Reconstructing disease trajectories of alpha-synucleinopathies using in vivo seeding models

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Prion/ADRD Conference 2024

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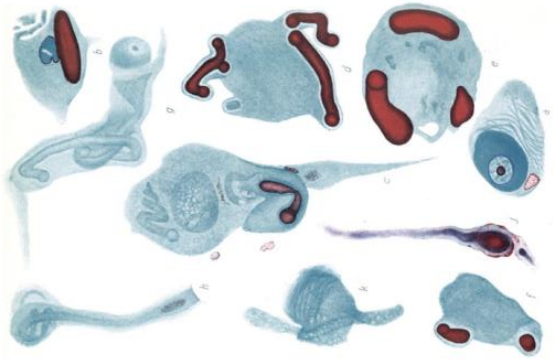
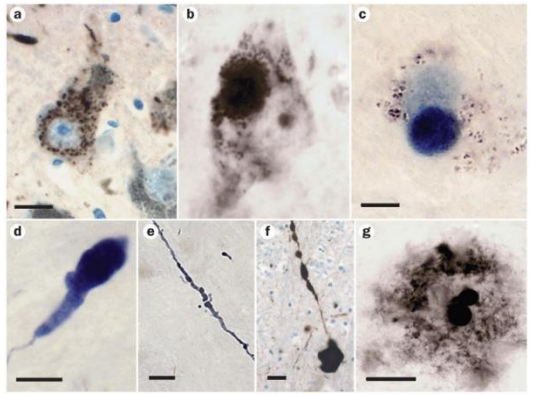
University of Pennsylvania

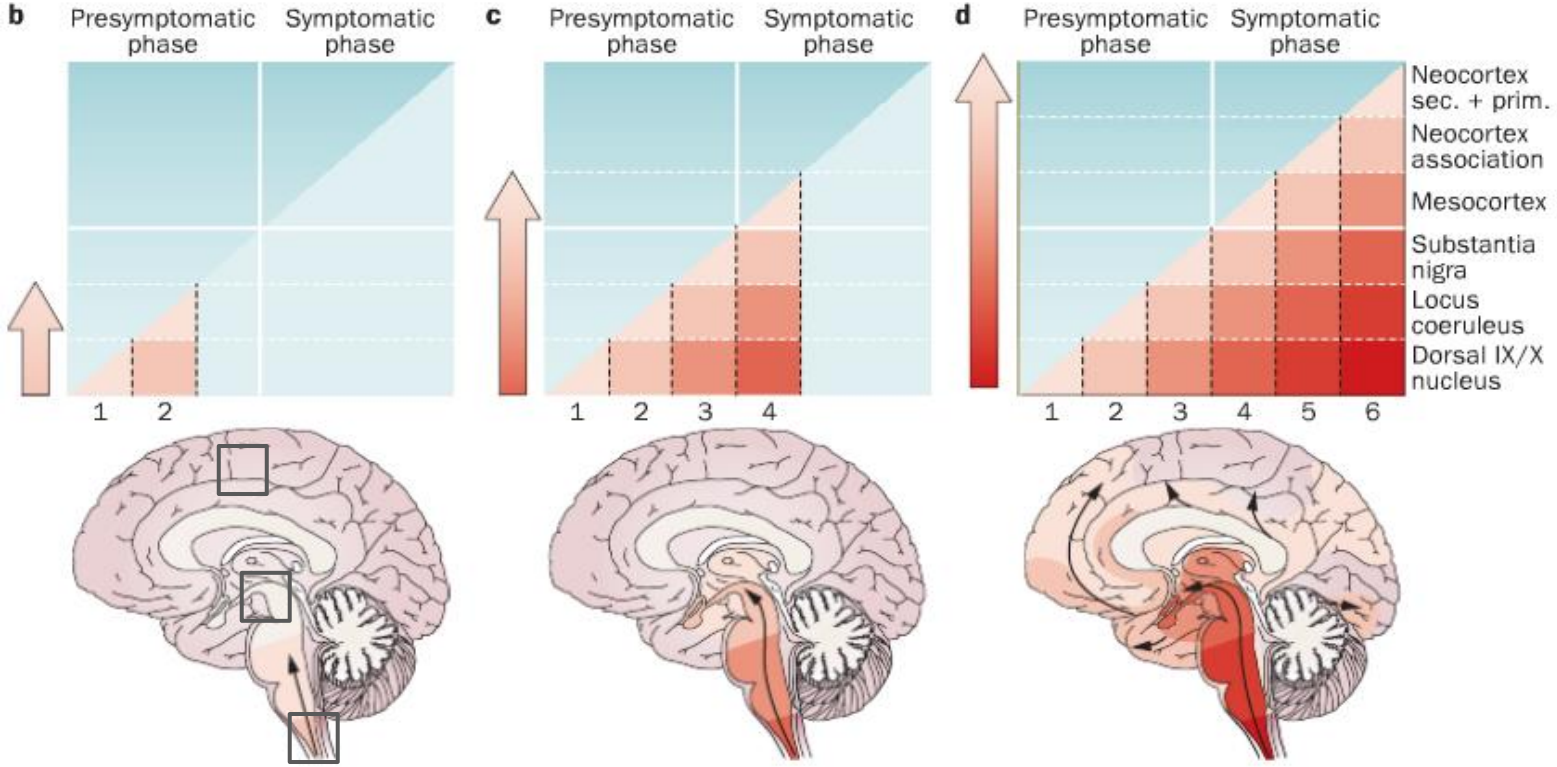
Alpha-synuclein misfolding is a central feature of multiple neurodegenerative disorders

1912



2009

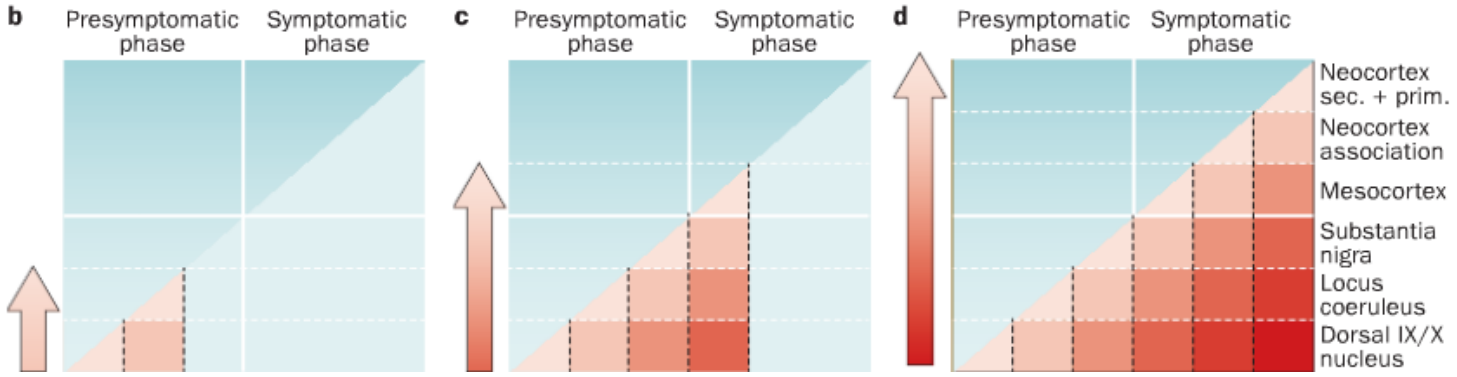




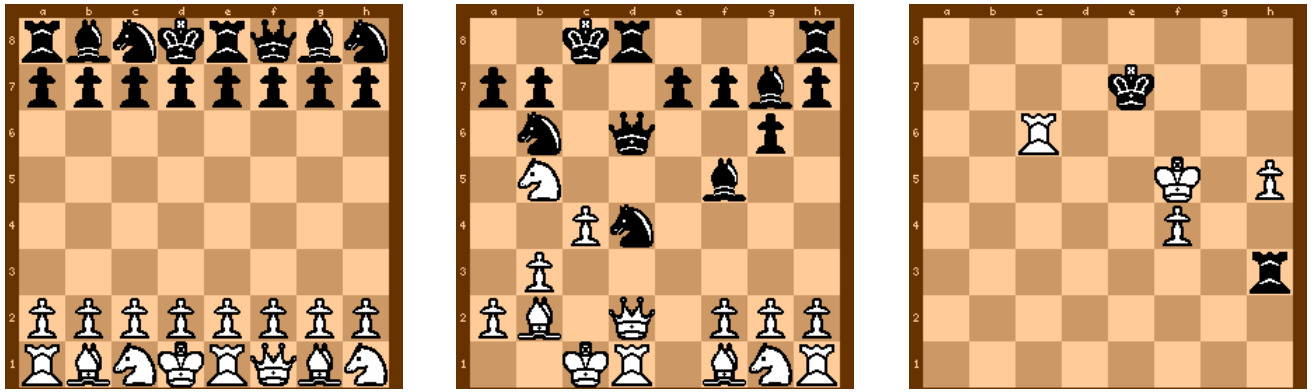
- Histopathological - Present in synucleinopathies (PD, PDD/DLB, MSA, and AD)
- Lewy pathology follows dynamic yet predictable pattern(s) that parallel disease progression and symptoms

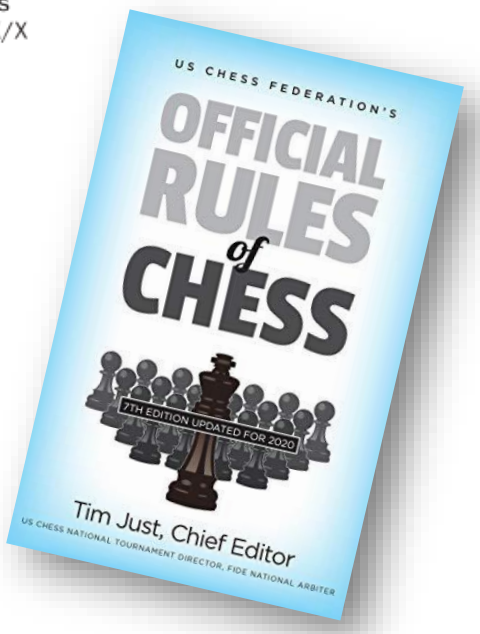
Braak et al., 2003; Jellinger et al., 2009; Dickson et al., 2010; Goedert 2012

Lewy pathology develops in predictable pattern(s) that parallel disease progression



- Disease occurs over protracted timecourse
- Significant clinical heterogeneity
- In vivo imaging is still under development

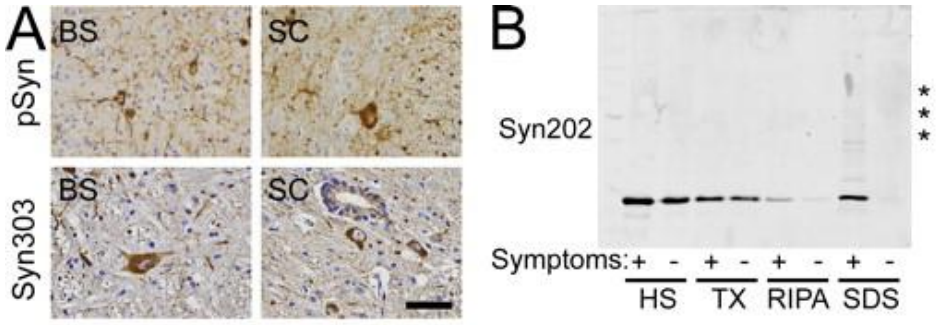


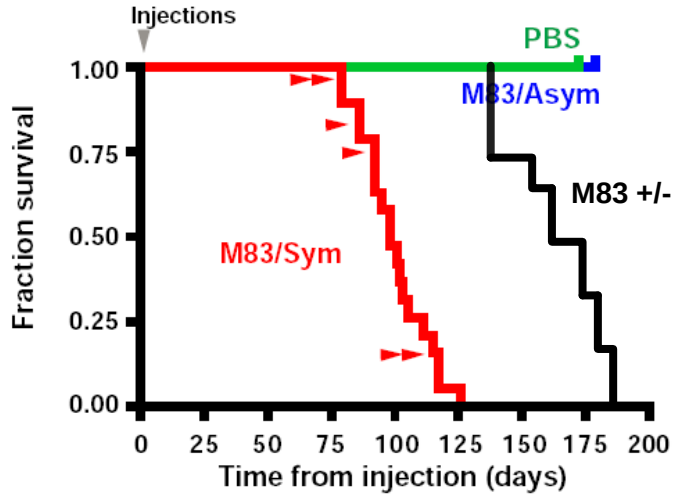


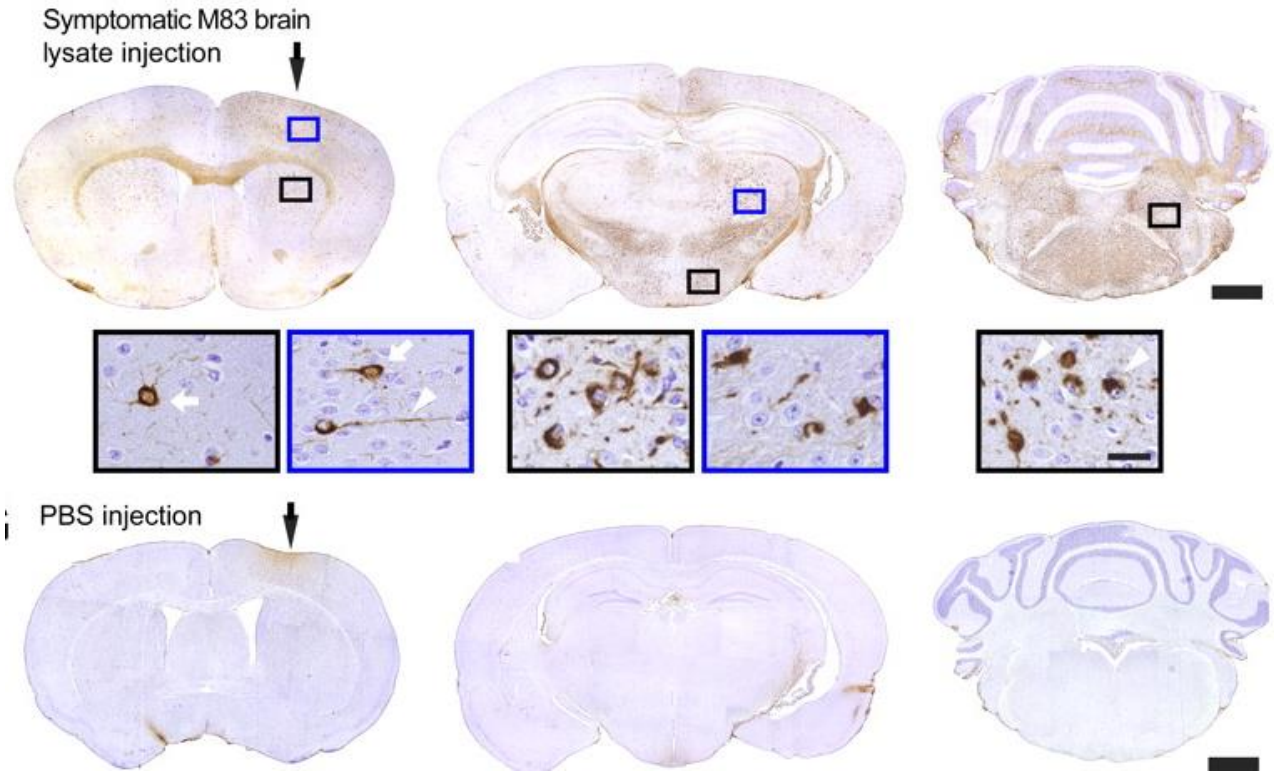
Long-term goal: interrogate the intermediate processes of synucleinopathy through cellular and in vivo models

aSyn pathology and disease can be transmitted in vivo

Hu-aSyn^{A53T} Tg mice

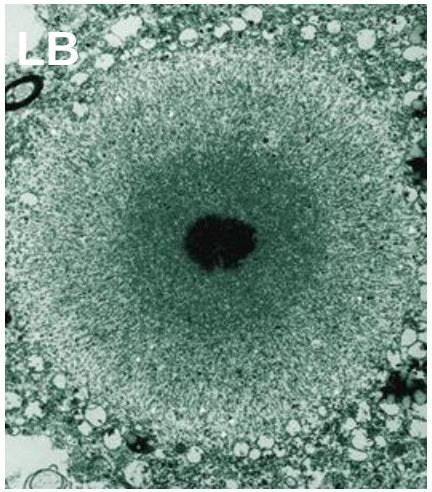




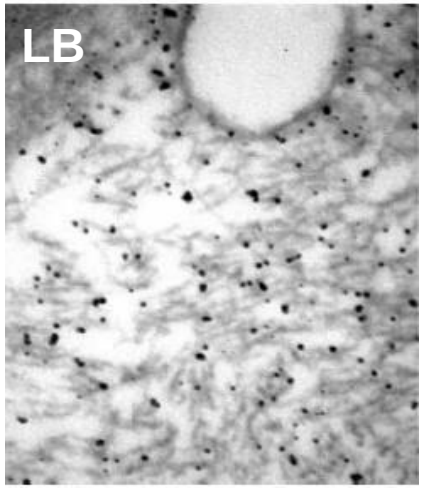


Luk et al, J Exp Med 2012

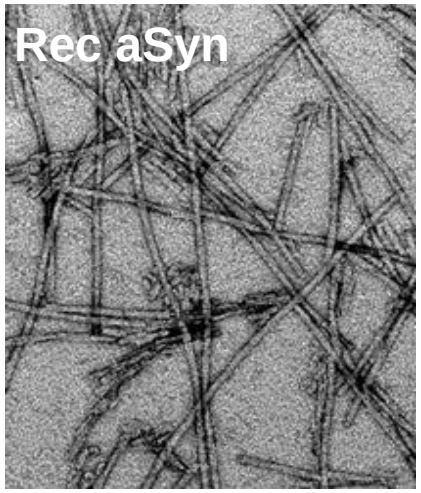
Leveraging the self-templating properties of aSyn fibrils

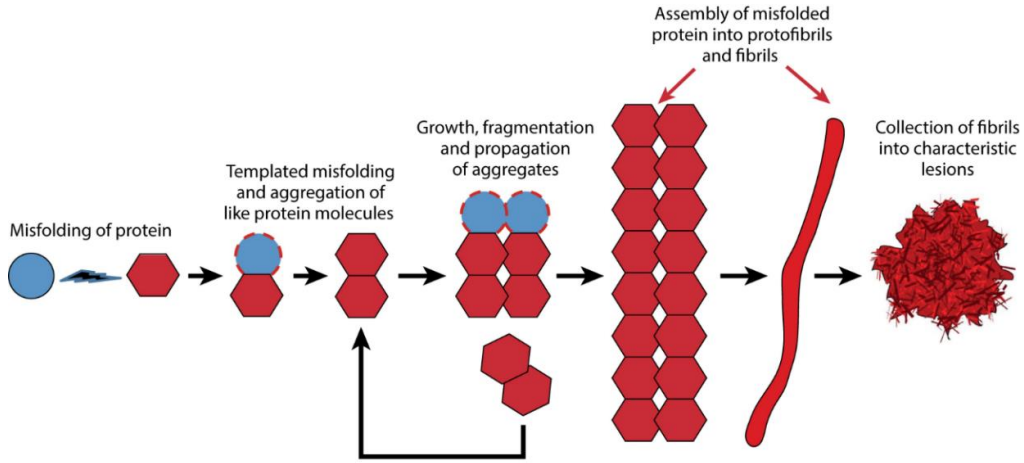


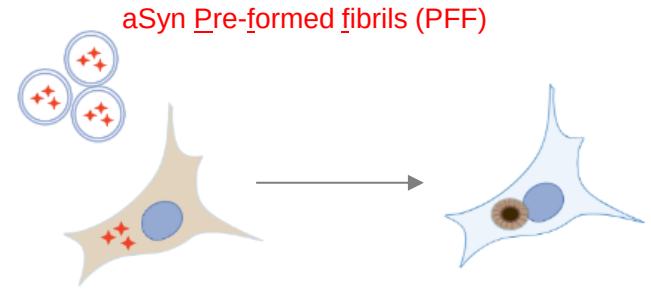
Forno et al, 1996



Giasson et al, 2002

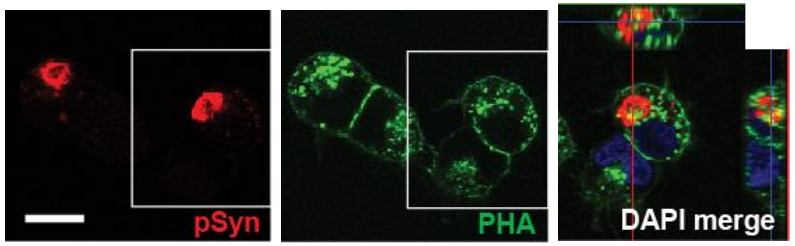


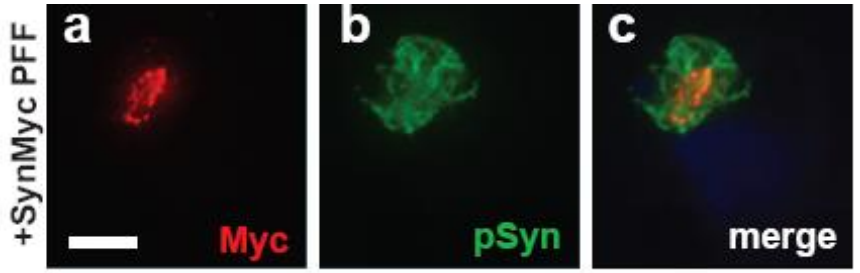




Non-neuronal cells

HEK293, SH-SY5Y, HeLa, COS7, SK-MEL-5… (+ liposome)



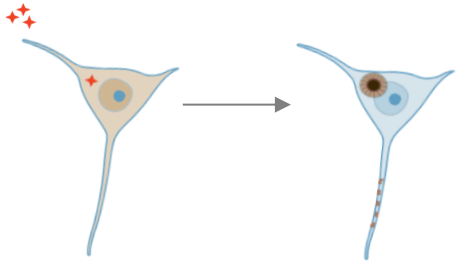


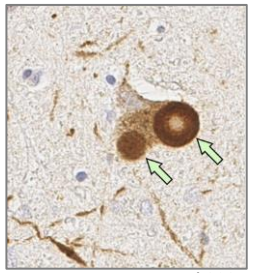
Luk et al., *PNAS* 2009

Nonaka et al., *J Biol Chem* 2010

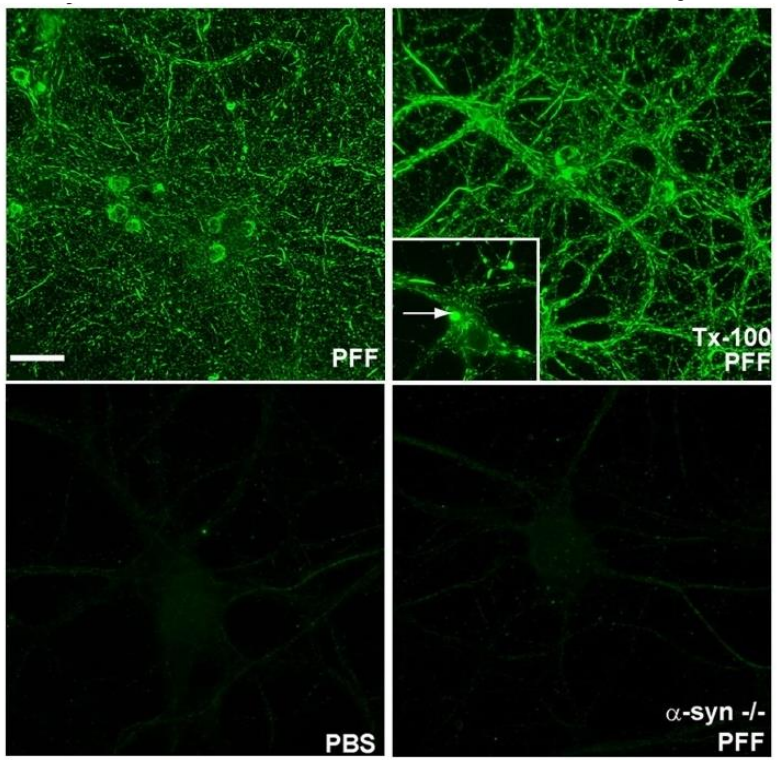
Internalized fibrils seed the conversion of endogenously-expressed aSyn

Neurons (non-Tg)
HC, Ctx, Str, VM/DA, iPSC-derived

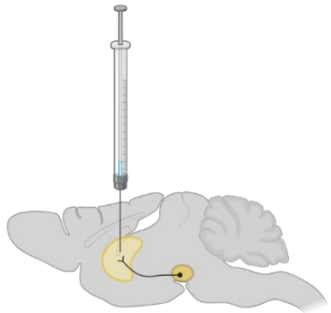


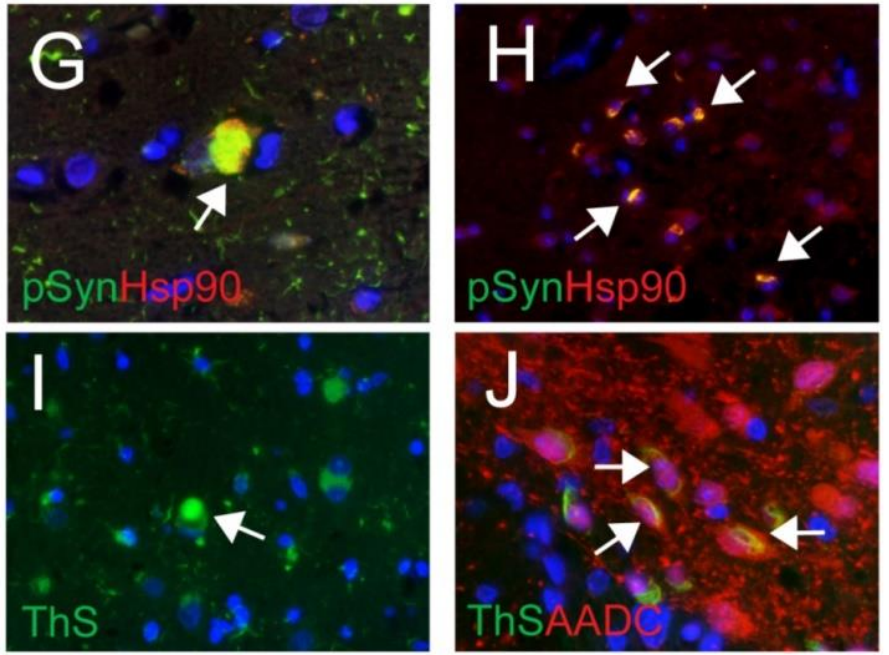


Koga et al 2021



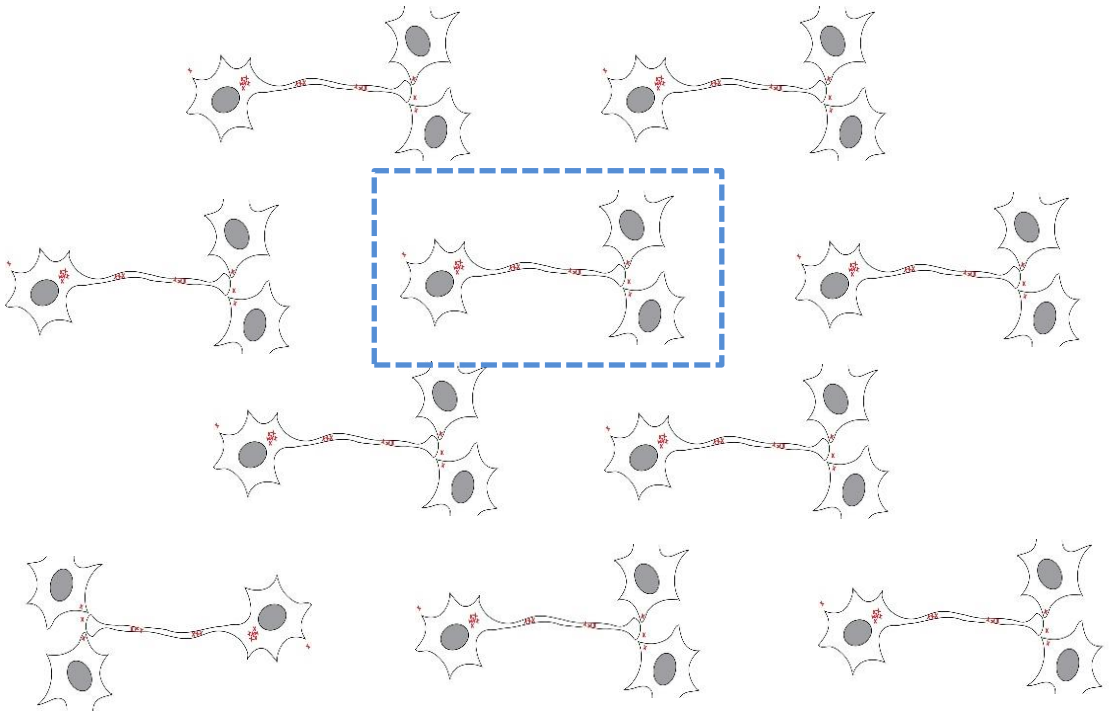
In vivo (non-Tg)
C57Bl/6, CD-1, S129, C3H, DBA
Rats, NHP



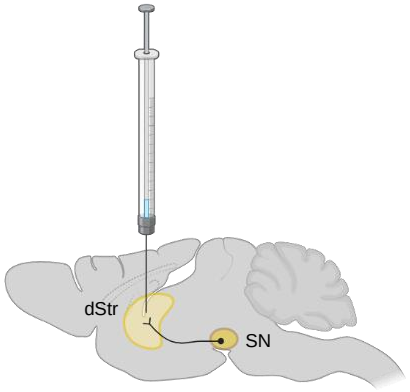


Volpicelli-Daley et al, *Neuron* 2011
Luk et al, *J Exp Med* 2012
Luk et al, *Science* 2012

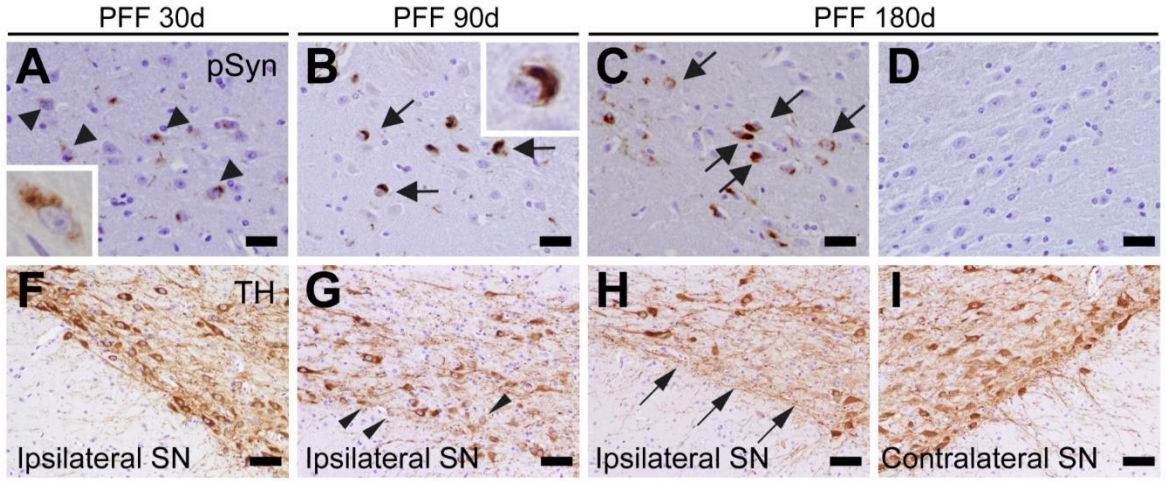
A working model of seeded aSyn pathology & transmission

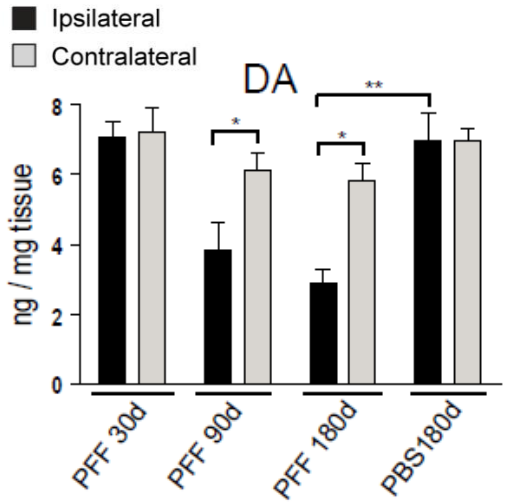


aSyn pathology leads to progressive DA cell loss rodents and NHPs

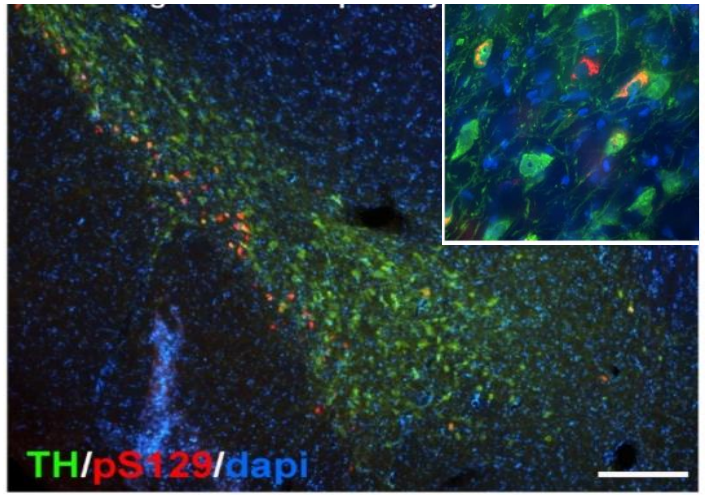


Mouse

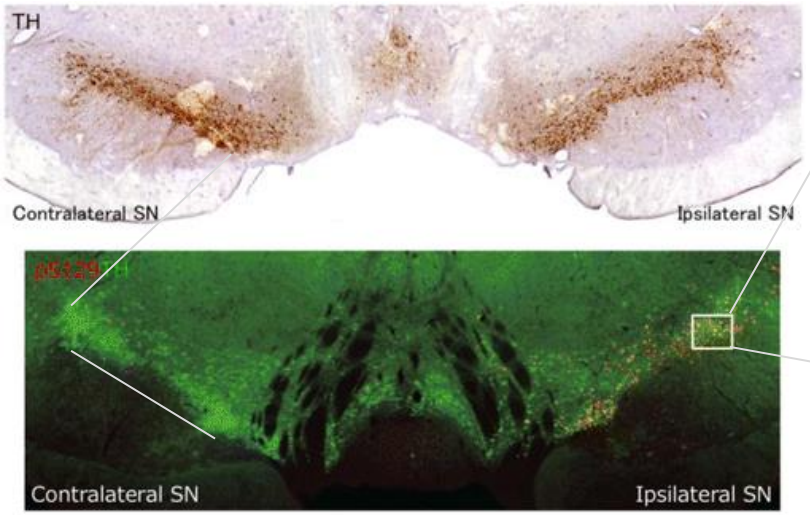


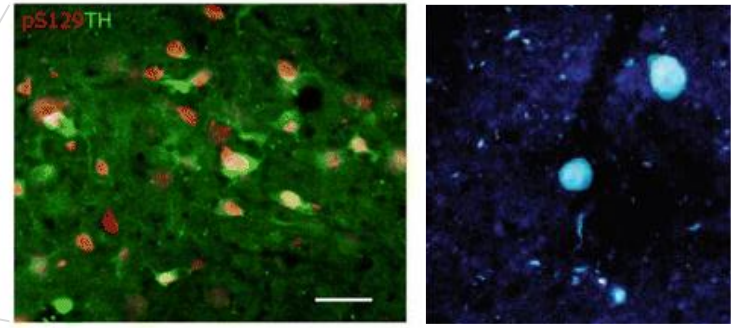


Rat



Marmoset/Macaque





Luk et al, *Science* 2012
Recasens et al, *Ann Neurol* 2014
Paumier et al, *Neurobiol Dis* 2015
Shimozawa et al, *Acta Neuropath Comm* 2017
Chu et al, *Brain* 2019

Seeding-competent aSyn species are present in human synucleinopathies

ANNALS of Clinical and Translational Neurology
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BRIEF COMMUNICATION

Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies

Graham Fairfoul[1], Lynne I. McGuire[1], Suvankar Pal[1,2], James W. Ironside[1], Juliane Neumann[3], Sharon Christie[4], Catherine Joachim[4], Margaret Esiri[4], Samuel G. Evetts[3], Michal Rolinski[3], Fahd Baig[3], Claudio Ruffmann[3], Richard Wade-Martins[5], Michele T. M. Hu[3], Laura Parkkinen[3] & Alison J. E. Green[1]

www.thelancet.com/neurology Vol 22 May 2023

Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study

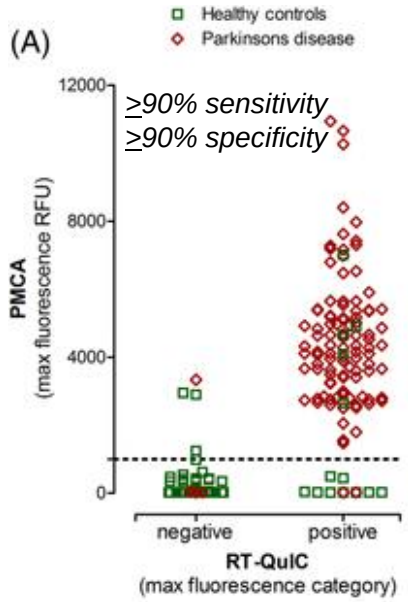
Andrew Siderowf*, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kieburtz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†

nature medicine
Article
https://doi.org/10.1038/s41591-023-02358-9

Propagative α-synuclein seeds as serum biomarkers for synucleinopathies

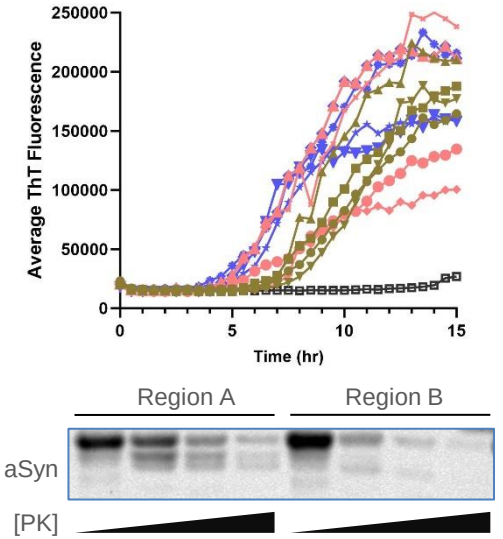
Received: 1 July 2022
Accepted: 21 April 2023
Published online: 29 May 2023
Check for updates

Ayami Okuzumi[1], Taku Hatano[1], Gen Matsumoto[2], Shuko Nojiri[3], Shin-ichi Ueno[1], Yoko Imamichi-Tatano[1], Haruka Kimura[1], Soichiro Kakuta[4], Akihide Kondo[5], Takeshi Fukuhara[6], Yuanzhe Li[1], Manabu Funayama[1], Shinji Saiki[1,7], Daisuke Taniguchi[1], Taiji Tsunemi[1], Deborah McIntyre[8], Jean-Jacques Gérardy[9], Michel Mittelbronn[9], Rejko Kruger[8,10], Yasuo Uchiyama[11], Nobuyuki Nukina[12] & Nobutaka Hattori[1,6]



Kang et al, Mov Dis 2019

PFF-injected mouse brain tissue



In vivo pathogenicity established for:

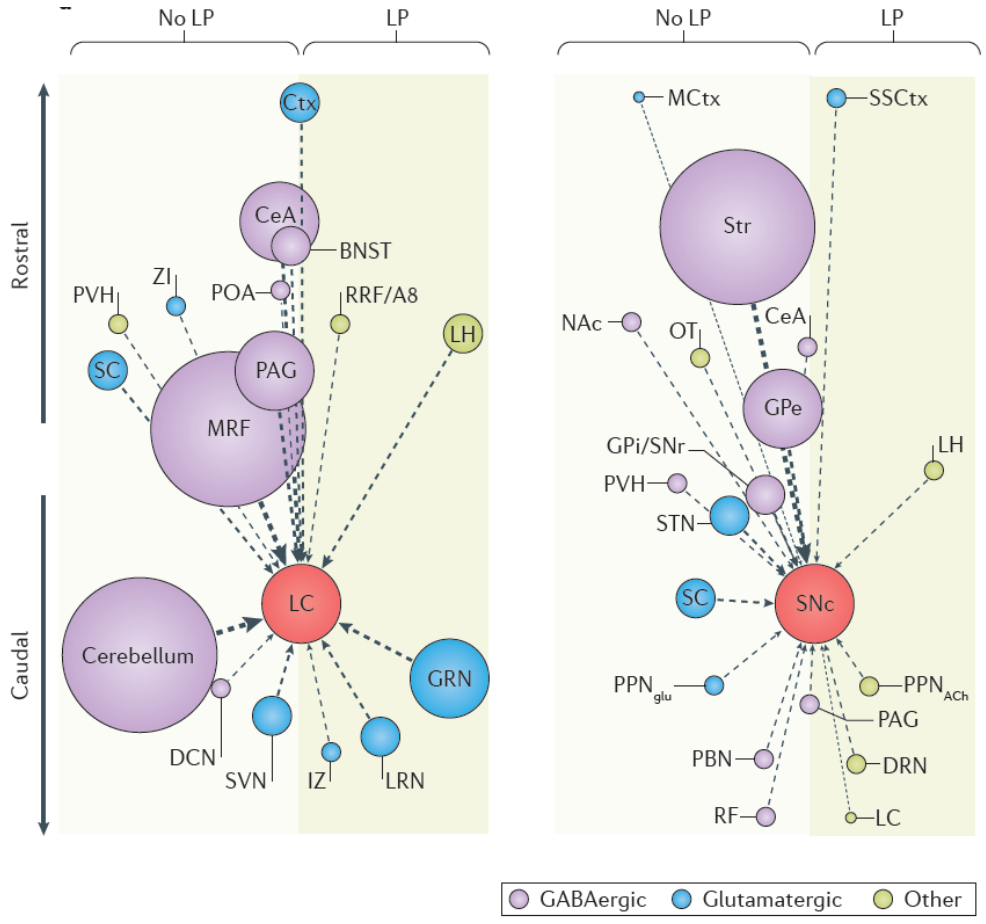
DLB → Masuda-Suzukake, *Brain* 2013

PD/PDD → Recasens, *Ann Neurol* 2014

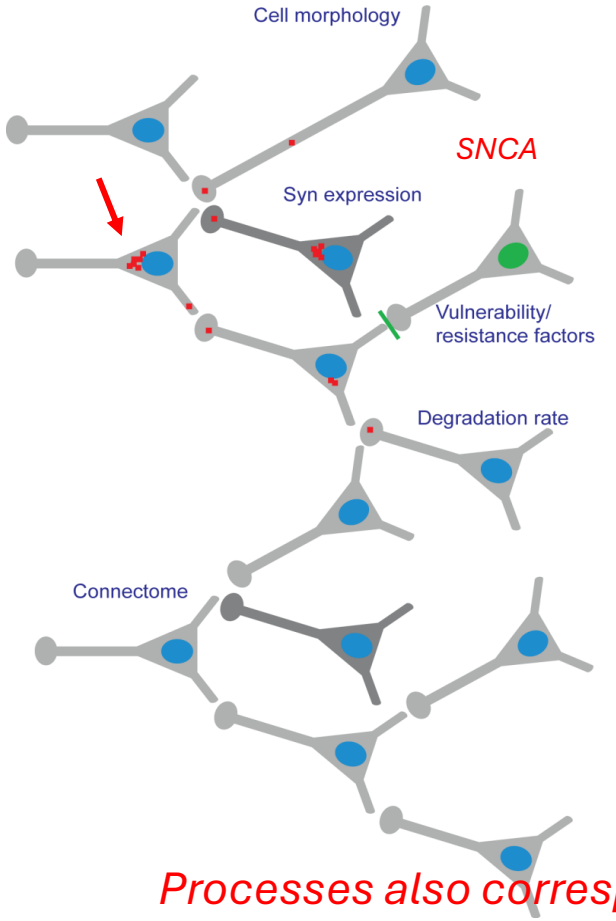
MSA → Watts, *PNAS* 2013; Peng, *Nature* 2018

ampLB → Uemura, *Nat Communications* 2023

PD is not “simply” a prion disorder



Surmeier, Obeso and Halliday, *Nat Rev Neurol* 2017



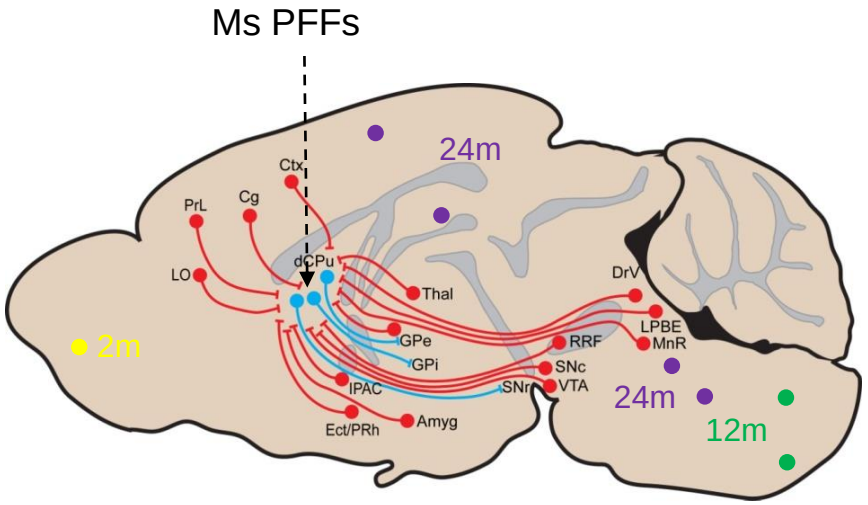
GBA, TMEM175, ATP13A2, PLA2G6, RAB29…

PRKN, PINK1, DJ1?

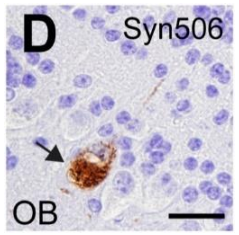
MAPT, LRRK2, VPS35

Processes also correspond to known human LB disease risk genes

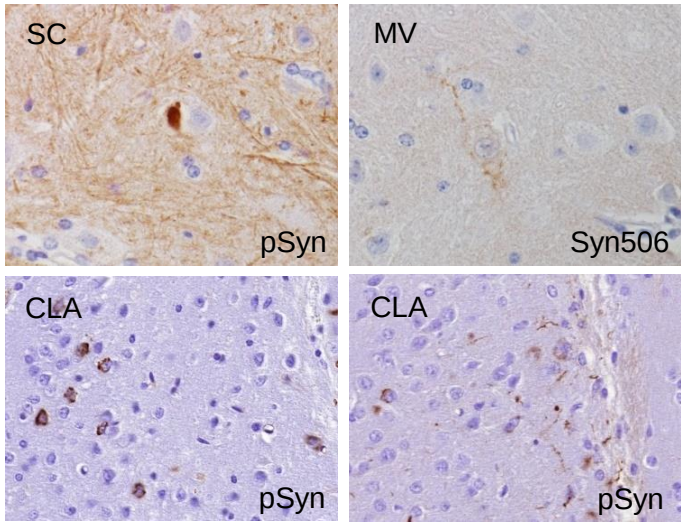
Progressive spread of α-Syn pathology in PFF-treated non-Tg mice



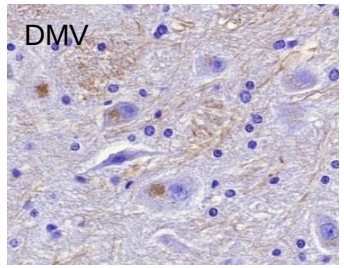
2M

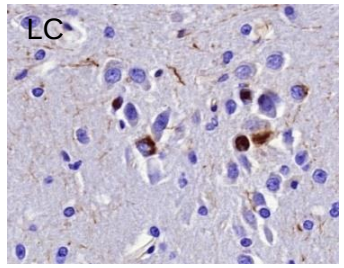


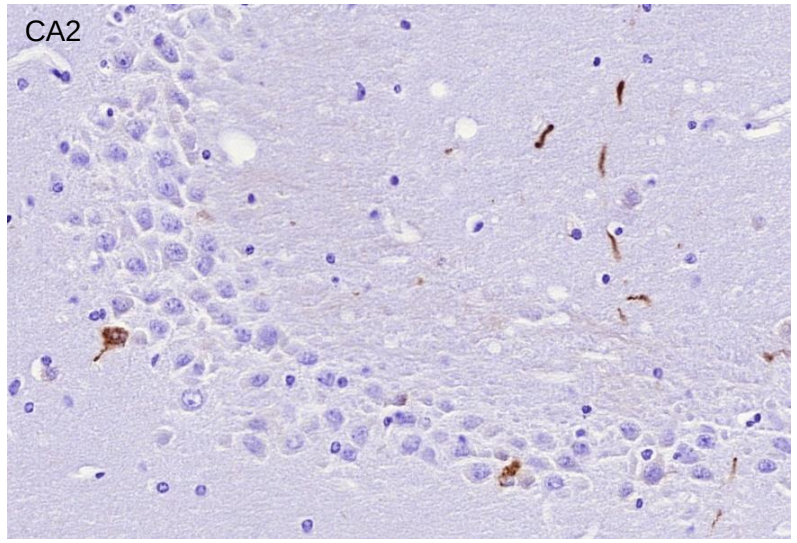
12M

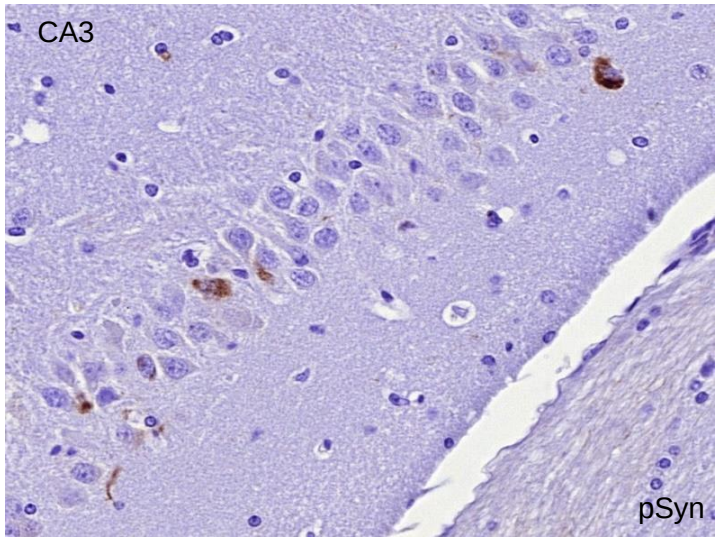


24M





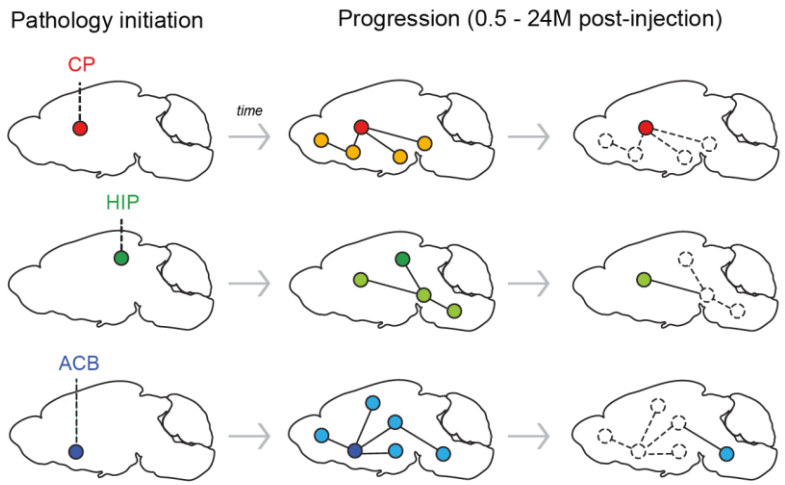




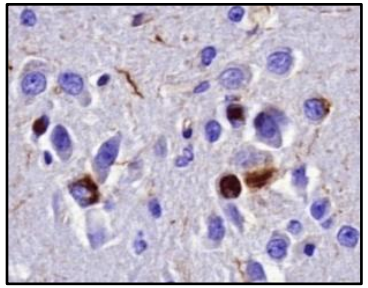
Rahayel et al, *Brain* 2022

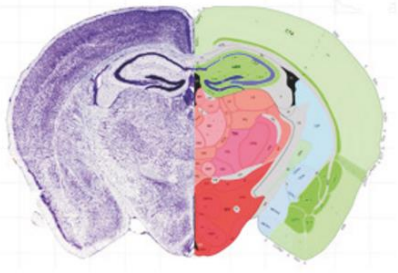
Global monitoring of α-Syn pathology trajectories in the mouse CNS

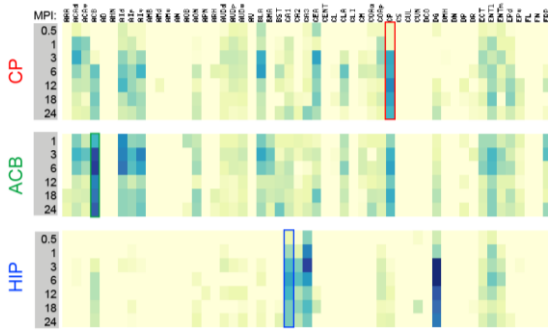
A. Seeding in different sites



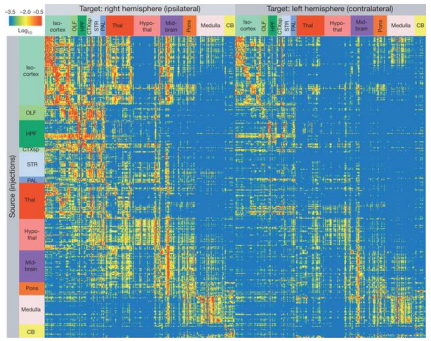
B. Pathology quantification and atlas registration



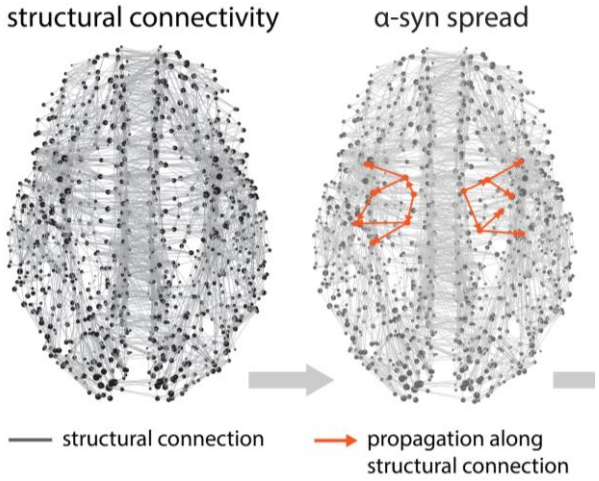


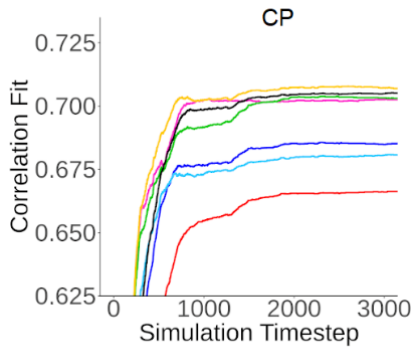


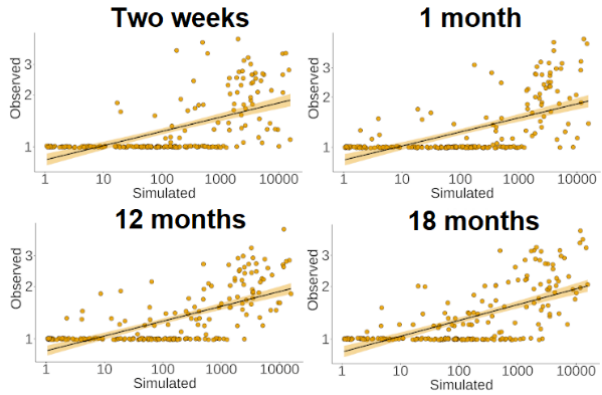
C. Determining fit against observed spatiotemporal datasets



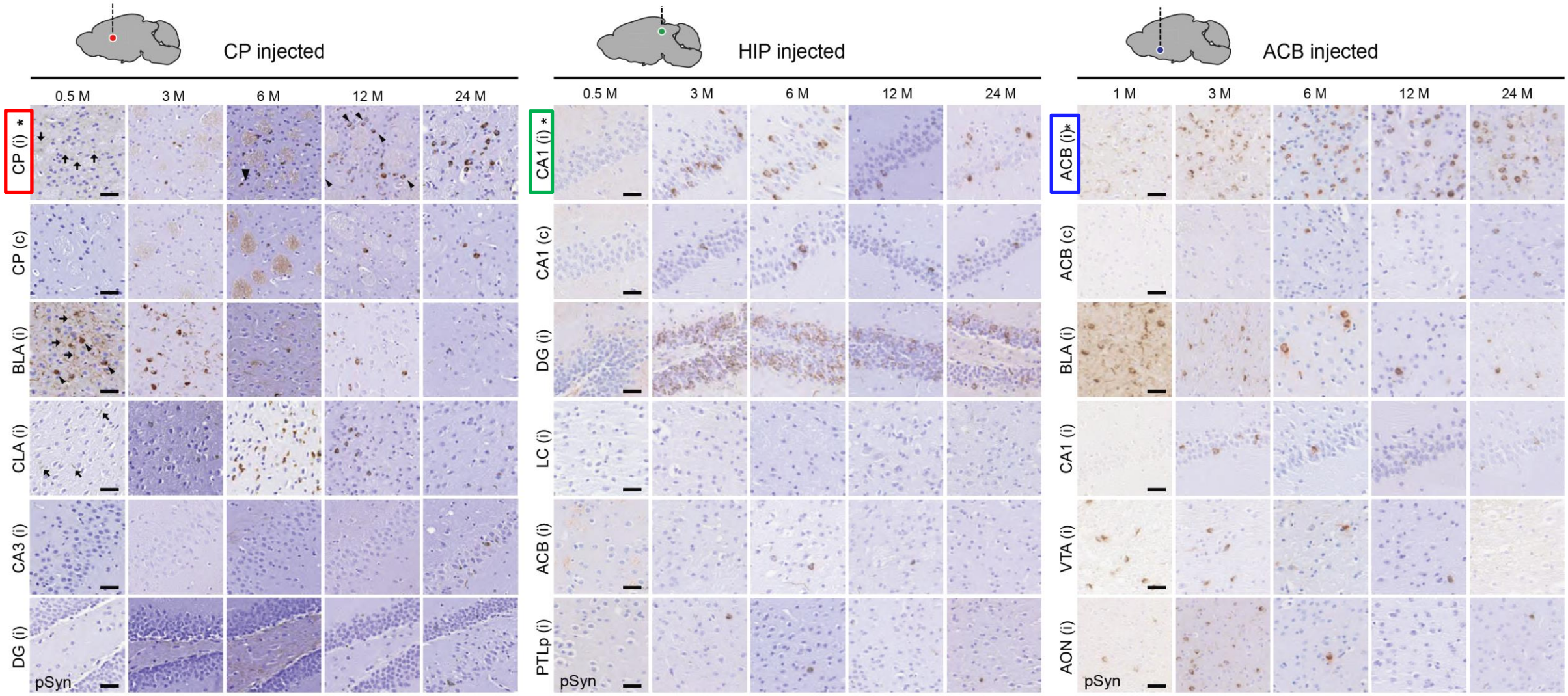
Publically available datasets
e.g. Mouse Brain Connectivity Atlas
Gene Expression Atlas





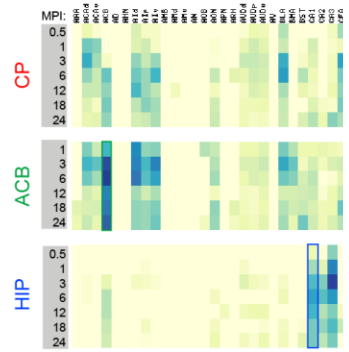


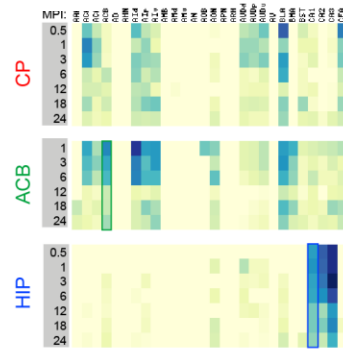
Spatial distribution of aSyn pathology points to multiple dynamic processes after an initial seeding event

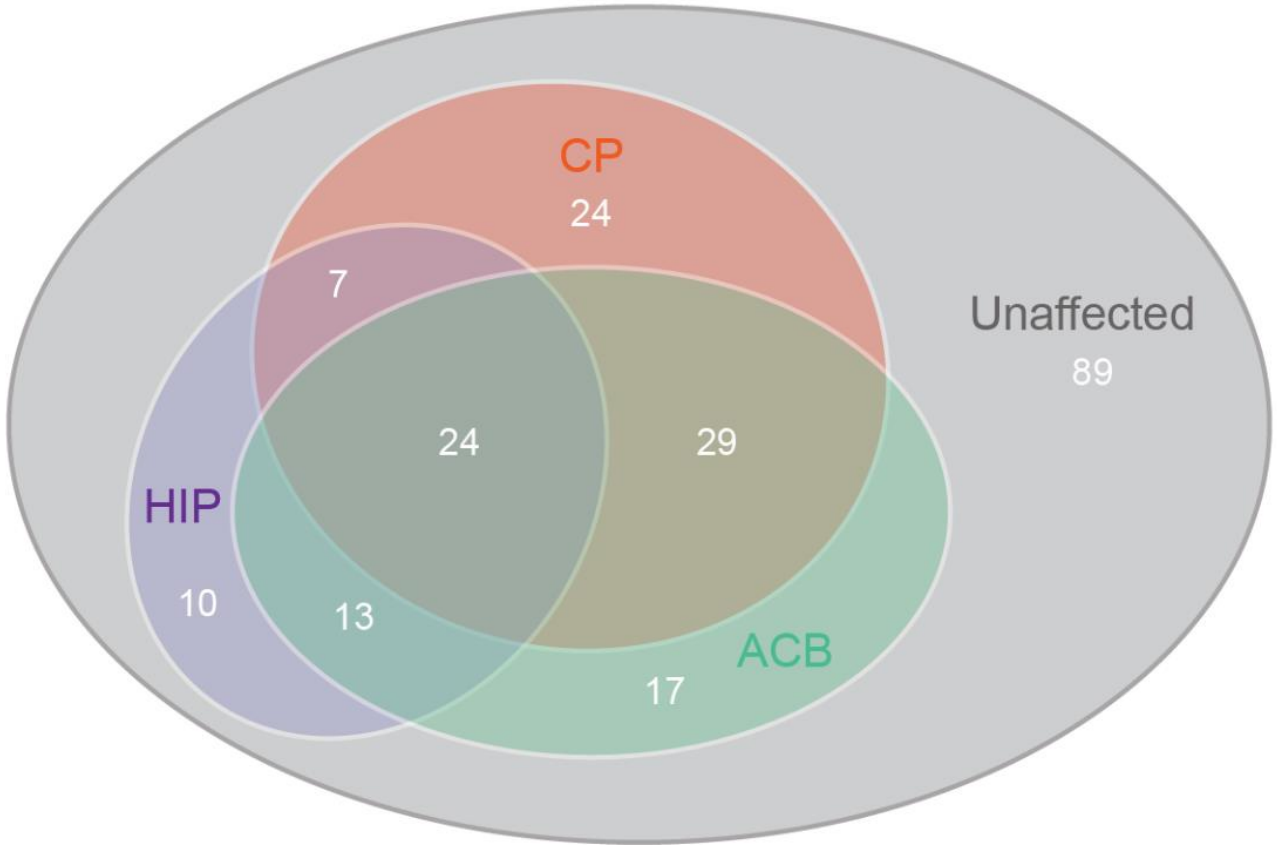


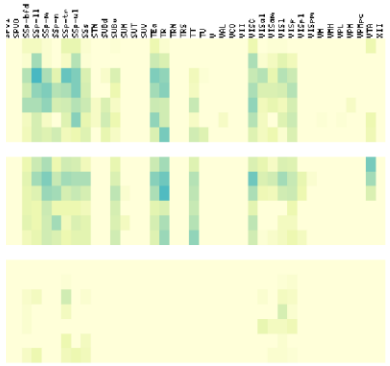
Rahayel et al, *Brain* 2022

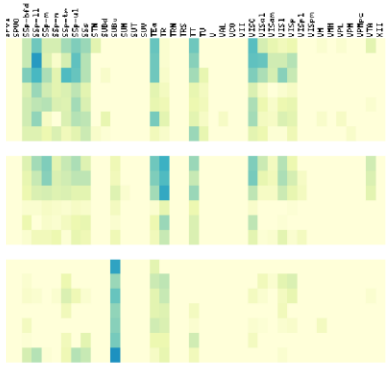
Site of initial pathology determines the evolution of synucleinopathy in vivo





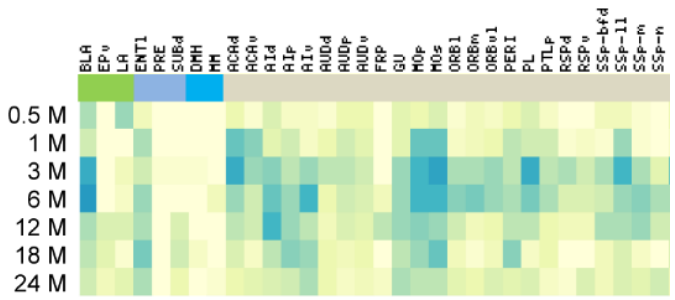


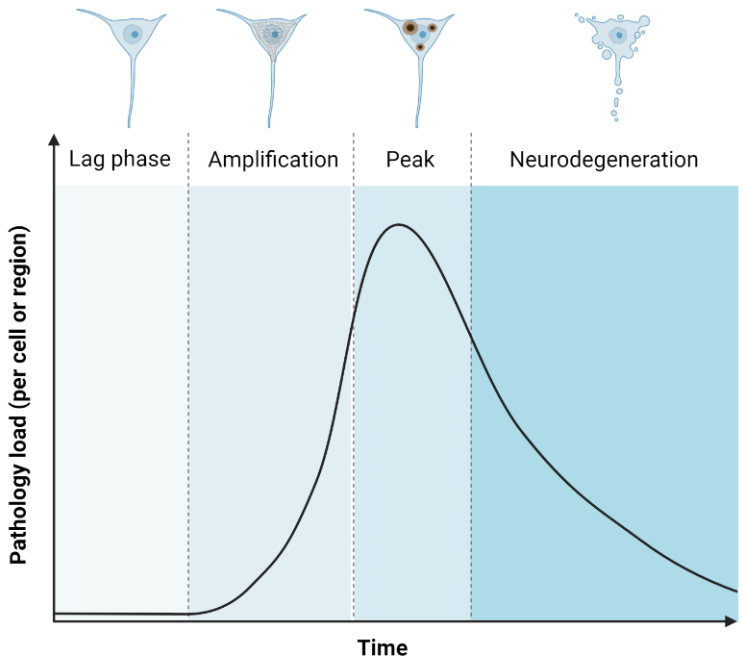


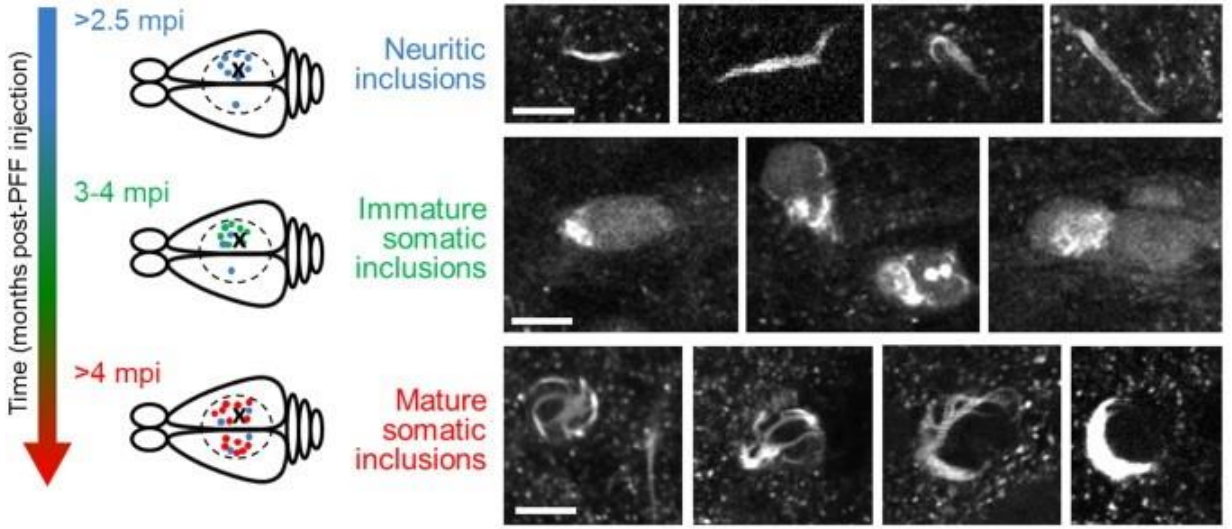


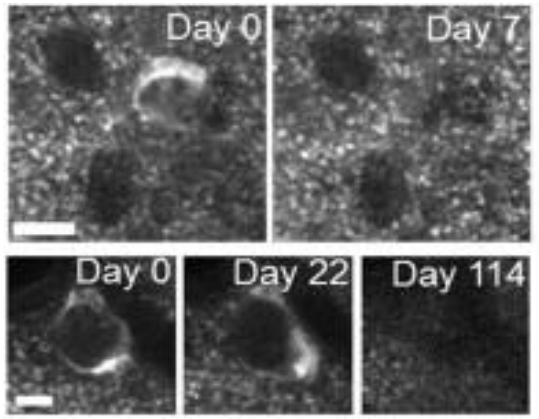
Rahayel et al, *Brain* 2022

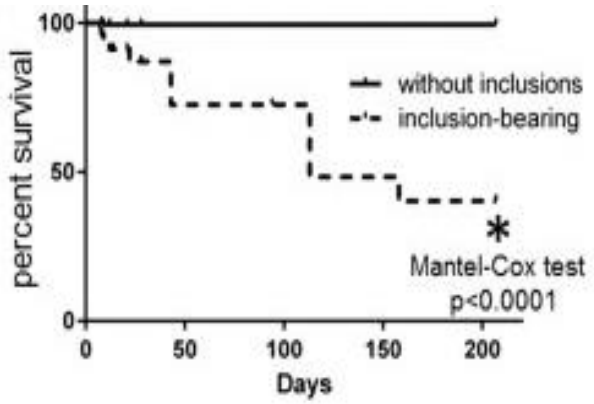
Local fluctuations in synucleinopathy mirror neuron loss





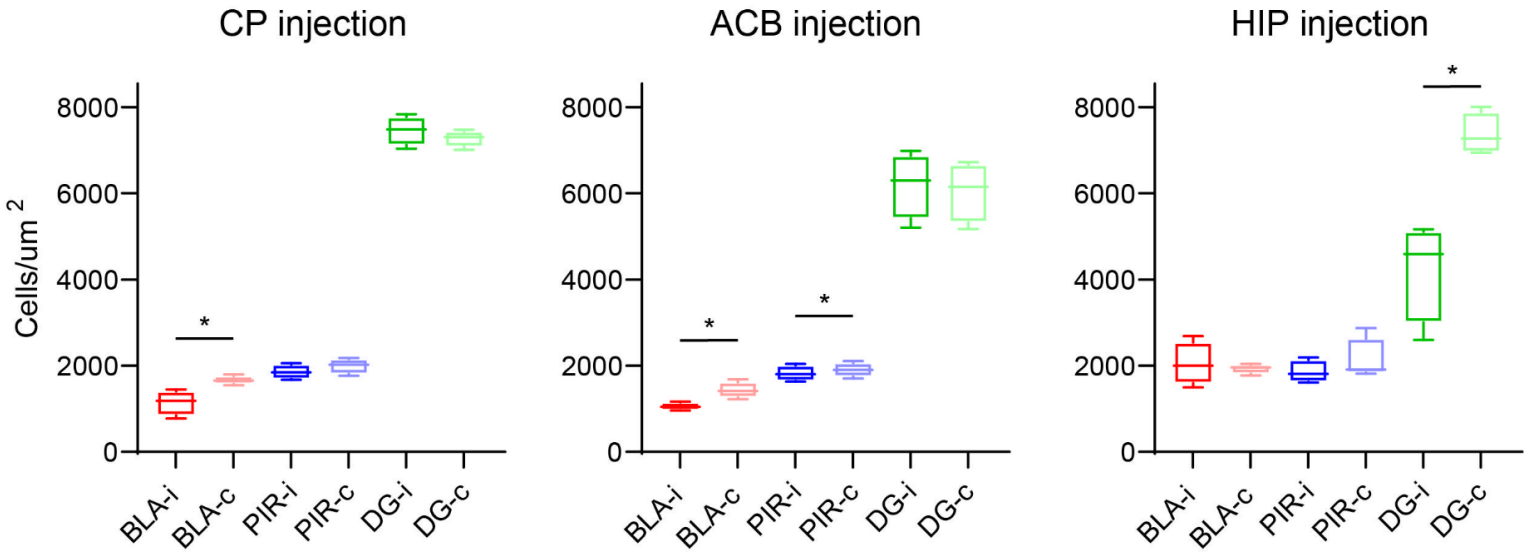


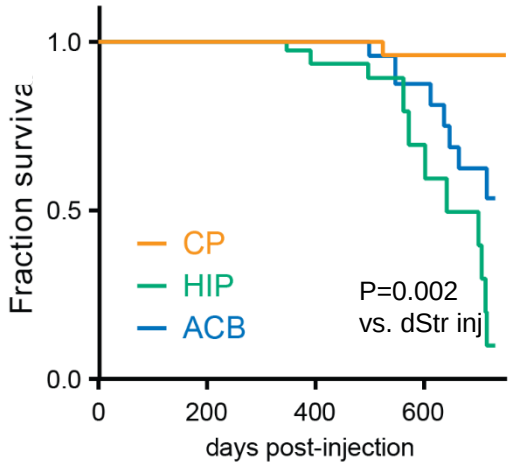




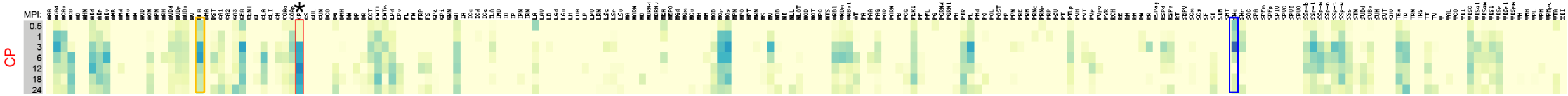
Osterberg et al [Unni Lab], *Cell Reports* 2015
Rahayel et al, *Brain* 2022

Synucleinopathy originating from different CNS regions elicit distinct cell loss patterns and phenotypes

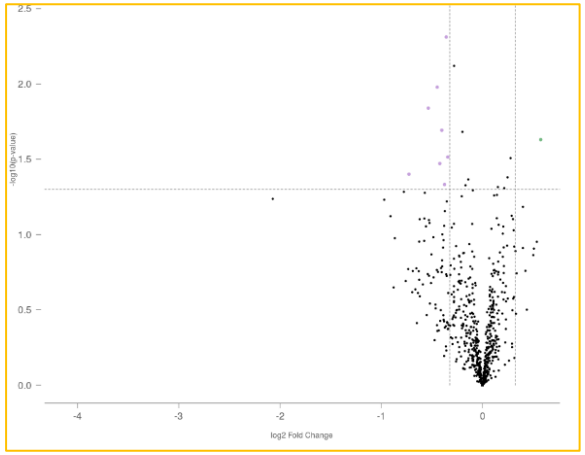




Seeded synucleinopathy induce regional transcriptomic signatures

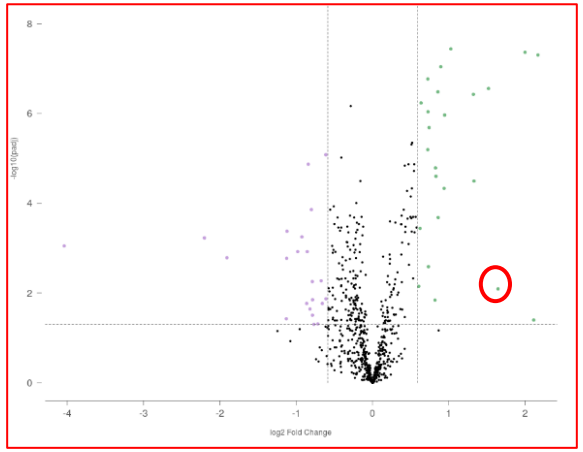


Amygdala



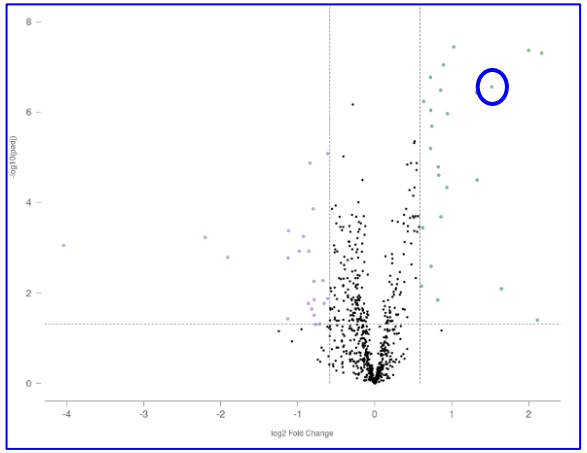
↓Synaptic function
↓Steroid signaling

Striatum

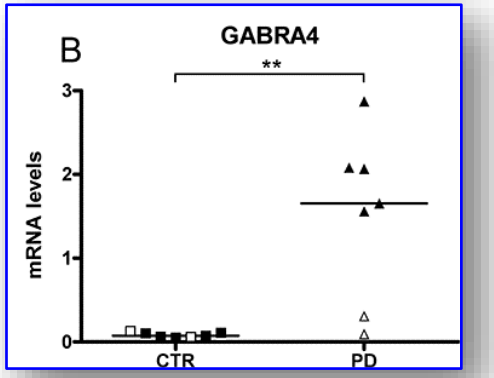


↓Synaptic function
↑Neuroinflammation

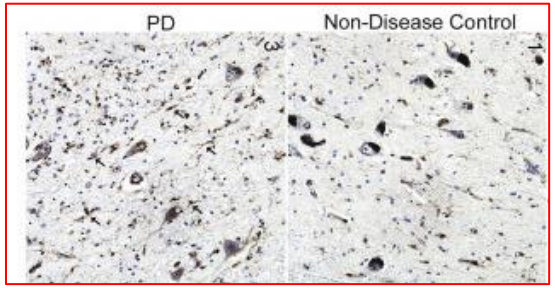
Midbrain

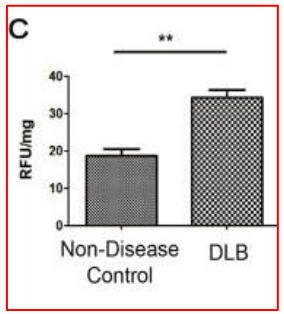


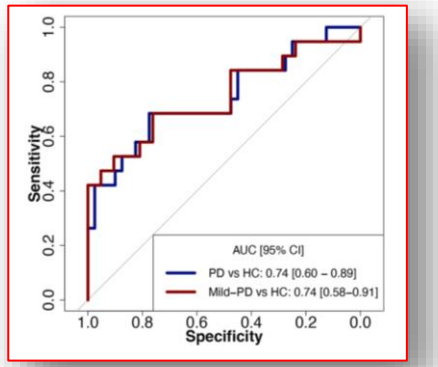
↓Synaptic function
↓Catecholamines



Lmp7/Psmb8

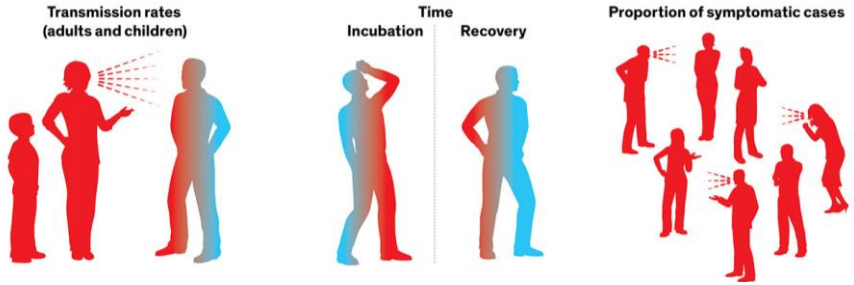


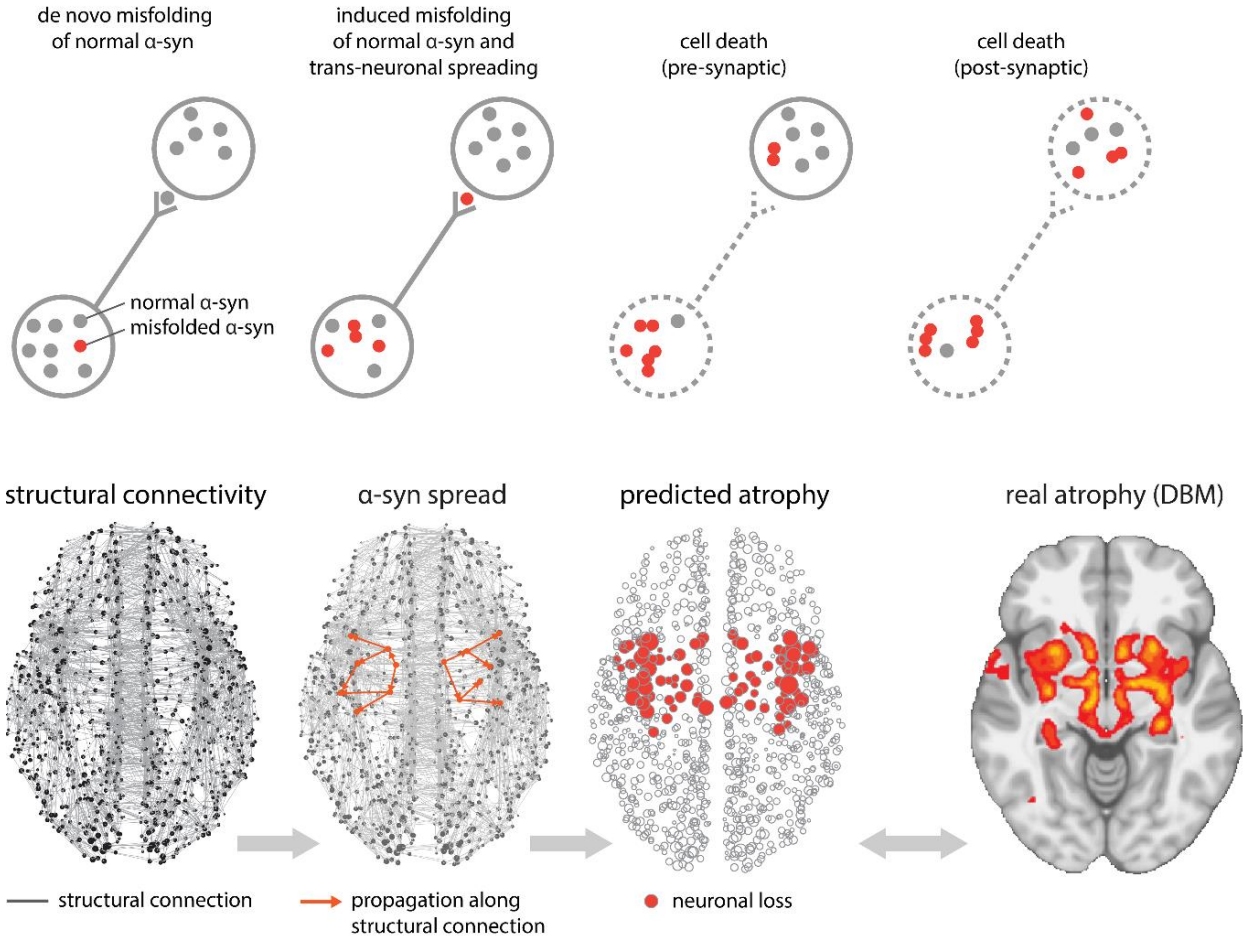




Ugras et al, eBioMedicine 2018 [Ischiropoulos lab]
Luchetti et al, Brain Pathol 2010
Nguyen et al, Parkinsonism Rel Disord 2023

Agent-based modeling of aSyn pathology spread



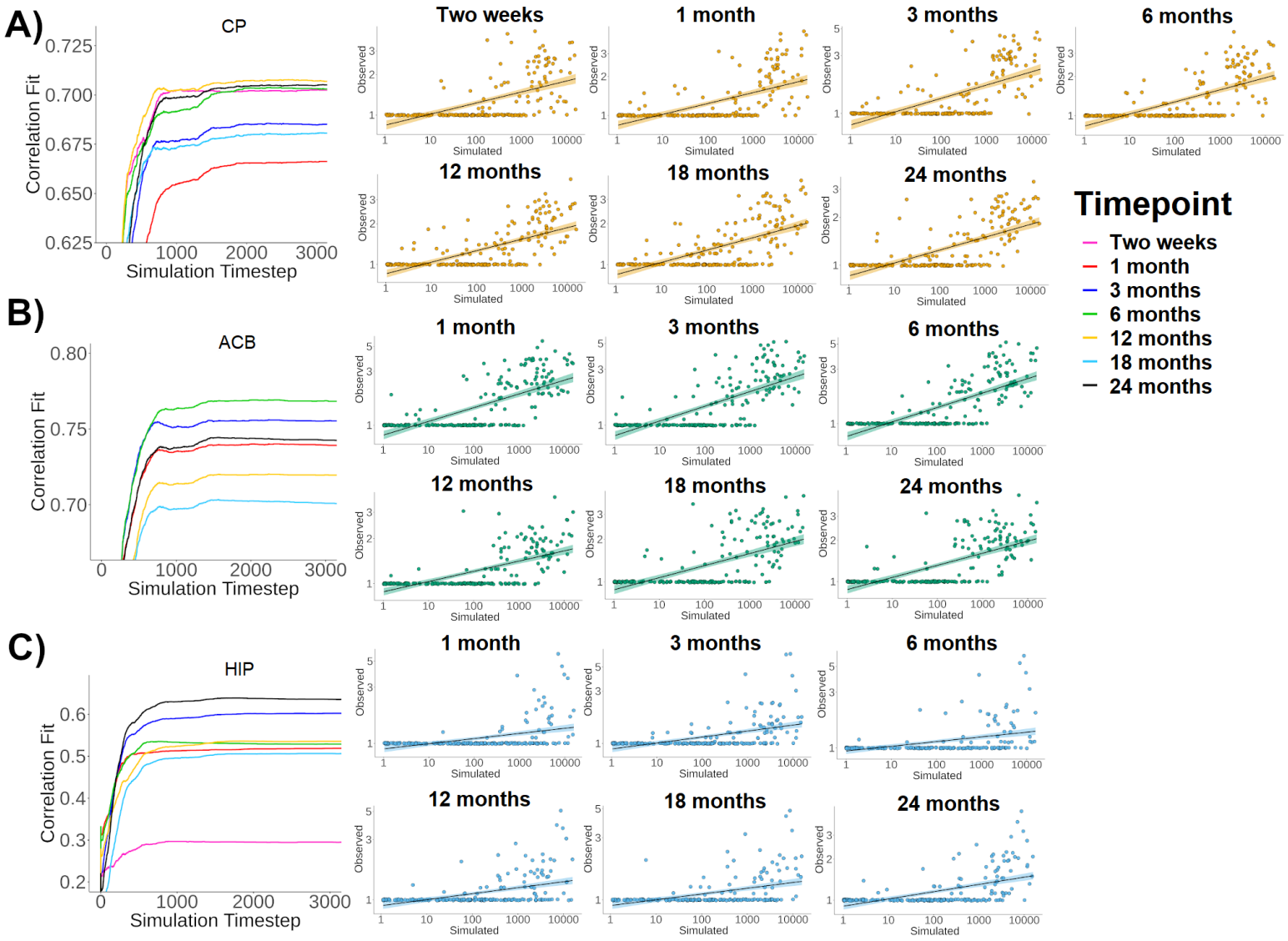


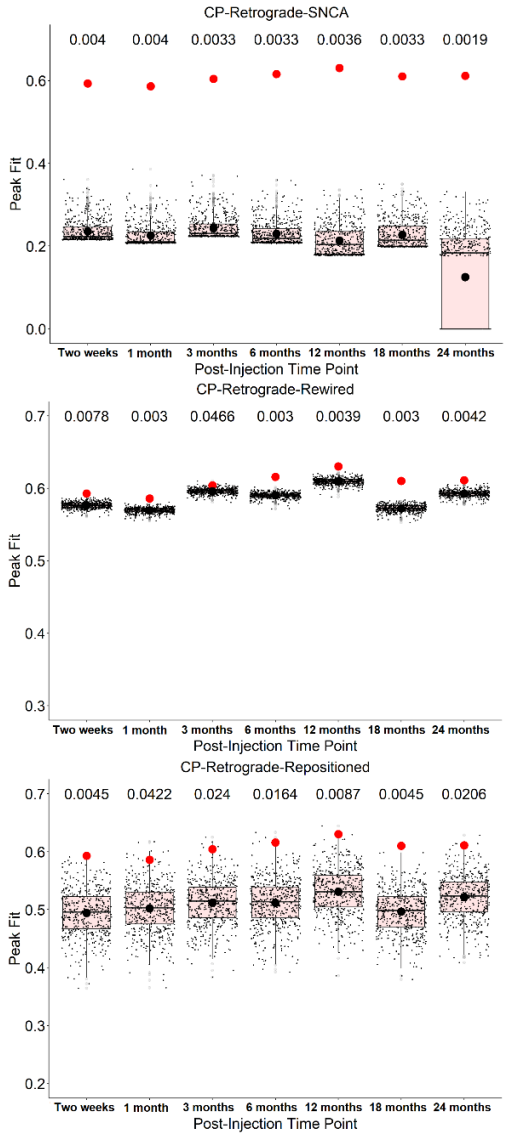
Susceptible-Infected-Removed (SIR) model

Production / Clearance / Misfolding / Propagation

Hutson, IEEE Spectrum 2020
Zheng et al. PLoS Biology 2019

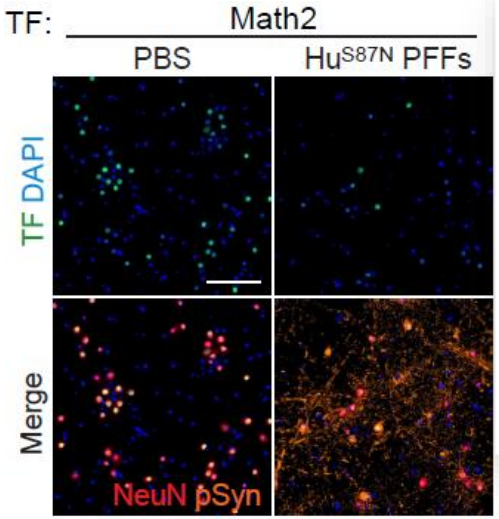
An agent-based (S-I-R) model closely recapitulates in vivo aSyn pathology spread





Rahayel et al, *Brain* 2022

Snca levels predict vulnerability to aSyn pathology among hippocampal glutamatergic neuron subtypes

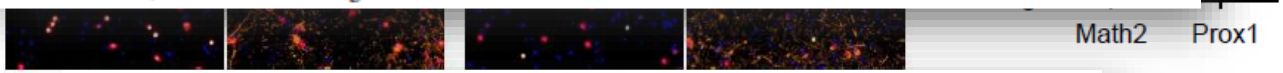


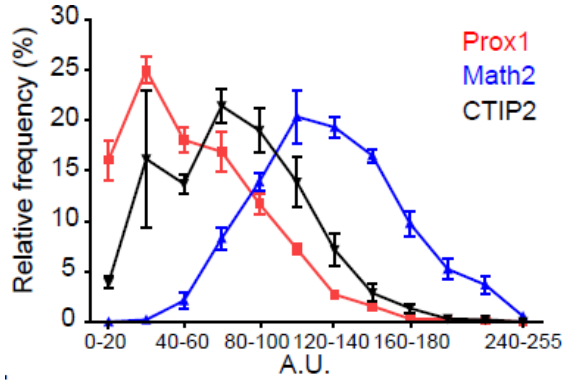
The Journal of Neuroscience, February 15, 2017 • 37(7):1675–1684 • 1675

Neurobiology of Disease

Hippocampal α-Synuclein in Dementia with Lewy Bodies Contributes to Memory Impairment and Is Consistent with Spread of Pathology

David H. Adamowicz,[1,2] Subhojit Roy,[1,3] David P. Salmon,[1] Douglas R. Galasko,[1] Lawrence A. Hansen,[1,4] Eliezer Masliah,[1,4] and Fred H. Gage[2]



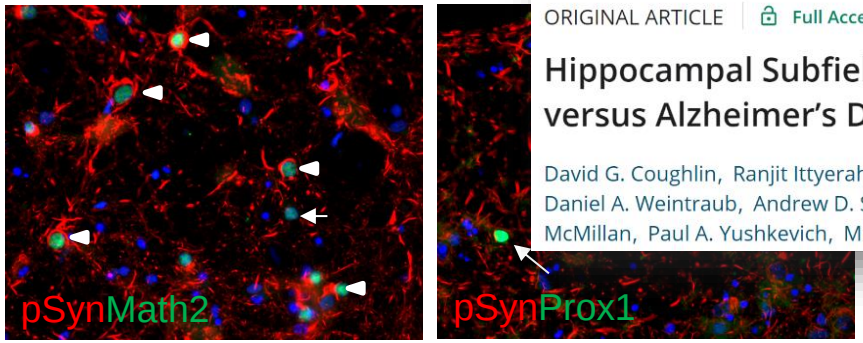


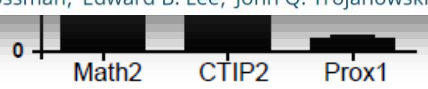
Neuropathology and Applied Neurobiology
BNS

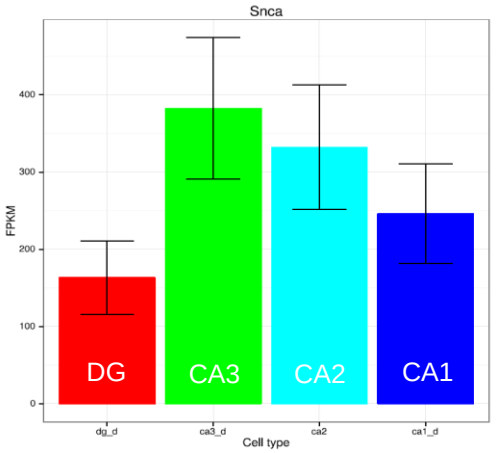
ORIGINAL ARTICLE | Full Access

Hippocampal Subfield Pathologic Burden in Lewy Body Diseases versus Alzheimer's Disease

David G. Coughlin, Ranjit Ittyerah, Claire Peterson, Jeffrey S. Phillips, Simon Miller, Katya Rascovsky, Daniel A. Weintraub, Andrew D. Siderowf, John E. Duda, Howard I. Hurtig, David A. Wolk, Corey McMillan, Paul A. Yushkevich, Murray Grossman, Edward B. Lee, John Q. Trojanowski, David J. Irwin

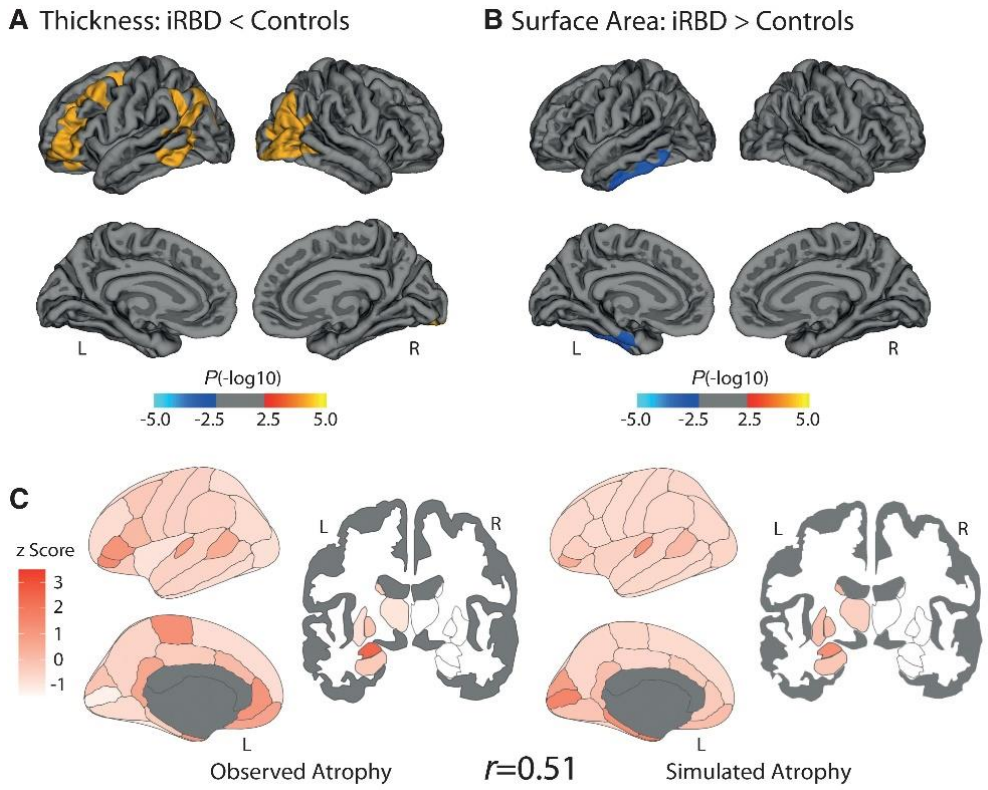


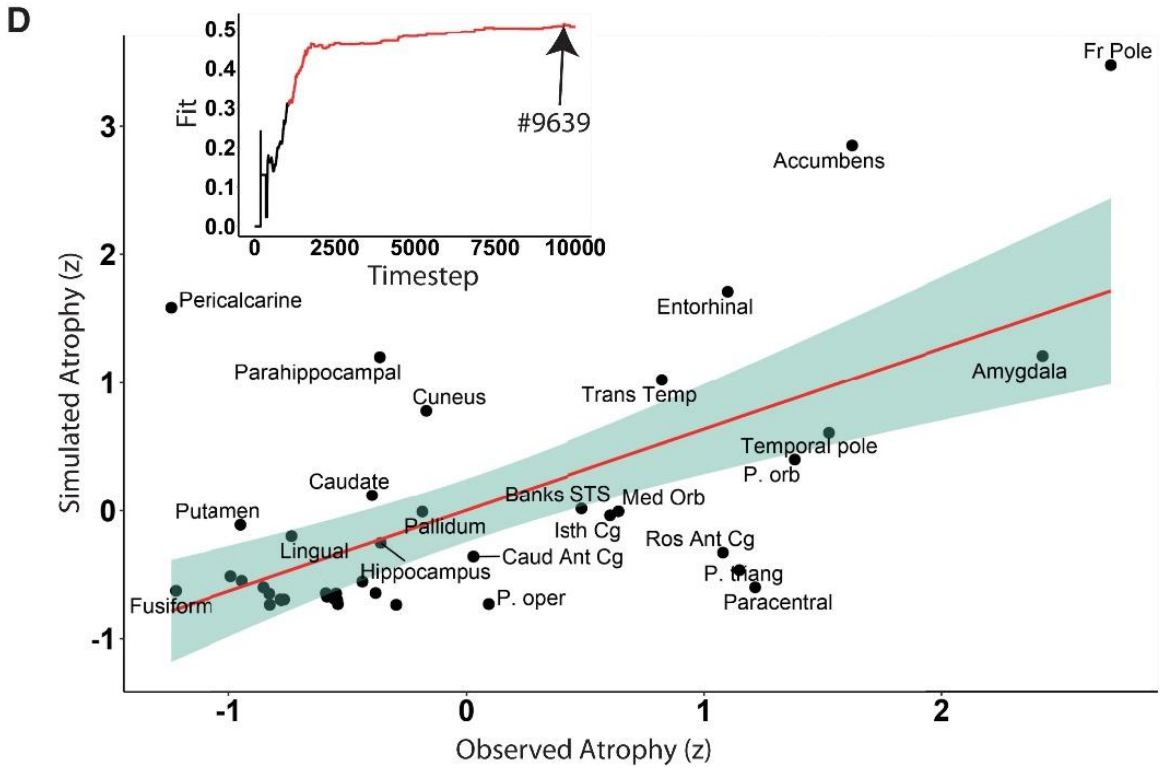




Luna et al, *Acta Neuropath 2018*
Cembrowski et al, *eLife 2016*

aSyn S-I-R models approximate atrophy patterns in iRBD patients





Rahayel et al, *Brain* 2022b

Connectivity and local aSyn expression are major (but not the only) drivers of pathological spread

ARTICLES
https://doi.org/10.1038/s41593-019-0457-5
nature neuroscience

Spread of α-synuclein pathology through the brain connectome is modulated by selective vulnerability and predicted by network analysis

Michael X. Henderson[1*], Eli J. Cornblath[2,3], Adam Darwich[1], Bin Zhang[1], Hannah Brown[1], Ronald J. Gathagan[1], Raizel M. Sandler[1], Danielle S. Bassett[2,4,5,6,7], John Q. Trojanowski[1] and Virginia M. Y. Lee[1]

SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

Determinants of seeding and spreading of α-synuclein pathology in the brain

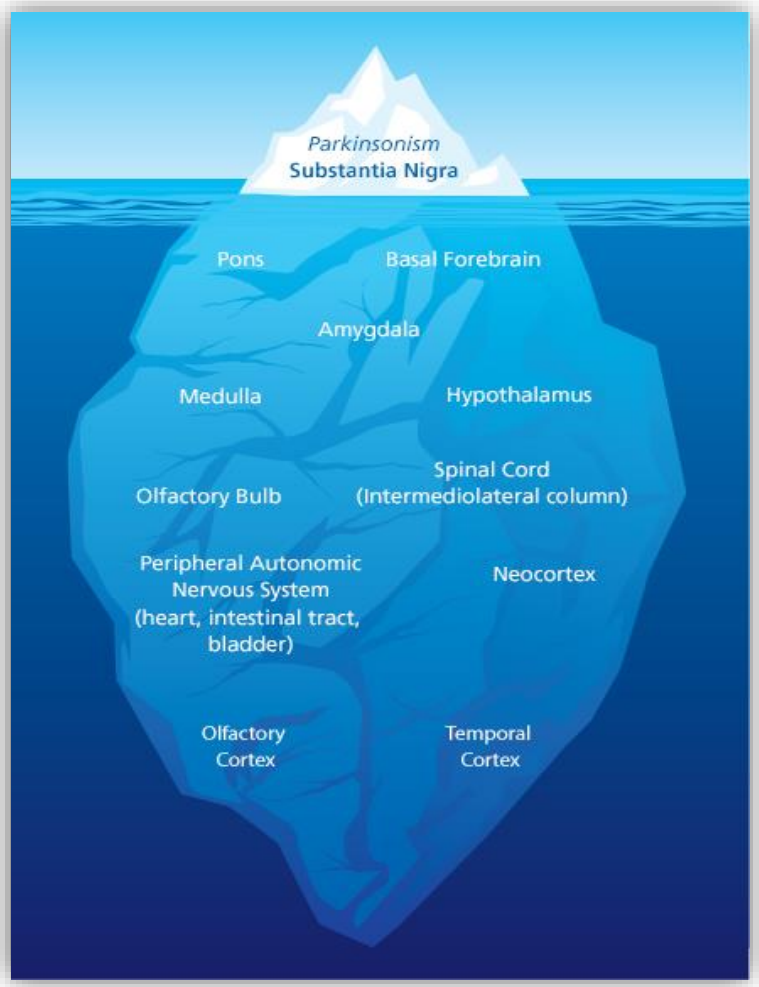
Martin T. Henrich[1,2*], Fanni F. Geibl[2*], Harini Lakshminarasimhan[1], Anna Stegmann[2], Benoit I. Giasson[3], Xiaobo Mao[4,5], Valina L. Dawson[4,5,6,7], Ted M. Dawson[4,5,6,8], Wolfgang H. Oertel[2†], D. James Surmeier[1†‡]

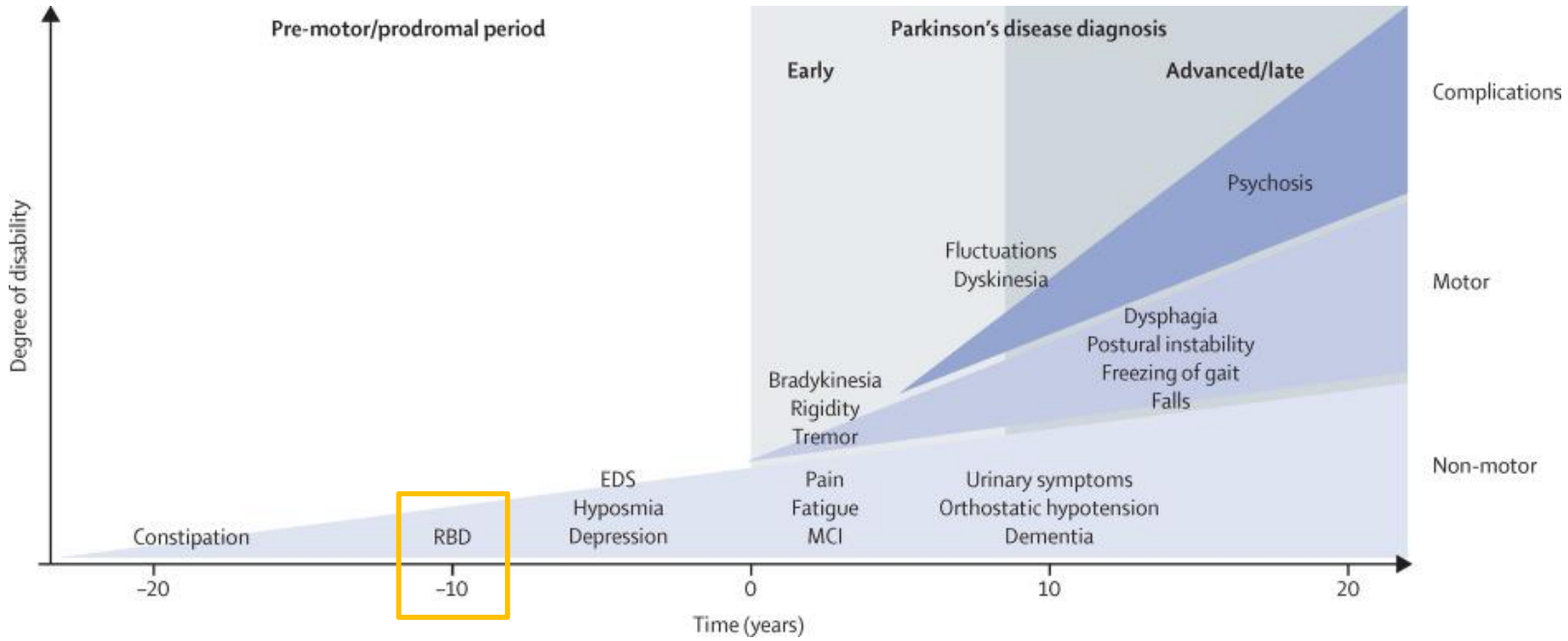
Spread is likely determined by

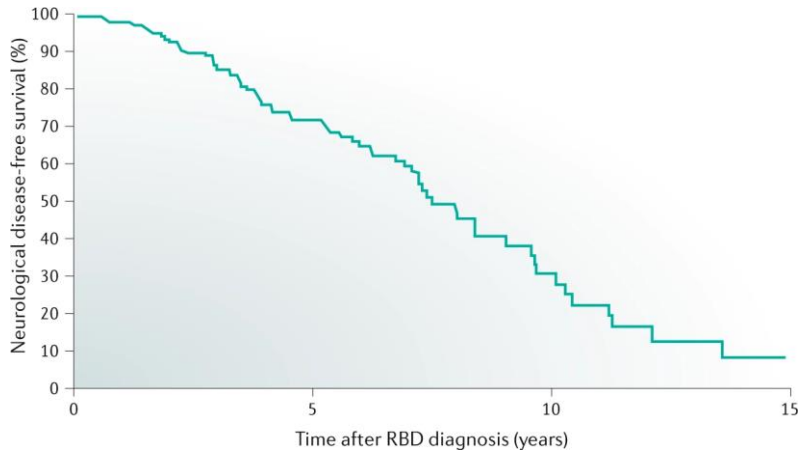
- Trans-synaptic spread of pathological aSyn
- Connectivity and network structure (necessary but not sufficient)
- Local (likely cellular) factors - aSyn levels

Additional network and/or cellular determinants?

Using contextual seeding to retrace the paths of synucleinopathy

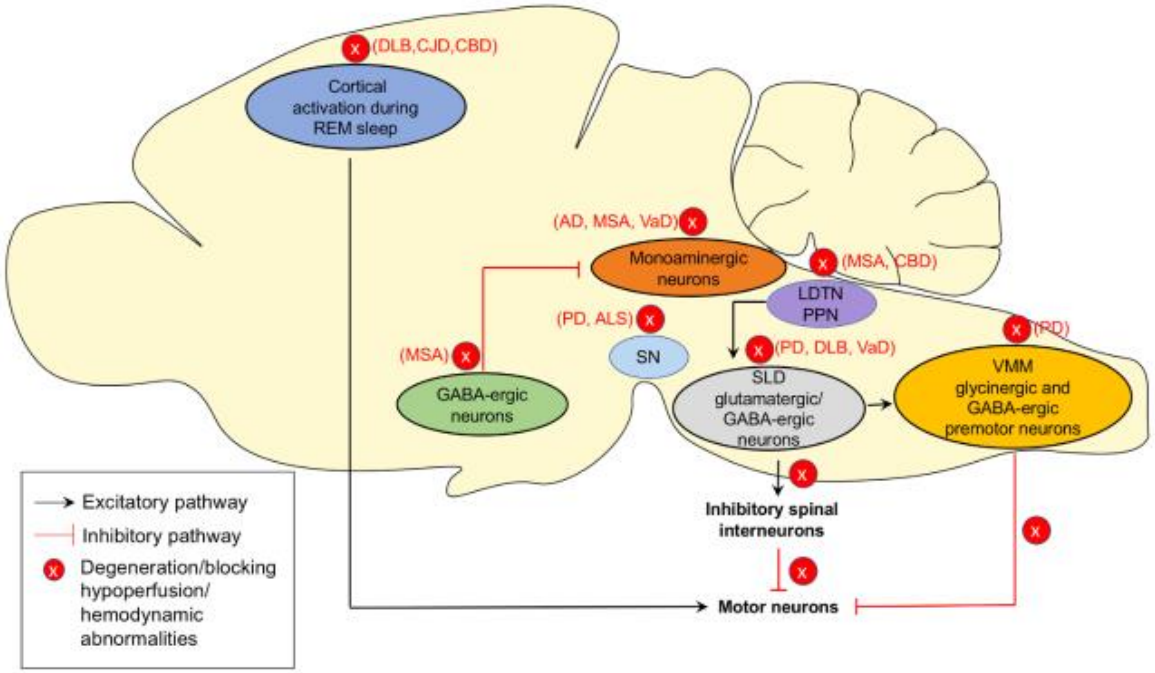


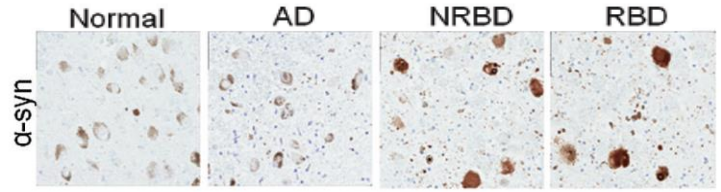


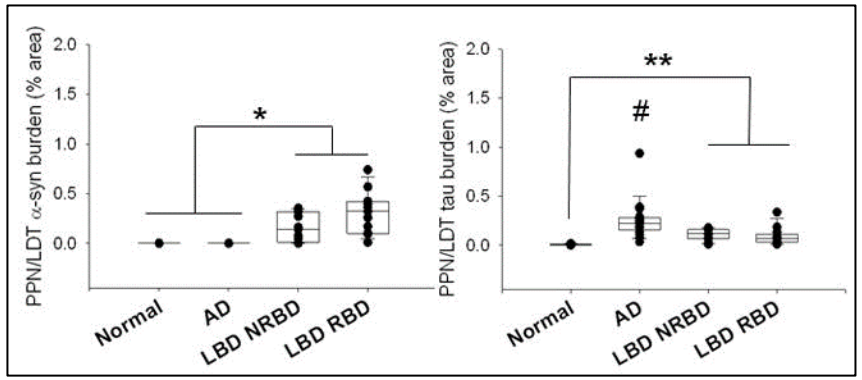


Langston, Ann Neurol 2006
Kalia and Lang, Lancet Neurology 2015
Dauvilliers et al, Nat Rev Neurol 2018

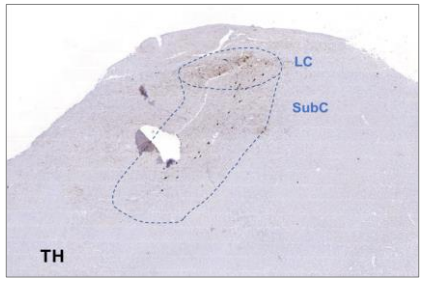
Subcoeruleus/SLD synucleinopathy induces RBD-like phenotypes in mice

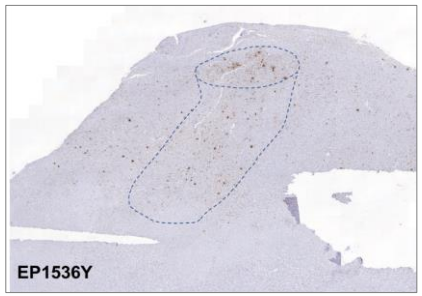


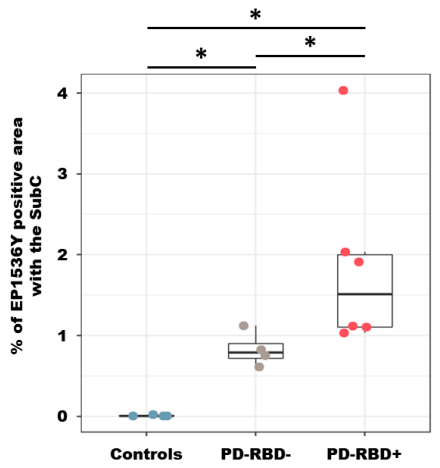




PD-RBD+

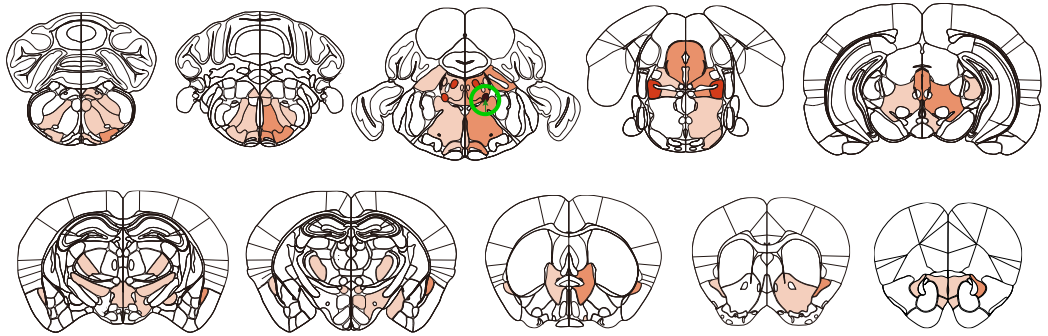


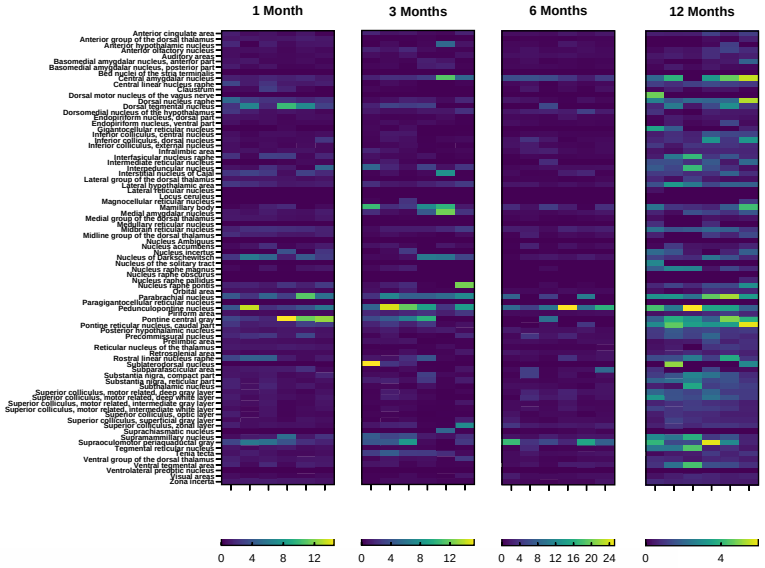


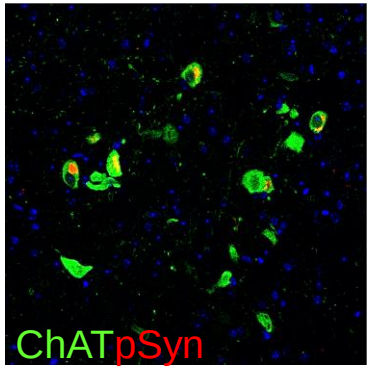


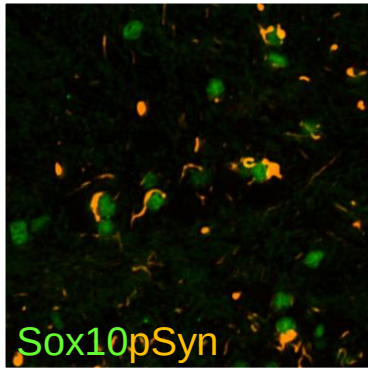
Zhang et al, *Aging and Disease* 2020; Dugger et al, *Neuropath App Neurobiol* 2012

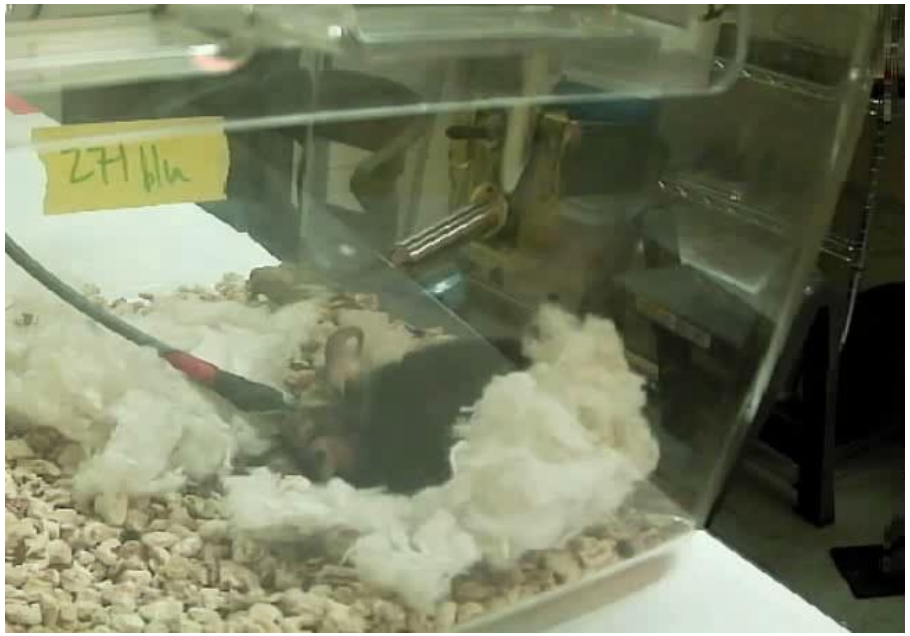
RBD-like phenotype correlates with aSyn-seeded proteinopathy in the subcoeruleus (SLD)

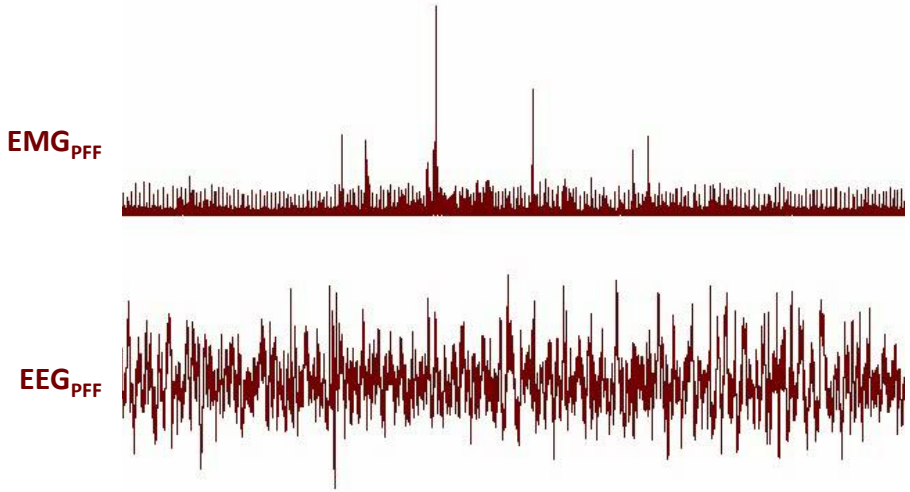






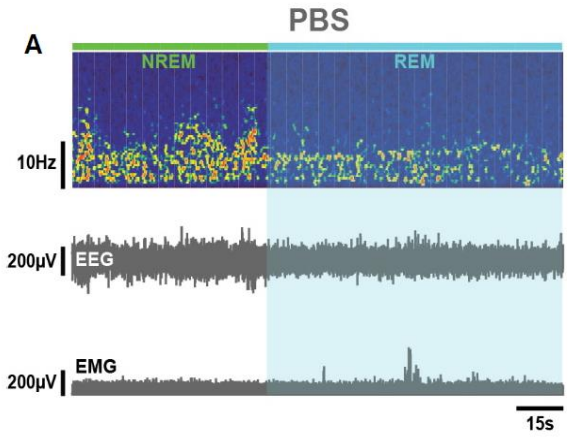


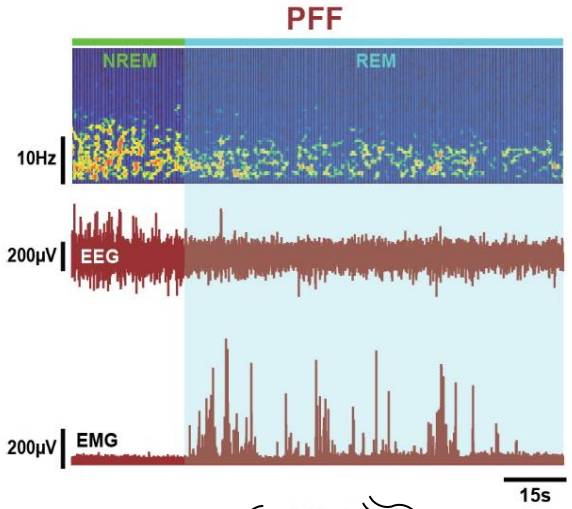


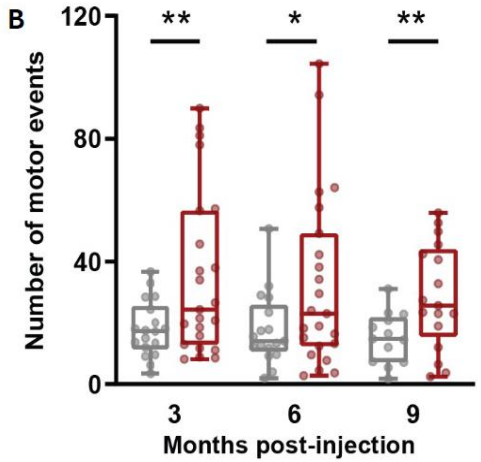


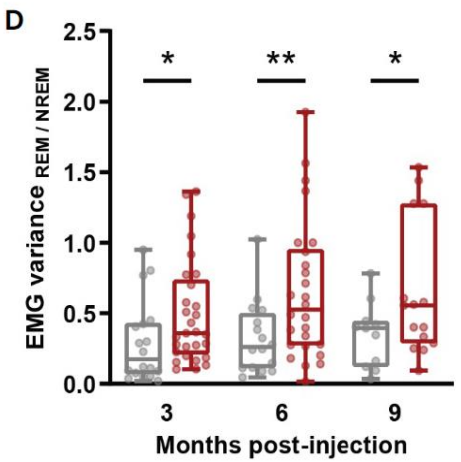
Hansoo Yoo [Penn/Yonsei University], Russell Luke [Peever Lab, U of Toronto], *unpublished*

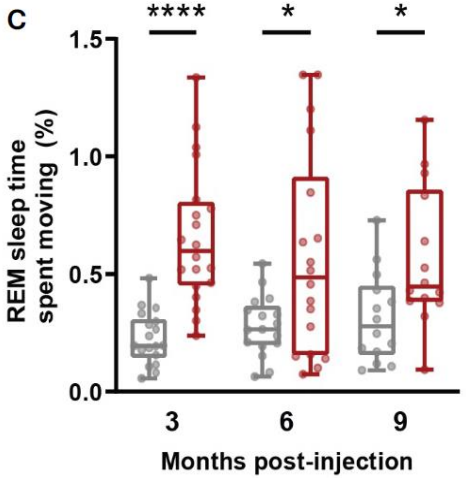
Higher levels of REM phasic muscle activity following PFF-seeding in SLD

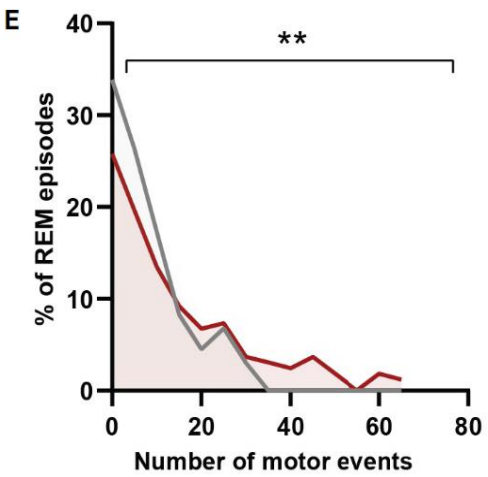


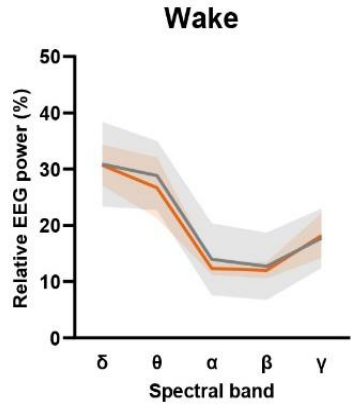


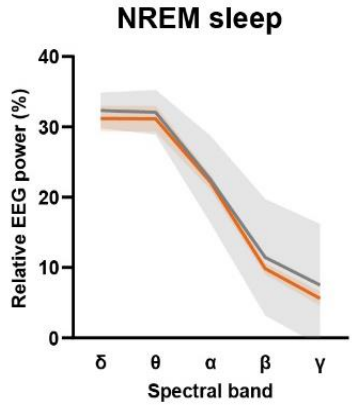


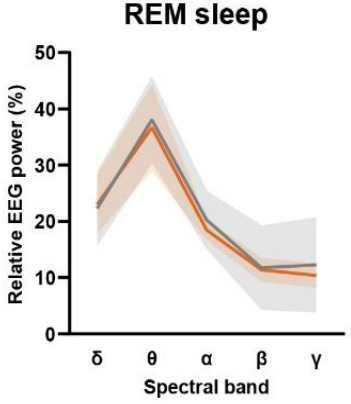












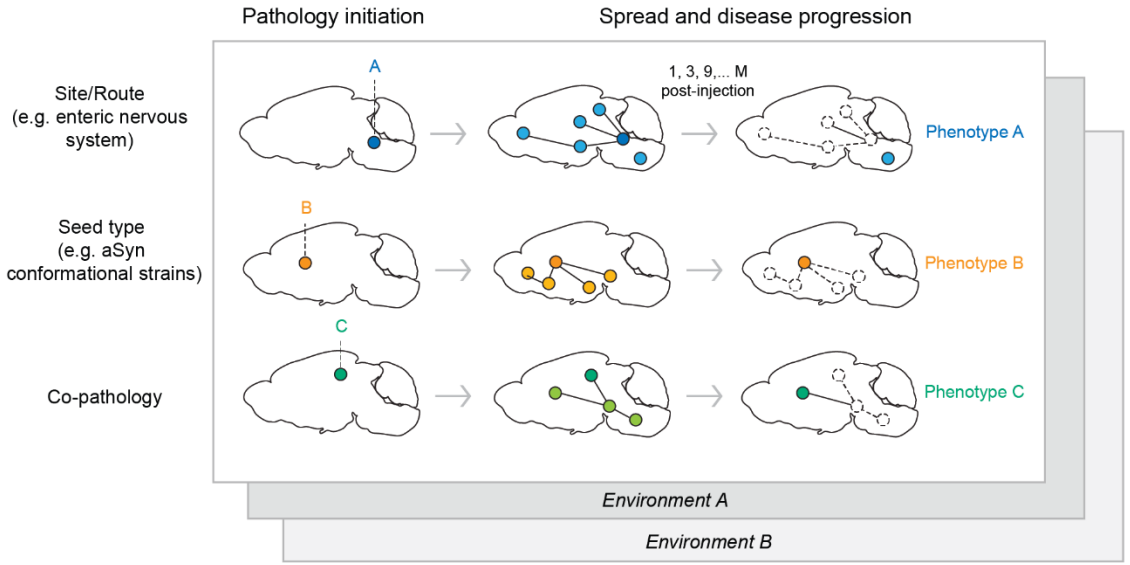
Hansoo Yoo [Penn/Yonsei University], Russell Luke [Peever Lab, U of Toronto], *unpublished*

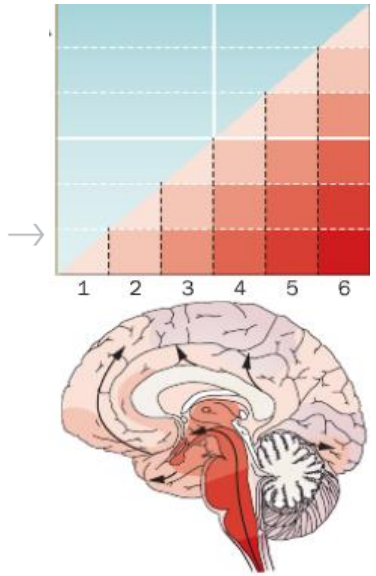
Summary

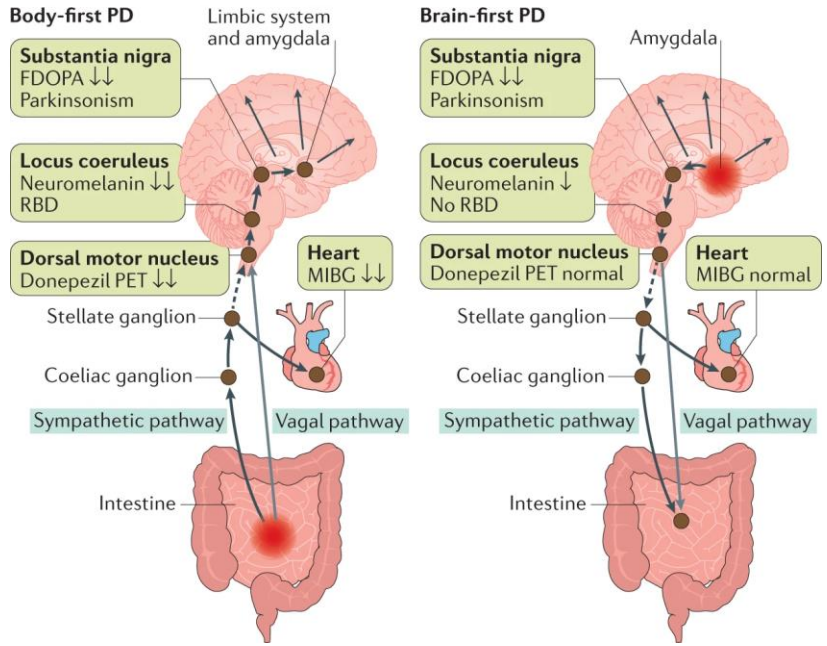
Cell-to-cell transmission of aSyn pathology and **local cellular heterogeneity** likely combine to produce the idiosyncratic patterns of neurodegeneration observed in synucleinopathy

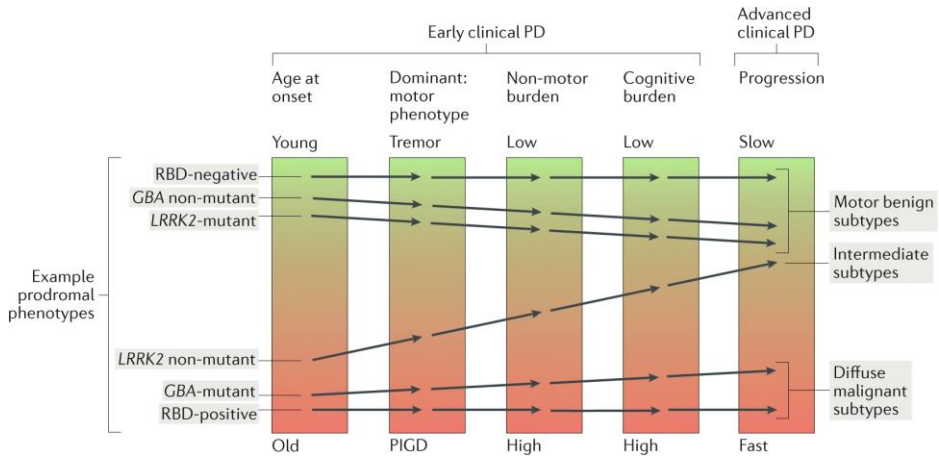
Contextual seeding approaches can potentially provide advance our understanding of mechanisms underlying human synucleinopathies and their heterogeneity

Summary









Berg et al, Nat Rev Neurol 2021

Acknowledgements

Luk Lab
Lindsay Agostinelli
Elif Cinar
Yuling Liang
Jonah Lourie
Chandler Song

Juliana Benitez
Anna Caputo
Sam Decker
Casey Durso
Jin Yong Hong
Mian Horvath
Shuo Jiang
Michael Kozak
Angela Lo
Esteban Luna
Jake Steltz
Lucy Torres
Cynthia Uzoukwu
Yiqun Yan
Allison Yearwood
Hansoo Yoo

Pathology/CNDR
Virginia Lee
John Trojanowski
Kurt Brunden
Sue Leight
John Robinson
Edward Lee

Penn
Alice Chen-Plotkin
Bob Mach
Dejian Ren

Collaborators
Alain Dagher, Shady Rahayel, Bratislav Misic (McGill)
Jeff Kordower (Arizona State)
Rehana Leak (Duquesne)
John Peever (U of Toronto)
Caryl Sortwell (Michigan State)
Vivek Unni (OHSU)
Mikko Airaavara (U Helsinki)

NIH
R01NS088322
U19AG062418
P01AG084497
U19NS110456

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