Abstract details

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CONNECTOME ARCHITECTURE, GENE EXPRESSION AND NEURONAL ACTIVITY SHAPE THE PROPAGATION OF MISFOLDED PROTEINS IN NEURODEGENERATIVE DISEASE.

Co-authors
Y.Q. Zheng[1], Y. Yau[1], Y. Zeighami[1], Y. Zhang[1,2], B. Mišić[1], A. Dagher[1].
[1]McGill University, Montreal Neurological Institute, Montreal, Canada.
[2]Université de Montréal, Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montreal, Canada.

Abstract text

Abstract body

Objectives

Propagating proteinopathy has been suggested as the hallmark of neurodegeneration. However, direct evidence in humans remains circumstantial. Here, taking PD as an example, we propose a Susceptible-Infectious-Removed (S-I-R) metapopulation structured model to test this hypothesis and identify the driving forces of regional pathology in neurodegeneration.

Methods

The proteins (alpha-synuclein) are modeled as independent agents that may get synthesized or metabolized (modulated by *SNCA* or *GBA* expression respectively, Allen Human Brain Atlas), or spread into connected regions (determined by anatomical connections and functional co-activation, Human Connectome Project) (fig 1). Modeled atrophy is derived as a function of time to compare with the empirical atrophy estimated from an independent dataset of PD patients (Parkinson's Progression Markers Initiative).

Results

i) Robust to variations in network density, the simulated atrophy replicates the empirical atrophy pattern, showing more predicative power than other measures *per se* that are integrated into the model.
ii) The model yields a disease epicenter in the substantia nigra.
iii) Disruptions of a) the connectome's spatial embedding or topology
b) *SNCA* or *GBA* expressions both significantly degrade model fit.
iv) Integration of neuronal activity improves model fit.

Conclusions

The model provides independent evidence for synucleinopathy progression in PD. It suggests that PD results from the interplay between 'pathogenic spread' (dominated by the connectome) and 'selective vulnerability' (modulated by regional gene expression), and reveals that connectome architecture, gene expression and neuronal activity collectively shape the patterning of regional pathology in PD.

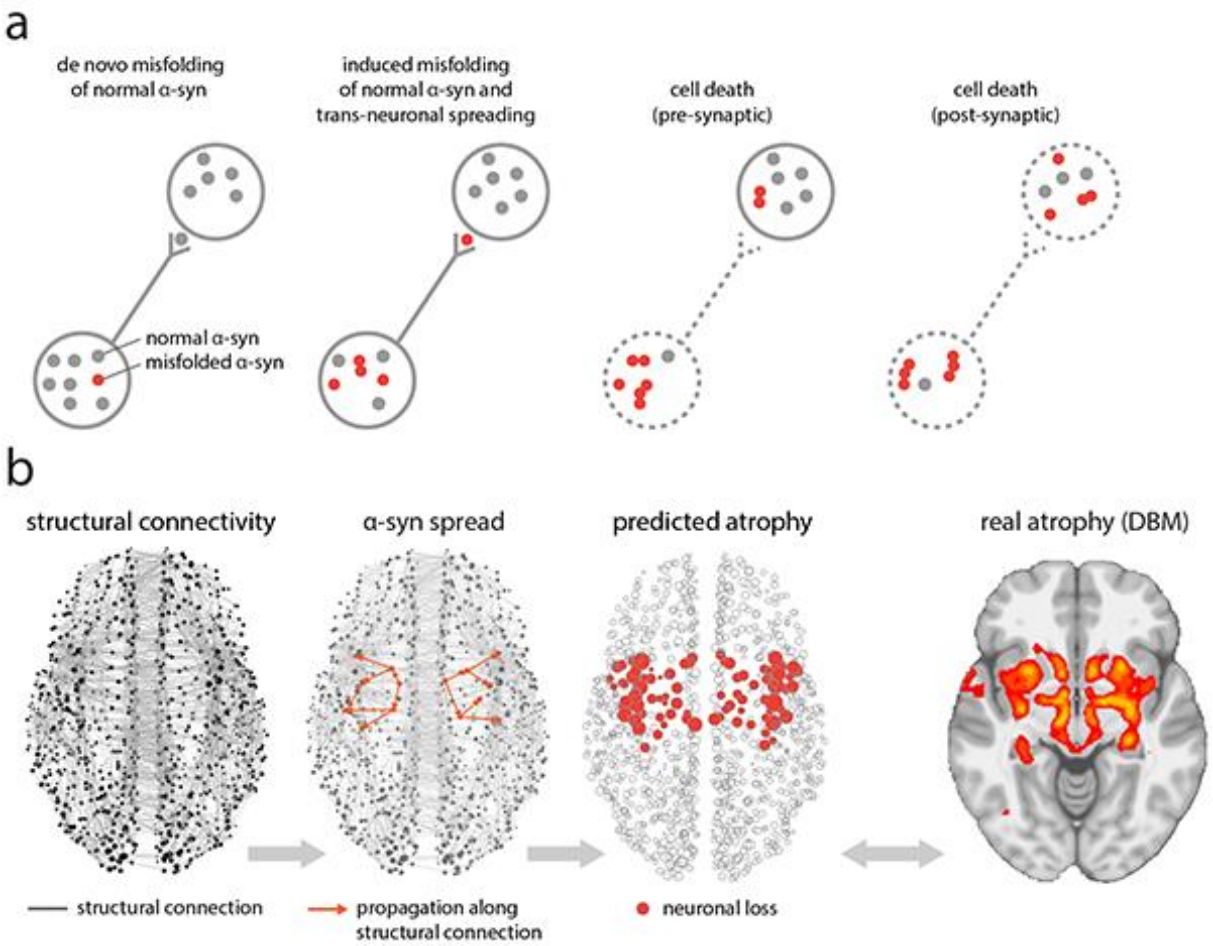

fig 1 schematic illustration: misfolded alpha-synuclein spreads through anatomical connections and induces atrophy

Keywords
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