An Epidemic Spread Model Replicates Atrophy Patterns in Parkinson's Disease

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Introduction

▶ Parkinson's Disease (PD) has been widely suggested to be a prion-like disease, resulting from the pathogenic spread of misfolded α-synuclein (α-syn), an infectious protein that may spread through neuronal connections, inducing further misfolding of endogenous α-syn and neuronal death.

▶ However, it remains unclear whether the actual spread of α-syn occurs in humans and how it leads to the neuronal loss identified in PD patients.

▶ Here, using multimodal neuroimaging and genetic data, we present an agent-based Susceptible-Infectious-Removed (S-I-R) spread model that integrates α-syn spreading and selective vulnerability to simulate the spread of misfolded α-syn and the spatial patterning of brain atrophy.

Materials

▶ *GBA* and *SNCA* transcription profiles were obtained from Allen Human Brain Atlas as measures of regional **clearance** and **synthesis** of α-syn respectively.

▶ **Structural connectivity (SC)** and **functional connectivity (FC)** were constructed from Human Connectome Project diffusion MRI and resting-state fMRI data.

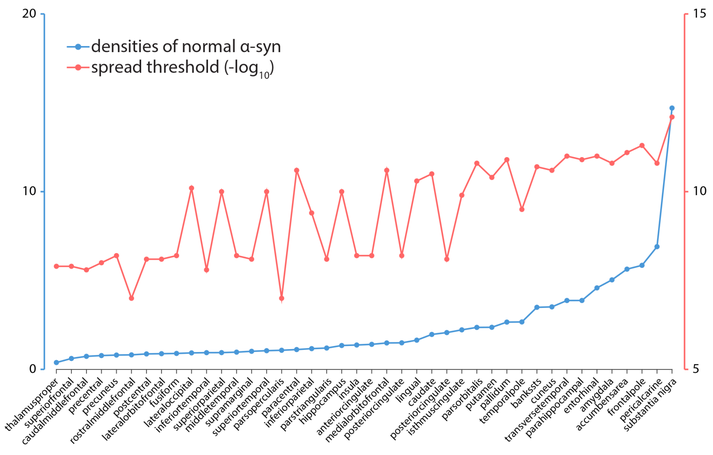
▶ **PD atrophy map** was derived from Deformation-Based Morphometry (DBM) values estimated from T1 MRI scans of 237 PD patients and 118 age-matched controls provided by Parkinson's Progression Markers Initiative (Zeighami et al., 2015).

▶ **42 regions, left hemisphere**, were adapted from an atlas-based segmentation (Cammoun et al., 2012). Substantia nigra was filled into the mask based on the ATAG atlas (https://www.nitrc.org/projects/atag).

Identifying the epicenter

▶ Substantia nigra has the lowest *spread threshold* and highest expression level of normal α-syn.

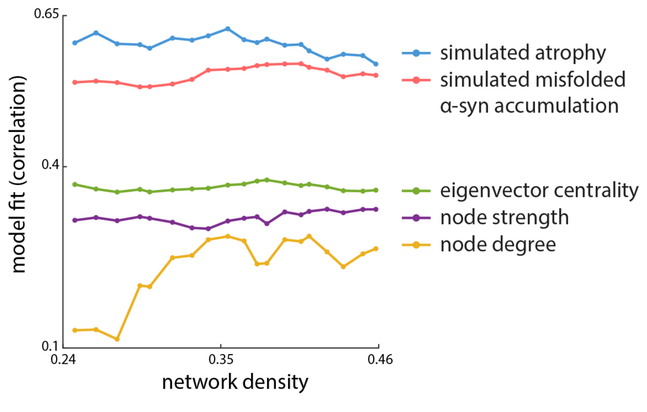
▶ Basal Ganglia is rich in normal α-syn at equilibrium of module I (before disease onset)



Robustness and comparison

▶ This simulated pattern is preserved across network densities ranging from 24% to 45%.

▶ Incorporating the gene expression data improves the predictive power of the S-I-R model over and above the network measures *per se*, including node degree, node strength, eigenvector centrality.



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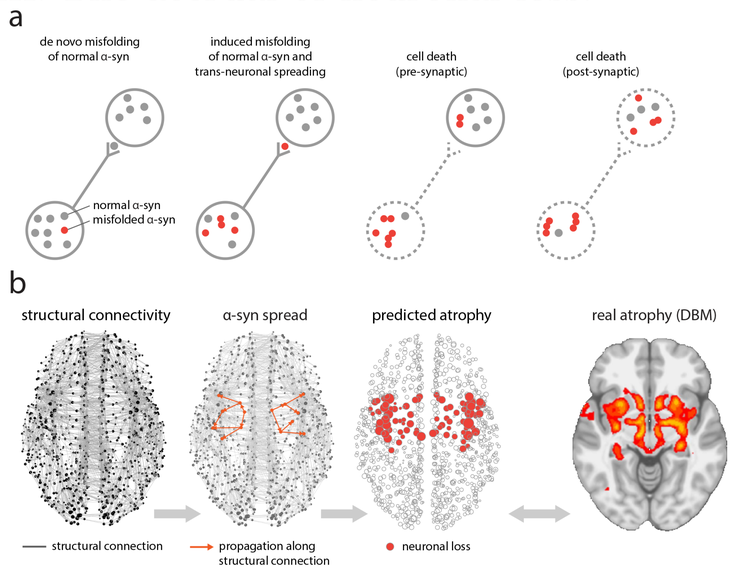
Methods

▶ Three modules were generated to simulate PD progression:

I. **The growth of normal α-syn**: one stable point, acting as the initial condition of II.

II. **The spread of misfolded α-syn**: two stable points, disease extinction or outbreak.

III. **The accrual of neuronal loss.**



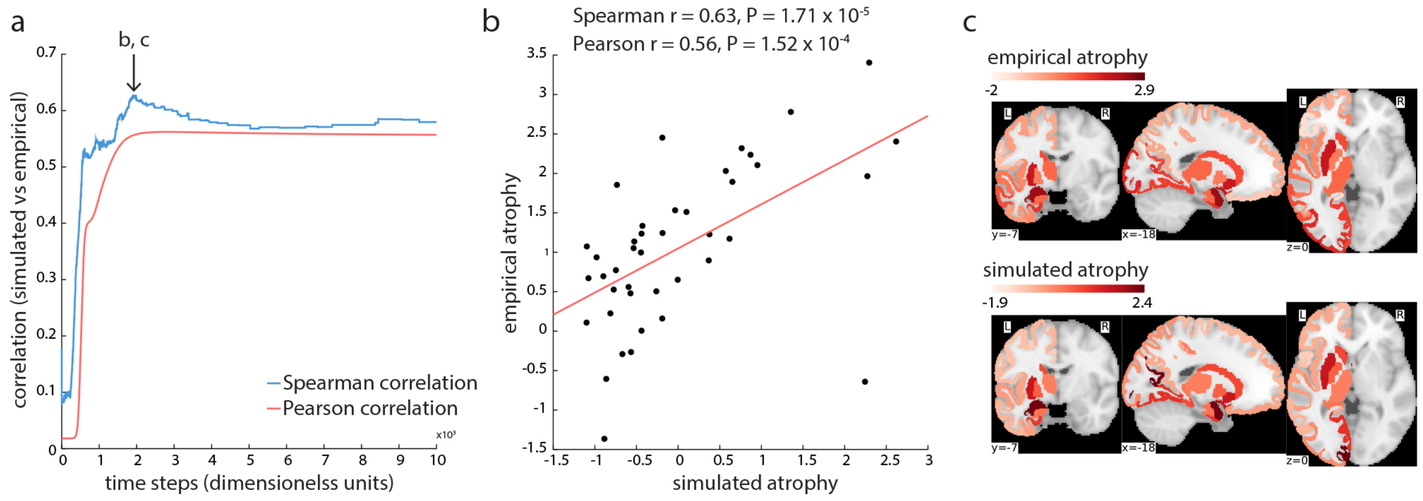
Strategies:

▶ Individual normal α-syn may
- get synthesized (per voxel) or cleared
- exit a region and enter a path
- exit a path and enter a region
- get misfolded via contact with misfolded α-syn

▶ Individual misfolded α-syn may
- get generated from normal α-syn (through misfolding process) or cleared
- exit a region and enter a path
- exit a path and enter a region

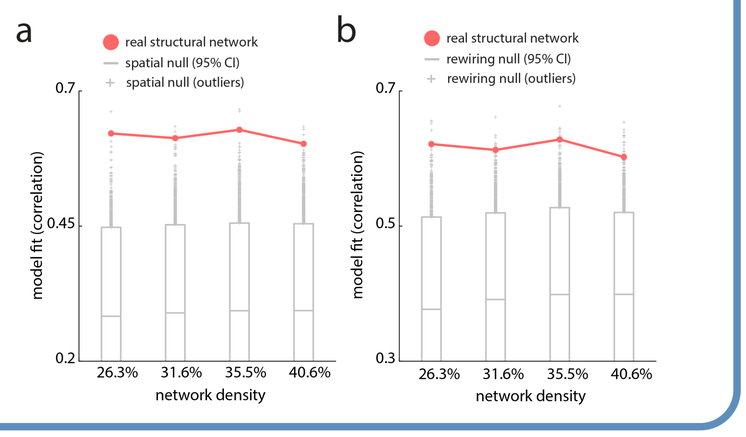
Model fit

▶ The simulated neuronal loss resembles the spatial patterning of atrophy identified in PD patients without any free parameters.



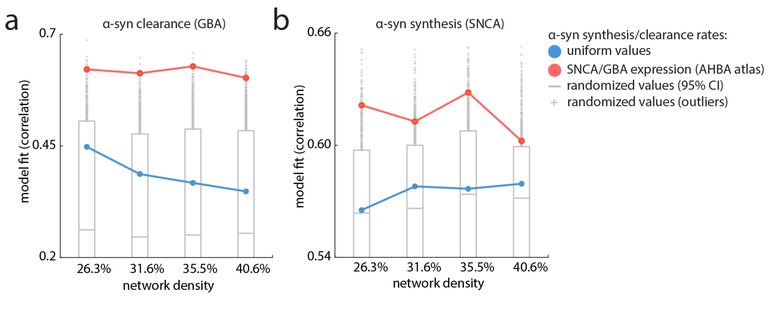
Role of SC

▶ Disruptions of the structural connectivity's wiring or spatial embedding remarkably degrade model fit.



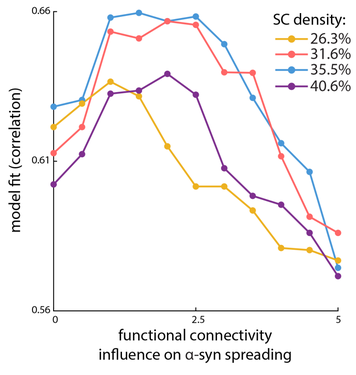
Role of gene expressions

▶ Shuffled *GBA* or *SNCA* expressions remarkably degrade model fit.



Contribution of FC

▶ Integration of functional connectivity improves model fit.



▶ Excessive influence of functional connectivity on α-syn spreading degrades model fit, suggesting that balanced influence of functional connectivity and structural connectivity is required in driving PD pathology.

Conclusions

▶ PD atrophy pattern results from the interplay between the routes of pathogenic spread and regional vulnerability to misfolded α-syn.

▶ Connectome structure dictates the mobility pattern of α-syn, while gene expressions modulates regional susceptibility to the infection on top of the network features.

▶ FC-biased spreading also improves fit, suggesting that neuronal activity may also drive disease spread.