Brain Alterations Associated with Cognitive Profiles in Prodromal and Parkinson's Disease Individuals

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Introduction and Objective

Detecting Mild Cognitive Impairment (MCI) in Parkinson's Disease (PD) has proven valuable in identifying individuals at risk of developing dementia and has been described as an important risk factor for individuals in the prodromal stage of the disease (Hobson & Meara, 2015). Therefore, we aimed at characterizing the cognitive profiles of prodromal and PD patients, and their brain morphology correlates, in a large sample of participants of the Parkinson's Progression Markers Initiative Program (PPMI; Marek et al., 2011).

Methodology

K-means clustering analysis was performed to identify distinct cognitive profiles in 551 PD patients (age: 63 ± 9 years) and 361 prodromals (age: 64 ± 6 years), based on the normalized scores of the 7 cognitive domains assessed by the Montreal Cognitive Assessment at baseline. The optimal cluster structure was determined using validation methods implemented in the NbClust R package (Charrad et al., 2014). Volumetric quantification of cortical, subcortical, cerebellar and ventricular regions was performed using AssemblyNet pipeline (Coupé et al., 2020) on T13D MRI brain images that survived visual and quantitative quality control (87.6%), using MRIQC software (Esteban et al., 2017).

Results

Three distinct cognitive profiles were identified among PD patients: Cognitively intact (n=260), Mildly affected (n=239) characterized by low performance (0.45) in the episodic memory domain, and Mostly affected (n=52), with notably lower performances in the language, abstraction and episodic memory domains (0.66, 0.35 and 0.36, respectively). Similarly, the Prodromal cohort clustered into three comparable profiles: Cognitively intact (n=171), Mildly affected (n=124) with low performance (0.41) in episodic memory, and Mostly affected (n=66), with low performances in language and episodic memory (0.51 and 0.53, respectively). Demographic analysis revealed significant sex proportion differences among the participants with distinctive cognitive profiles in both cohorts. Only Cognitively intact and Mostly affected in the Prodromal cohort showed significant age differences.

In the PD cohort, decreased right cerebellar white matter volume in Mostly affected participants ($p<0.05$), was identified when contrasting to Cognitively intact subjects. In the Prodromal cohort, overall decreased brain volume was evident in the Mostly affected group in contrast to the Cognitively intacts, with the right hemisphere being the most affected ($p=0.017$). Right cerebellar white matter ($p<0.01$) was significantly reduced in volume, while lateral ventricular volume was increased ($p<0.05$). After conducting the analysis comparing with a Control cohort without MCI (n=144), PD participants showed alterations in brainstem volume ($p<0.01$), while prodromal individuals exhibited changes in the gray matter volume of the left cerebellum ($p<0.05$) and hippocampus ($p<0.01$). All p-values were FDR-corrected ($q < 0.05$).

Conclusion

Similar cognitive profiles observed in both Prodromal and PD cohorts suggest the presence of comparable cognitive deficits in these individuals, being the PD patients and the episodic memory domain the most affected. Specific brain volume alterations were evident, particularly a reduction in cerebral and cerebellar white matter volume in the most cognitively affected participants. Interestingly, the prodromal cohort showed the greatest morphological differences, suggesting that PD involves diverse morphological alterations (volume increments and decrements) that result in less evident differences between cognitive profiles. These results highlight the relevance of correlating clinical features and structural brain properties to better characterize the complex alterations in both prodromal and PD patients, potentially identifying risk factors and early brain changes before the onset of the disease.