New model may explain the mystery of asymmetry in Parkinson's disease

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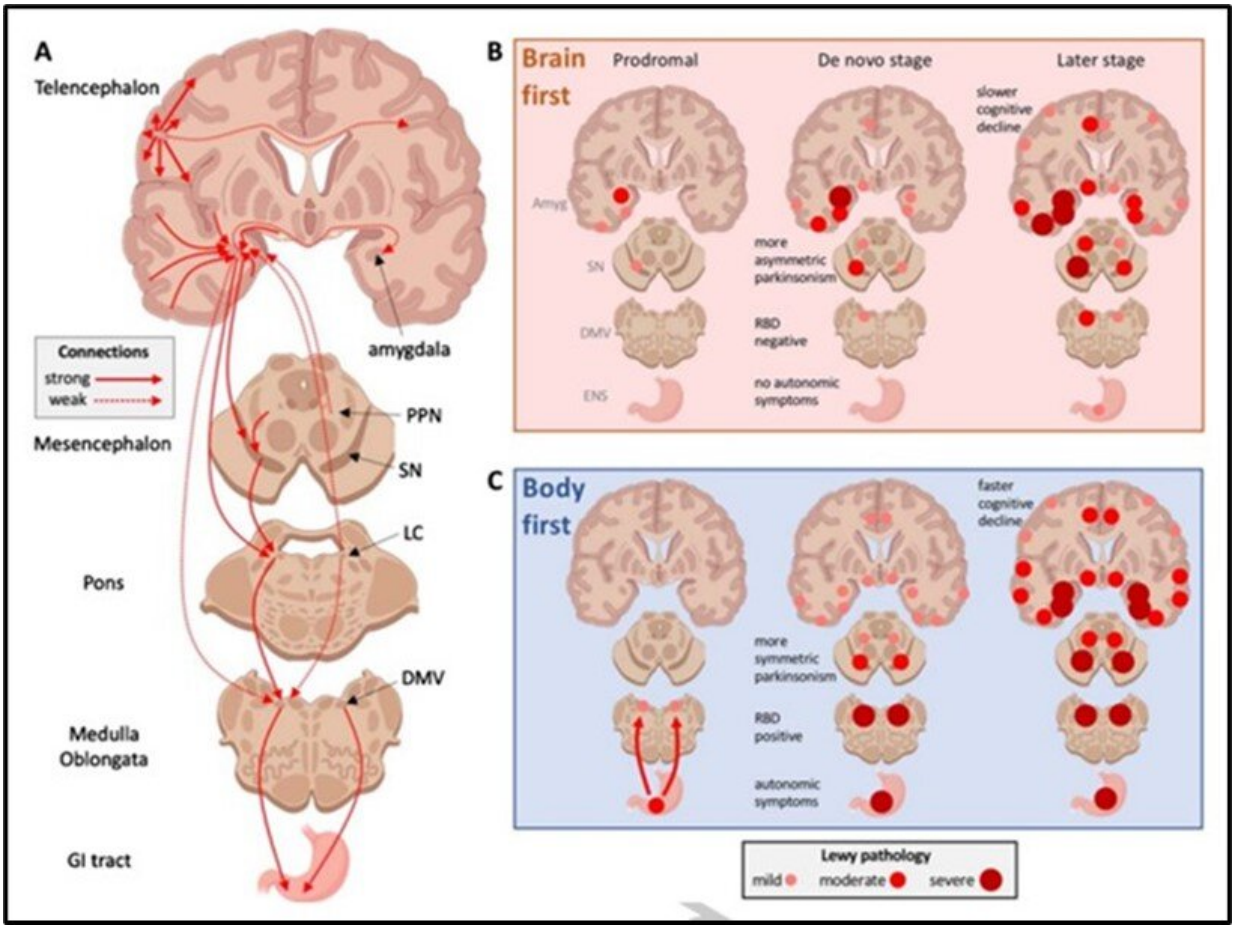

(A) Schematic representation of important connectome details in Parkinson's disease (PD). (B) Brain-first PD: the asymmetric distribution of alpha-synuclein persists into later disease stages. (C) Body-first PD: the symmetric alpha-synuclein pathology leads to more symmetric motor symptoms. Credit: *Journal of Parkinson's Disease*

Parkinson's disease (PD) is characterized by slowness of movement and tremors, which often appear asymmetrically in patients. The new model of PD described in this review article published in the *Journal of Parkinson's Disease* may explain these perplexing asymmetrical motor symptoms and other known variations such as different degrees of constipation and sleep disorders.

PD is a heterogenous disorder. Symptoms and the speed with which symptoms progress vary greatly among patients. In three-quarters of patients, motor symptoms initially appear in one side of the body. Some patients develop constipation, loss of smell, sleep disorders, and other symptoms several years before diagnosis, but others do not. Although it is possible to define several subtypes of PD characterized by similar constellations of symptoms, the underlying causes of these differences are poorly understood. Aggregation and neuron-to-neuron spread of the protein alpha-synuclein is thought to be involved.

The alpha-synuclein Origin and Connectome (SOC) model presented by Per Borghammer, MD, Ph.D., DMSc, Department of Nuclear Medicine & PET, Aarhus University Hospital, Aarhus, Denmark, proposes a unifying model, which may explain much of this variation among patients. The SOC model is fundamentally based on two ideas: the location or origin of the first alpha-synuclein aggregates, and the importance played by the neural connectome in transmitting the alpha-synuclein pathology to other parts of the nervous system.

This model was developed by integrating already available evidence from clinical and imaging studies of patients, animal models of PD, and postmortem findings in brain tissue from PD patients. This unifying model seems capable of explaining why PD is often an asymmetric disease in the first place, but also why some patients show more asymmetry than others and some no asymmetry at all. It also explains why certain subtypes of PD seem to exist, including why constipation

and sleep disorders emerge prior to diagnosis only in some patients.

"Imaging studies of living PD patients and studies of biopsies and gut and brain tissue from biobanks clearly suggest that PD patients display different profiles of neuronal damage," explained Dr. Borghammer. "In some patients, the brain is damaged before the peripheral nervous system, and in others the opposite pattern is seen. This new model, which is an extended version of the body-first versus brain-first hypothesis we described in this journal in 2019, proposes a simple explanation for motor asymmetry, while simultaneously offering explanations for several other unexplained phenomena in PD."

The model postulates that the first instance of pathological alpha-synuclein typically starts in a single location, and then spreads from this origin site using permissible neural connections. The origin site can occur in the enteric nervous system of the gut, leading to a body-first subtype of PD. This type is characterized by early symptoms from gut and other peripheral organs and also sleep symptoms stemming from the lower parts of the brainstem.

In contrast, the first alpha-synuclein pathology can also start inside the brain leading to a brain-first subtype. "Such patients will often develop motor symptoms quite quickly, whereas sleep symptoms and autonomic symptoms develop only later," noted Dr. Borghammer. "At later disease stages, the two types of patients will have a similar burden of motor and non-motor symptoms, but early on they are very different."

The second component of the SOC model pertains to how neurons are wired to each other, known as neuronal connectivity. One brain hemisphere communicates mainly to itself with only 1% of neuronal connections crossing the midline to the other hemisphere. Therefore, if the first occurrence of pathological alpha-synuclein arises in a single location in the brain, it will by definition be in either the left or the right

hemisphere. The subsequent spreading of pathology will therefore happen primarily via "same-sided" connections including to the dopamine cells on the same side of the brain. This leads to asymmetric damage of the dopamine neurons causing asymmetric motor symptoms in patients.

"In short, we think that the motor asymmetry in PD must be understood in a brain-first vs. body-first context. In brain-first PD, the initial pathology starts in one hemisphere and initially damages that hemisphere via the predominantly same-sided connections, leading to marked asymmetry," noted Dr. Borghammer. "With time, the other hemisphere is also involved, evidenced by the increasingly symmetric motor symptoms in the patient."

Dr. Borghammer explained that the model also predicts that body-first PD patients will be different and generally have more symmetric motor symptoms. This is because the pathology spreads from the gut to the brain in a more symmetric fashion due to left/right overlapping connections in the peripheral nervous system. This then leads to a "wave" of spreading pathology inside the brain, which is more symmetric than that seen in brain-first patients. They therefore display more symmetric dopamine loss and motor symptoms, and this is exactly what clinical and imaging studies have been reporting. The model also predicts that at diagnosis, body-first patients already have a larger, more symmetric burden of alpha-synuclein pathology, which in turn promotes faster disease progression and accelerated cognitive decline.

"It is known that PD patients of the body-first type are at an increased risk of developing dementia. According to the SOC model this increased risk follows from the fact that, at the time of a PD diagnosis, the alpha-synuclein pathology is more widespread, more symmetrical, and shows more involvement of certain brainstem neurons, which are themselves involved in cognitive decline and dementia," Dr. Borghammer added.

Asked about the future outlook for the SOC model, Dr. Borghammer responded that it will now be tested in future studies. "A good scientific model should be testable and falsifiable, and the present model lives up to these requirements. The scientific community now needs to study whether the SOC model has more explanatory power than previous models of PD pathogenesis. It is certainly not a complete description of what goes wrong in PD and needs to be further refined," he concluded.

PD is a slowly progressive disorder that affects movement, muscle control, and balance and is characterized by a broad range of motor and non-motor symptoms. It is the second most common age-related neurodegenerative disorder affecting about 3% of the population by the age of 65 and up to 5% of individuals over 85 years of age.

More information: Per Borghammer. The α-Synuclein Origin and Connectome Model (SOC Model) of Parkinson's Disease: Explaining Motor Asymmetry, Non-Motor Phenotypes, and Cognitive Decline, *Journal of Parkinson's Disease* (2021). DOI: 10.3233/JPD-202481

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