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EVENT ABSTRACT

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Principal component discriminant analysis of mild cognitive impairment in Parkinson's disease reveals early functional changes in the resting state

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Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease. It is a complex multisystem disorder encompassing tremor, bradykinesia and posture instability as well as a range of cognitive, autonomic and neuropsychiatric disturbances. Mild cognitive impairment in PD (PD-MCI) is common with a prevalence of 15-20% at diagnosis, and up to 80% of PD patients may ultimately develop dementia (Hely et al., 2008).

PD-MCI and its posterior dementia stage PD dementia (PDD) contribute to poorer quality of life, increased falls, hallucinations and increased carer burden. The Movement Disorder Society commissioned a Task Force to delineate the guidelines for the clinical diagnostic criteria for PD-MCI by assessing five cognitive domains commonly altered in PD: executive, attention, memory, semantic fluency and visuospatial perception. These are evaluated using at least two neuropsychological tests per domain (Litvan et al., 2012) and if the patient fails two of these in any of the cognitive domains, PD-MCI is diagnosed. However, the criteria do not define the exact threshold for passing or failing each of the tests. Previous clinical research has suggested three thresholds to differentiate PD-MCI from PD patients with normal cognition (PD-NC): 1.0 standard deviation (SD), 1.5 SD and 2.0 SD below normal cognitive values (Lawson et al., 2014). The most widely used threshold in clinical research is 1.5 SD. However debate still continues as previous investigations have suggested that the 2.0 SD cut-off shows superior sensitivity and specificity in differentiating PD-MCI from PD-NC (Goldman et al., 2013).

Methods: In the current study we assessed three clinical thresholds for diagnosing PD-MCI; 1.0, 1.5 and 2.0 SDs using resting state functional MRI (rs-fMRI) in patients recently diagnosed with PD (n=99) and clinically classified with a modified PD-MCI criteria; only one test for visuospatial perception was implemented (Yarnall et al., 2014).

Rs-fMRI from age matched controls (n=30) was also acquired. From this cohort of controls, we estimated canonical resting state networks (RSNs) using the group MELODIC tool within the FMRIB Software Library toolbox (FSL, v5.0). A total of 70 RSNs were estimated and visually inspected. 26 RSNs were identified of biological interest according to the previous literature and used in our posterior analyses.

Individual network time series were extracted for each of the canonical RSNs using dual-regression (26 time series per PD participant). Then, inter-network functional connectivity matrices (dimension 26 x 26) were estimated with FSL-Nets. Connectivity matrices were adjusted for age, gender, years of education and Levodopa equivalent daily dose (LEDD) by regressing out these covariates from the mean connectivity amplitudes.

Discriminant analysis of principal components (PC-DA) was implemented with the Classification Toolbox (Ballabio and Consonni, 2013) in Matlab (R2012a Mathworks, Natick MA). For the PC-DA model the feature matrix X was comprised of 99 rows (patients) and 325 column variables which are the connectivity matrix elements. The Classification Toolbox estimated that 16 PCs showed the lowest estimation error for the three MCI thresholds and these PCs were used in all model estimations.
Statistical significance for all classifications was estimated using non-parametric permutations with classifier accuracy (proportion of correct classifications) as the test statistic. At each permutation, participants were randomly shuffled among the predefined groups and classification accuracy estimated. This was repeated 10,000 times to obtain a null distribution for accuracy.

Results: When the 1.0 SD cut-off is applied, 36 patients were diagnosed as PD-NC (n=36) and 63 patients as PD-MCI (n=63). For the other two thresholds the group ratios were: 1.5 SD - PD-NC (n= 62) and PD-MCI (n= 37), and for 2.0 SD - PD-NC (n=78) and PD-MCI (n=21).

The classification experiments to differentiate PD-MCI patients from PD-NC for the three criteria thresholds resulted in the following:

*PD-MCI at 1.0 SD: 0.87 sensitivity, 0.72 specificity, 0.82 accuracy, p-value = 0.0005
*PD-MCI at 1.5 SD: 0.43 sensitivity, 0.82 specificity, 0.67 accuracy, p-value = 0.676
*PD-MCI at 2.0 SD: 0.33 sensitivity, 0.95 specificity, 0.82 accuracy, p-value = 0.818

Conclusions: The results revealed that functional connectivity is able to differentiate MCI in PD. The best classification was obtained for the 1.0 SD threshold, which was the only one that reached significance (p-value = 0.0005). The current results also highlight that rs-fMRI is able to successfully differentiate functional changes at more subtle levels of impairment (1.0 SD below normative values) compared to levels of significant cognitive decline. This suggests that there is an inflexion point in functional activity that can help differentiate PD-MCI from PD-NC and 1.0 SD is the best diagnostic threshold from a resting state network perspective. Further research is needed to assess the clinical criteria for MCI in PD and the neural correlates with other neuroimaging modalities including rs-fMRI, along with its relationship to developing dementia.

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