Body-First and Brain-First Parkinson's Disease as a Route to Biological Trajectory-Aware Care

Author: *Massimiliano Passaretti[1]

1. Karolinska Institutet, Stockholm, Sweden
*Correspondence to massimiliano.passaretti@ki.se

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SUMMARY OF KEY FINDINGS

Background
Parkinson's disease (PD) is clinically heterogeneous, and its pathology begins years before motor symptoms appear. The Synuclein Origin and Connectome (SOC) model proposes two phenotypes: 'body-first' PD, in which α-synuclein pathology starts in the peripheral autonomic nervous system and spreads symmetrically from the bottom up, and 'brain-first' PD, which begins in the central nervous system and spreads asymmetrically from the top down. Until now, these phenotypes had not been tested longitudinally across both prodromal and clinical stages, nor linked to their underlying imaging and genetic mechanisms.

Methods
The author analysed 910 prodromal and 1,120 clinical PD cases from the Parkinson's Progression Marker Initiative (PPMI), with longitudinal clinical, imaging, and genetic data spanning 12 years.[1]

Results
Body-first cases showed greater motor dysfunction, anxiety, and depression at baseline, and faster longitudinal motor decline and attention loss than brain-first cases, in both prodromal and clinical stages, together with a higher risk of conversion to PD and to PD dementia. The phenotypes were stable over time and reproducible using unsupervised deep learning. Imaging supported divergent spreading: body-first cases showed more caudal locus coeruleus involvement and symmetrical striatal and glymphatic alterations (bottom-up, consistent with Braak staging), whereas brain-first cases showed rostral locus coeruleus changes and asymmetric alterations (top-down). Genetic analysis identified phenotype-specific variants, including *TRIM40* and *IP6K2*, associated with worse motor and cognitive outcomes in prodromal cases.

Conclusion
Body-first and brain-first PD are distinct biological entities with specific clinical, imaging, and genetic profiles that are identifiable from the prodromal stage. Recognising them supports earlier, trajectory-aware prognosis and more targeted therapeutic strategies.

WHAT CHALLENGE DOES THIS ADDRESS?

PD is still staged, treated, and enrolled on trials as a single disorder, yet patients with apparently similar motor diagnoses follow strikingly different courses. Existing subtyping approaches (tremor-dominant versus non-tremor, or cognitive classifications) are clinically unstable and cannot be applied before motor onset. This leaves an unmet need: a biologically grounded way to identify, from the earliest stages, which patients face faster decline, greater cognitive risk, and a more aggressive multisystem course, the very patients in whom accurate prognosis and early intervention matter most. By anchoring phenotypes to the presumed site and pattern of α-synuclein spread, and showing that they are stable and detectable already in the prodromal phase,

this work addresses the gap between PD's recognised heterogeneity and the tools available to act on it.

RELEVANCE TO EUROPEAN PRACTICE

The practical message is that a given level of motor impairment today does not translate into the same disease burden tomorrow: its prognostic weight depends on the individual disease trajectory. Identifying individual disease features with widely available clinical questionnaires, such as rapid eye movement sleep behaviour disorder screening and autonomic assessment, would let us move from a 'one-box' model of PD towards trajectory-aware staging, placing patients not only on a severity axis but on the correct rail. This matters most in prodromal and early disease, where recognising a poorer-prognosis course could concentrate monitoring and support a comprehensive, holistic strategy aimed at pre-empting the many non-motor complications of complex PD, in particular falls, psychiatric and cognitive decline, and urinary tract infections.

Moreover, this approach can begin to reshape clinical research: by improving the granularity of trial inclusion criteria and, once distinct underlying aetiologies can be demonstrated, by targeting specific mechanisms and directing future disease-modifying therapies to those who stand to benefit most. Phenotype could likewise inform decisions on advanced therapies, such as focused ultrasound, deep brain stimulation, or levodopa infusion, as pathology and compensatory capacity evolve. In short, it reframes PD heterogeneity as structured and clinically usable, rather than random noise.

WHAT ARE THE NEXT STEPS FOR THE RESEARCH?

The classification currently relies on clinical scales that carry subjective bias, so more objective confirmation (metaiodobenzylguanidine scintigraphy, α-synuclein seeding assays, and fluid biomarkers) is needed, alongside larger and more representative cohorts than PPMI to ensure generalisability. Future genome-wide studies should extend the phenotype-specific genetic signals (*TRIM40, IP6K2, RIT2, CTSB*) and clarify genotype–phenotype relationships, ideally integrating the genome with the exposome (early-life environmental and occupational exposures). The broader goal is a mechanism-aware staging framework that combines initiation phenotype, a dynamic index of motor compensation, and multisystem biomarkers. Such a framework could sharpen clinical-trial enrolment around shared biological pathways and match interventions to the impaired pathway; for example, gut-barrier and microbiota strategies in body-first cases, or lysosomal-targeted drugs such as ambroxol in *GBA* carriers. Confirming these phenotypes as reliable, actionable markers is the key question that remains.

Reference

1. Passaretti M et al. Clinical progression and genetic pathways in body-first and brain-first Parkinson's disease. Abstract OPR-098. EAN Congress, 27-30 June, 2026.