
Beach TG, et al. Acta Neuropathol. 2010;119:689-702

Salivary gland axonopathy in PD

Axonopathy in submandibular glands in PD

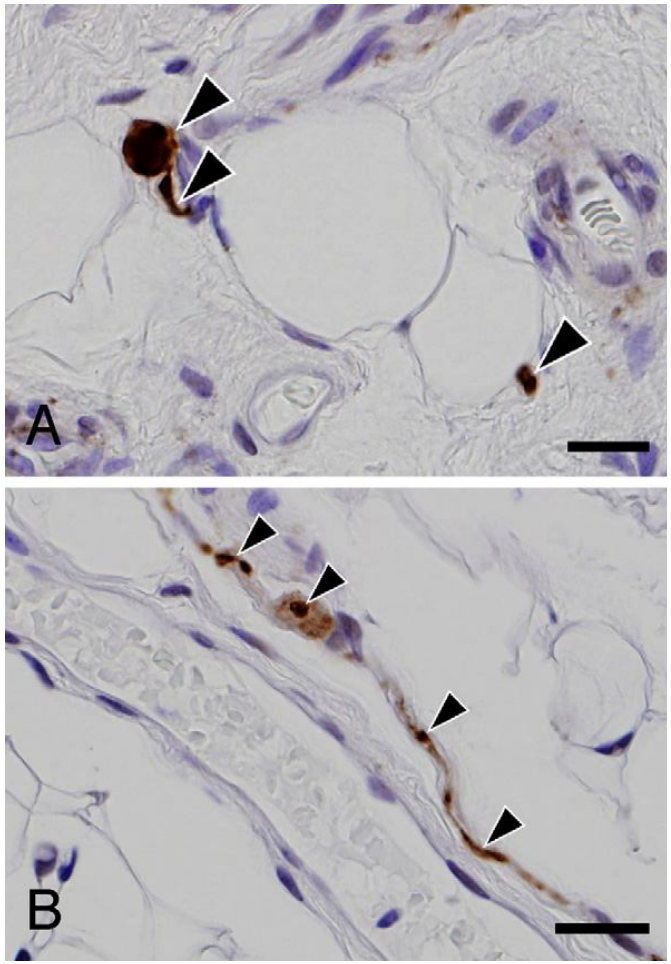


Del Tredici K et al. Acta Neuropathol 2010;119:703-13

Skin axonopathy in PD

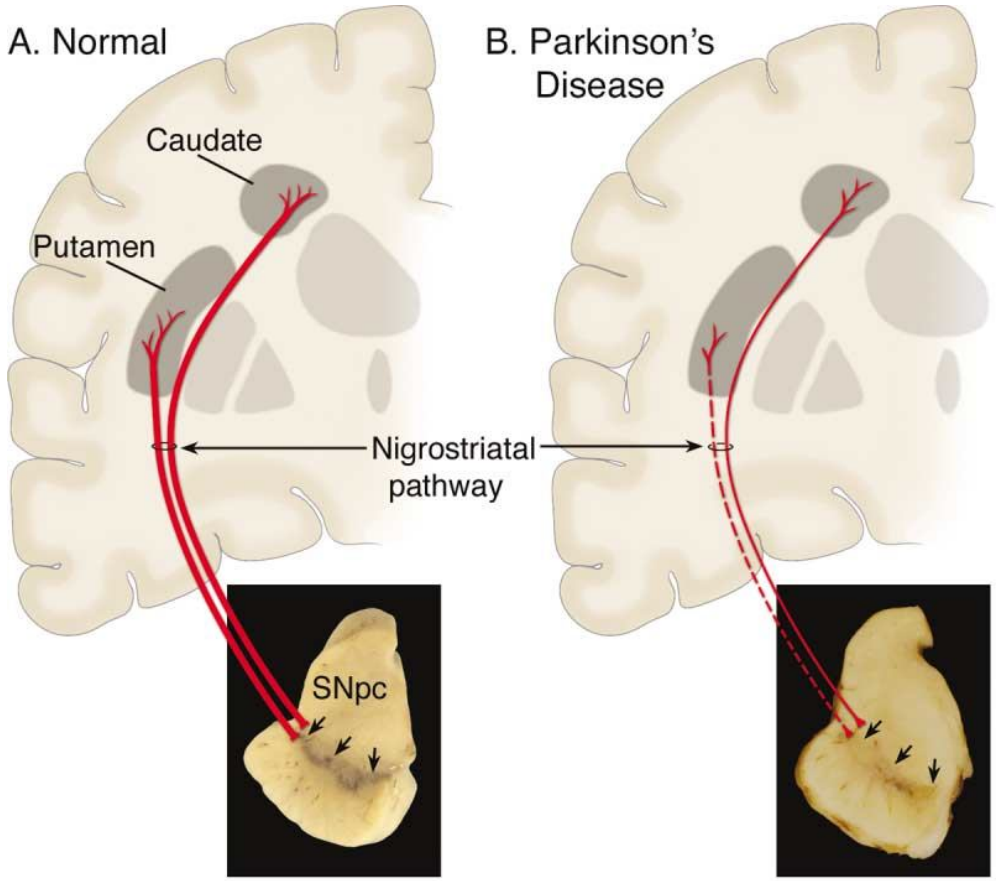
α-Synuclein

Autopsy sries: 20 of 85 (24%)
Clinical PD series: 2 of 20 (10%)



Ikemura M, et al. J Neuropathol Exp Neurol 2008; 67:945-953
Miki Y, et al. Neurosci Lett 2010;469:357-359

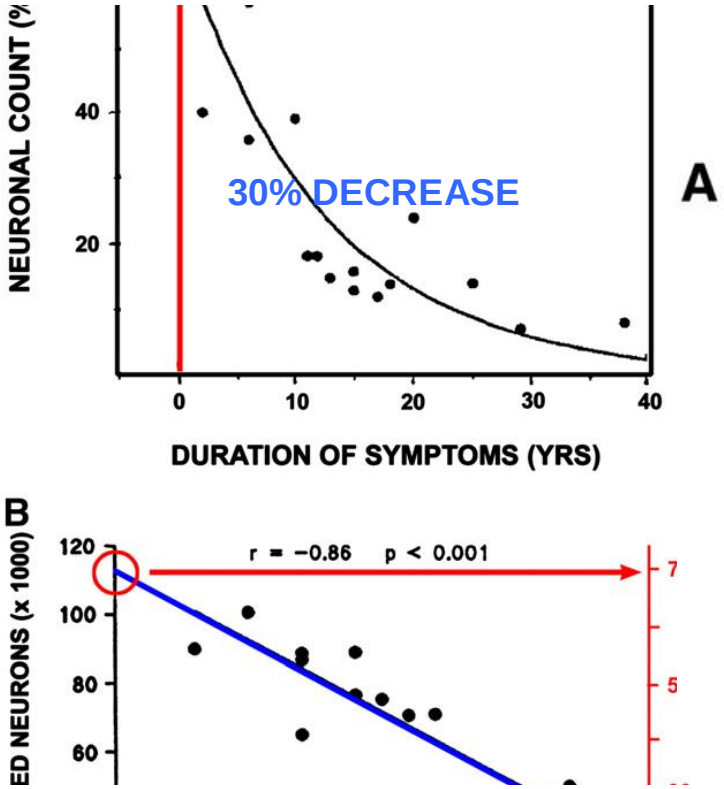
Nigrostrial degeneration in PD



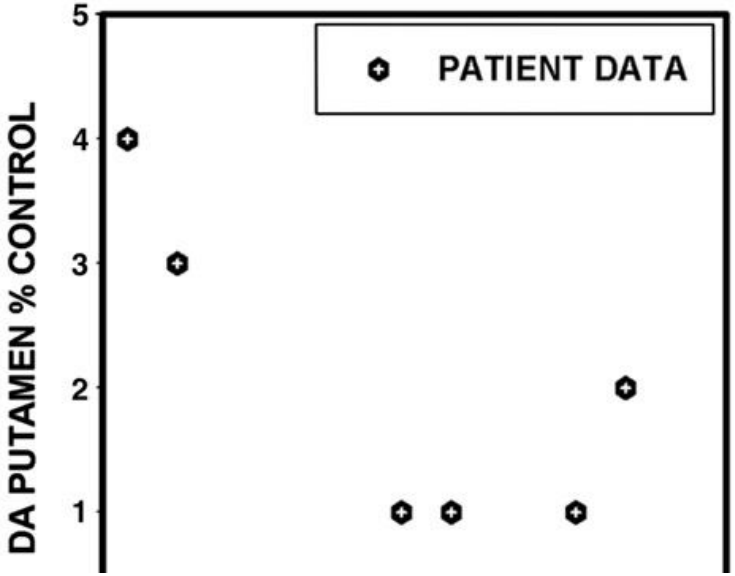
Disproportionate striatal terminal loss to S.nigra neuronal loss suggests a dying back axonopathy

Neuron 2003;39:889-909

Striatal terminal loss and nigral neuronal loss at autopsy



S.Nigra neurons



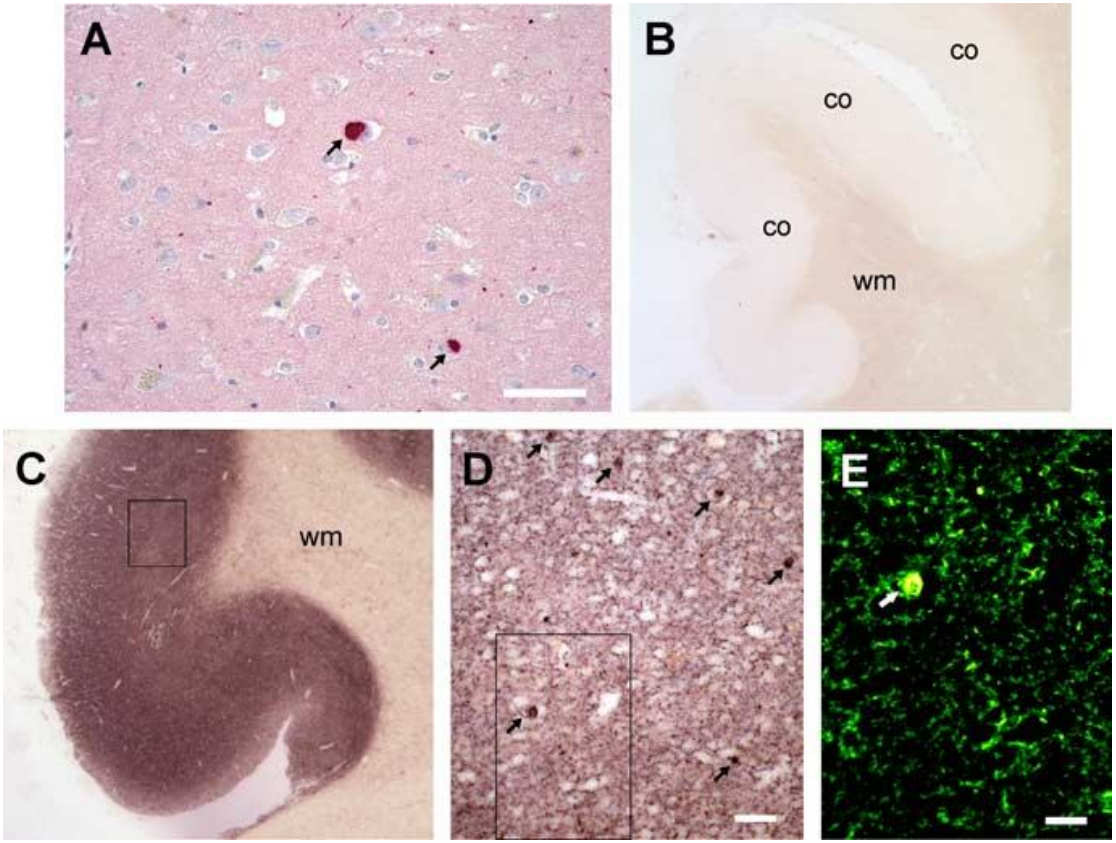
Striatal dopamine terminals

Cheng H-C. et al. Ann Neurol 2010:715-725

Presynaptic pathology

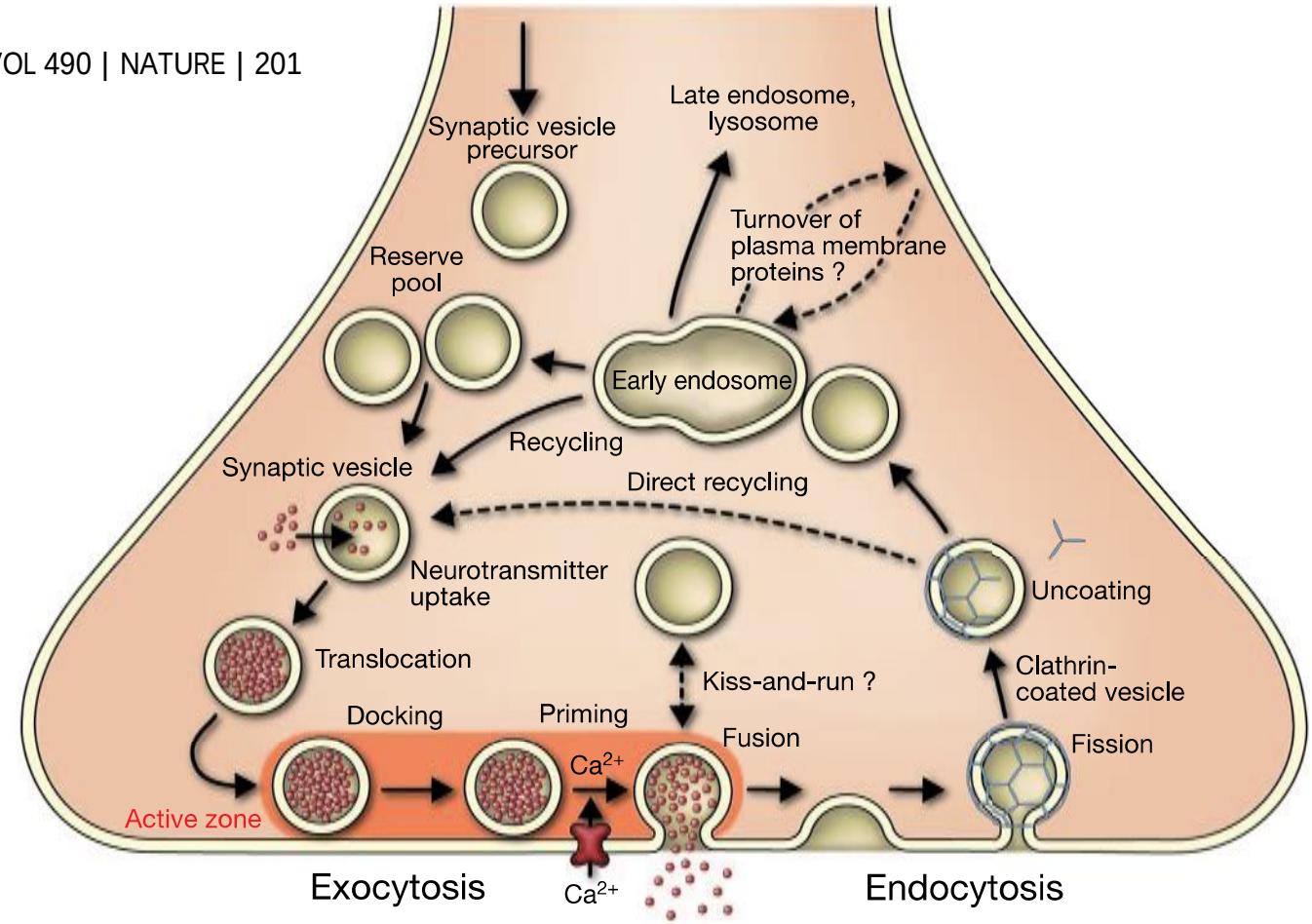
Routine a-synuclein immunohistochemistry

PET blot- abnormal insoluble a synuclein



Pervasive presynaptic (axon terminal) a synuclein **micro-agregates** in cerebral cortex correlate with dementia

Kramer ML and Schuluz-Schaeffer WJ. J Neurosci 2007; 27:1405-1410



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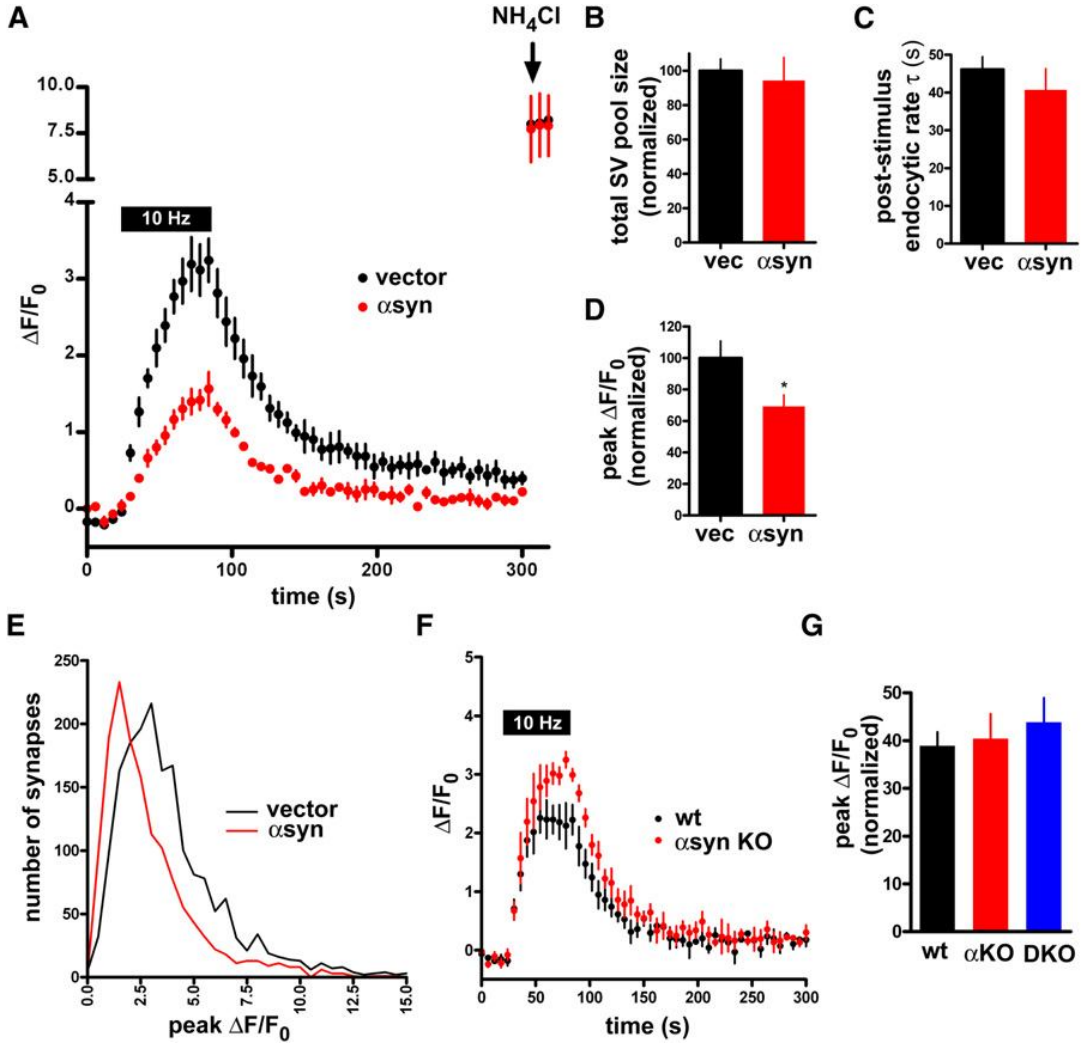
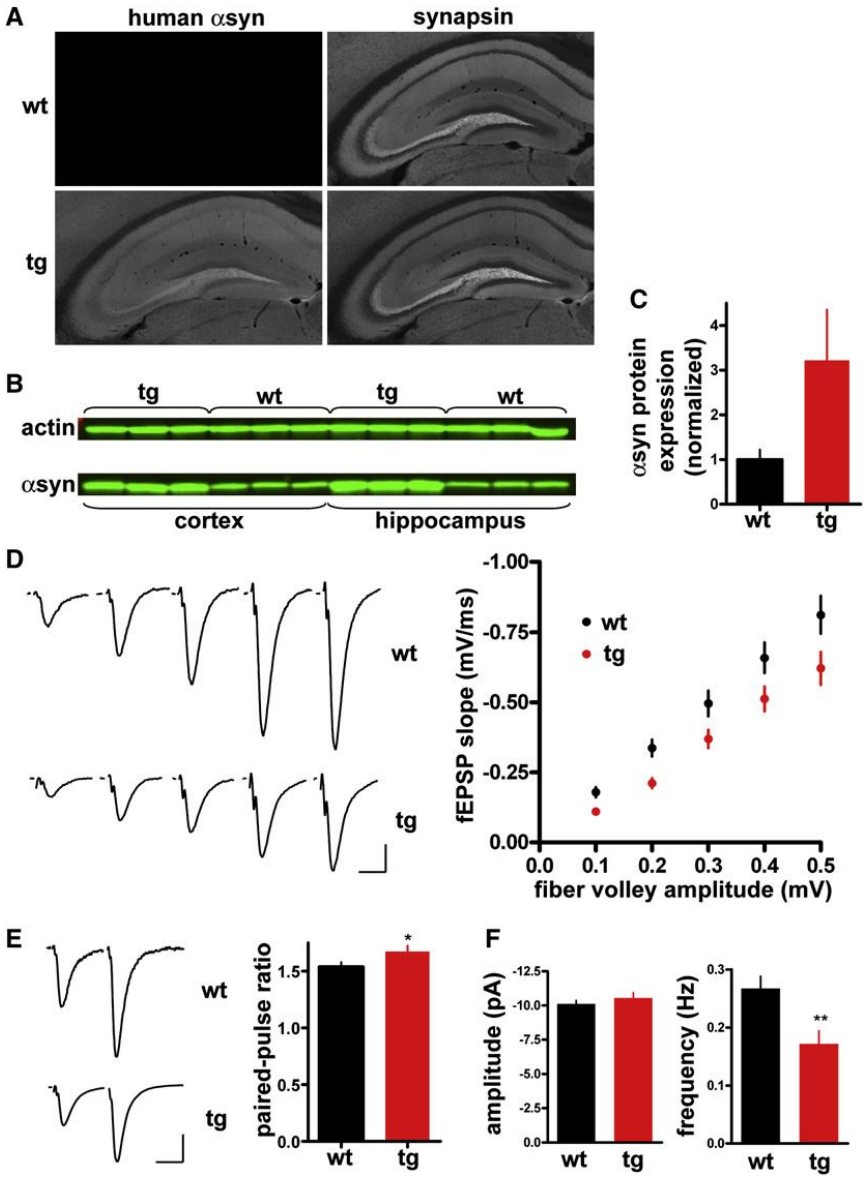
Overexpression of α-Synuclein Inhibits Synaptic Vesicle Exocytosis



Nemani.Neuron.2009.12.023

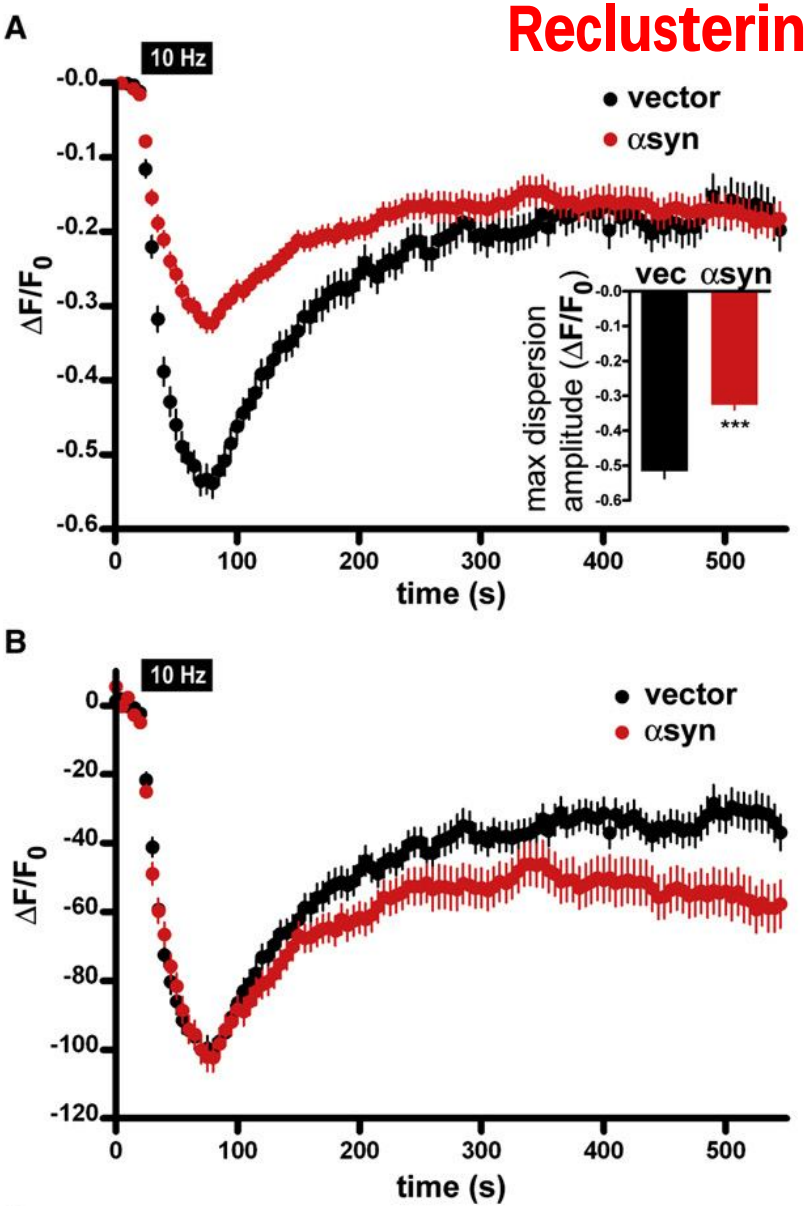
α-Synuclein Overexpression in Trans-genic Mice Inhibits Synaptic Transmission

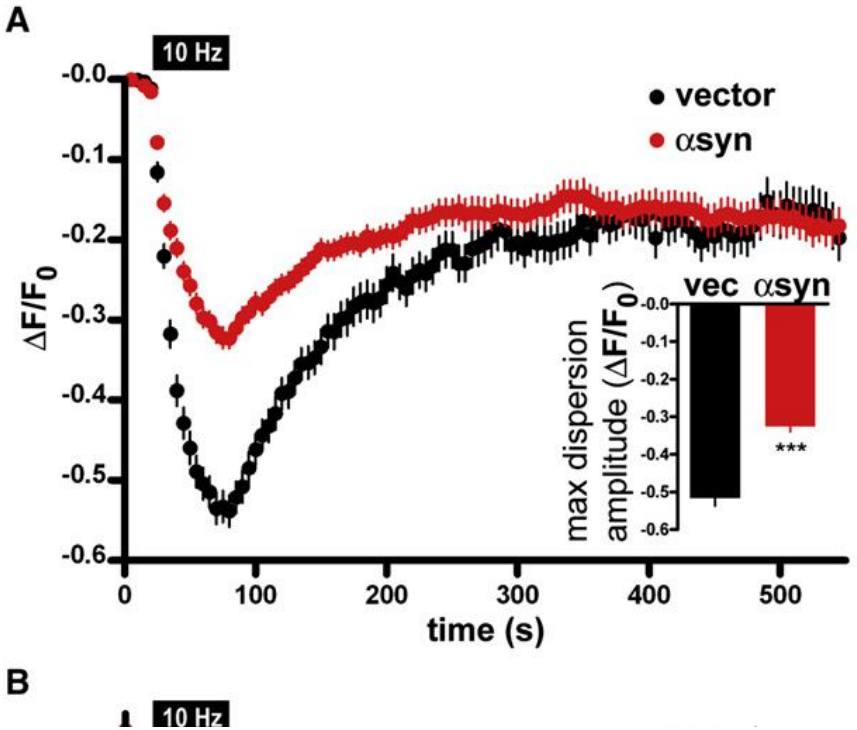
Nemani.Neuron.2009.12.023



Field excitatory postsynaptic potentials From hippocampal slices

Overexpression of a-Synuclein Inhibits Synaptic Vesicle Reclustering after Endocytosis





Nemani.Neuron.2009.12.023