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Towards biomarker-based clinical subtyping of Parkinson's disease

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Parkinson's disease (PD) was formally described by James Parkinson in the classic Essay on the Shaking Palsy published in 1817.¹ More than 200 years later, PD remains largely defined clinically based on a combination of motor and non-motor symptoms. PD is a complex neurodegenerative disorder involving dysregulations in multiple neurotransmitter systems beyond dopamine, and studies continue to shed light on the molecular, genetic and pathophysiological aspects of the disease. Identifying different subtypes of PD has been an active area of research with promising prospects to improve the understanding of disease mechanisms, to predict prognosis, and ultimately to develop personalized disease modifying therapies. Subtypes of PD have been defined according to clinical symptoms and demographic characteristics, however, data-driven clinical subtyping has failed to predict patterns of aggregation of α -synuclein^{2,3}, and was found not to be stable over time or reproducible.^{4,5} Therefore, an alternative to subtyping PD patients on the basis of co-occurring clinical symptoms is to identify biological-based subtypes, or biotypes, based on shared and distinguishable neuroanatomical signatures.

In their study in this issue of Neurology, Wang et al. employed a data-driven clustering approach to T1-weighted brain-structural MRI data from a large open-available database of 314 PD patients with the aim to objectively identify distinguishable anatomical PD biotypes.⁶ The authors employed deformation-based morphometry (DBM), a technique which allows the detection of morphological differences over the entire brain because it does not rely on assumptions about the distributions of gray or white matter and has a high sensitivity to capture subcortical neuroanatomical features. In an initial step, the authors identified voxels in the caudate, putamen, thalamus, hippocampus, supplementary motor area, and orbital frontal gyrus whose deformation values were significantly correlated with clinical scores at baseline. Using a hierarchical cluster analysis approach, two brain-structural biotypes were identified; one characterized by subcortical brain volumes smaller than healthy controls ('biotype 1') and another characterized by larger subcortical brain volumes as compared to healthy controls ('biotype 2'). In a second step, the authors explored separable functional impairments and neurobiological disease progression in the two identified biotypes. The two biotypes showed distinctive longitudinal progression, and neuroimaging profiles. At baseline, biotype 1 exhibited pronounced impairments in the domains of cognition, behavior and mood (higher MDS-UPDRS Part I score), autonomic dysfunction (SCOPA total score), and worse rapid eye movement sleep behavior disorder (RBD) compared to biotype 2. Furthermore, over the course of 5 years biotype 1 was characterized by an accelerated deterioration of most motor symptoms (with the exception of the tremor score), cognitive decline and functional impairments in daily-live activities. Moreover, on the neural level biotype 1 exhibited a marked progression of denervation on dopamine functional neuroimaging indices in the left caudate and left putamen over an

average of four years. There was no difference in CSF biomarker levels at baseline between the two biotypes.

The study by Wang et al. has several major strengths including the large sample size of early onset PD patients with homogeneous disease duration, the longitudinal follow-up on several important symptoms particularly many non-motor manifestations and imaging biomarkers, the rigorous methodology, and the novelty of the computational approach focusing on neuroanatomical biotypes instead of data-driven clinical subtyping. In their discussion the authors hypothesize that the different rates of symptom progression may be related to different brain reserves. Biotype 1 patients may have less brain reserve and thus less capacity to compensate the progressive functional impairments associated with PD over time, resulting in a faster disease progression rate. The concept of brain reserve classically refers to the ability to tolerate age-related changes and disease related pathology in the brain without developing observable clinical symptoms or functional impairments on the behavioral level.⁷ Higher brain reserve, however, is not necessarily associated with a slower disease progression per se, and differences in progression may additionally be mediated by different compensatory mechanisms.⁷ The study by Wang et al. suggests that larger subcortical volume may attenuate the negative impact of PD pathology during disease progression, suggesting that subcortical brain morphological differences may support the maintenance of function despite progressing pathology. However, using brain volume as sole proxy for brain reserve has limitations. It does not detail the biological substrate of brain reserve, and subtle individual differences in brain reserve may not be captured by a volumetric measure.⁸

Another limitation of the study is the overlap in clinical scores at the individual level. Therefore, the implication of the findings in a clinical setting remains limited. The authors agree that future research is needed to investigate more refined biotypes. Moreover, patients included in the PPMI database have higher level of education, are younger and have less baseline disability than the general PD population, and thus the generalizability of the present findings needs to be determined in future studies.⁹ Brain based-biotypes determined by advanced neurocomputational approaches are only as good as data they are made from and validation of the biotypes in another cohort will be important.

In conclusion, a subtype of PD patients with a broad range of key non-motor symptoms including cognitive impairment, RBD, dysautonomia, and faster progression of motor and non-motor symptoms is associated with smaller subcortical brain volumes. Despite these promising results subtyping based on biological indices may be further improved by adding information from other brain imaging modalities, as well as blood, CSF, and genetic biomarkers to ultimately identify unique pathophysiological groups. Nevertheless, the present study provides important insights into the feasibility of deriving brain-based subtypes of PD characterized by distinguishable behavioral and progression profiles and emphasizes that future research should focus on biomarker driven subgroups. Future clinical trials should target recruitment of PD patients who meet biomarker-based inclusion criteria with the ultimate goal of developing personalized disease modifying therapies.¹⁰

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