

## Reduced Functional Connectivity of the Executive Network Predicts Mild Cognitive Impairment in Parkinson's Disease

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**Introduction:** Resting state fMRI (RsfMRI) is now an established method to assess cerebral network function in health and disease based on the temporo-spatial coherence (functional connectivity[FC]) in the low-frequency (< 0.1 Hz) range of spontaneous brain activity [1, 2]. There is increasing evidence that RsfMRI allows to characterise dysfunctional network organisation in Parkinson's in motor and non motor networks[3-6]. This study aimed to explore the most prominent features of abnormal brain oscillatory function in non demented patients with PD, and specifically to investigate whether abnormalities in cognitive networks precede significant cognitive impairment.

**Method:** All study participants gave written informed consent, and the study was approved by the relevant governance bodies. 11 patients (65.7±4.6years, 5 male, with disease duration of 2.53±2.3years) and 9 controls (63.2±4.7years, 5 male) were included. All subjects underwent cognitive assessment using the Addenbrooke's test battery (ACE) and multimodal MRI scans at 3T (Philips Achieva). This included RsfMRI (TR/TE = 2200/35 ms, flip angle 90°, matrix size = 64 x 64 x 35, slice thickness = 3 mm). A total of 145 volumes were acquired. Data were pre-processed and analysed using FSL (www.fmrib.ox.ac.uk), including motion correction using MCFLIRT and removal of non-brain structures with Brain Extraction Tool. Gaussian spatial smoothing was applied with a full width half maximum of 5mm, and high pass temporal filtering was used; independent component analysis (ICA) was performed after temporal concatenation to generate group components (maps). ICs reflecting the main resting state networks were subjected to dual-regression analysis[7], and spatial differences in individual networks between controls and patients were tested for by permutation (n=5000). Significant between groups differences in network extent were identified using the threshold free cluster enhancement with corrected P ≤ 0.05. Interrelations between cognitive performance and network abnormalities were explored using Pearson's correlation analysis.

**Results:** ICA identified 36 components including all main resting state networks. Dual regression analysis identified a disease effect only in the dorsal attention network (DAN): patients with PD showed reduced connectivity between the DAN (including the posterior parietal cortex and the frontal eye fields, interconnected by the superior longitudinal fasciculus[8, 9]) and the left inferior parietal cortex and precuneus [Fig1]. In PD, we found strong correlations between the connectivity of the precuneus and DAN (expressed as regionally averaged Z score of individual DAN component) and cognitive performance with  $r^2=0.48, p=0.029$  for total ACE, and  $r^2=0.43, p=0.018$  for the memory subscore.

**Discussion:** Using dual regression ICA analysis in non demented patients with PD, the most prominent network abnormality was found in the dorsal attention network also known as the executive-attention network. Patients with PD showed reduced fc in DAN. Importantly, reduced connectivity of the precuneus with the dorsal attention predicted cognitive performance in a group of patients with no sign of dementia. Our RsfMRI findings also confirm a previous PET study [10] positing that the precuneus and inferior parietal lobule form part of dysfunctional cognitive network in non-demented PD.

**Conclusion:** This preliminary study suggests that reduced functional connectivity in the dorsal attention network is an early feature in PD preceding clinical relevant cognitive impairment. We also show that reduced DAN function may explain mild cognitive impairment in PD patients with little cognitive impairment. The findings further add to the evidence that RsfMRI is a particular powerful tool to phenotype neurodegenerative diseases allowing to track network specific dysfunction.

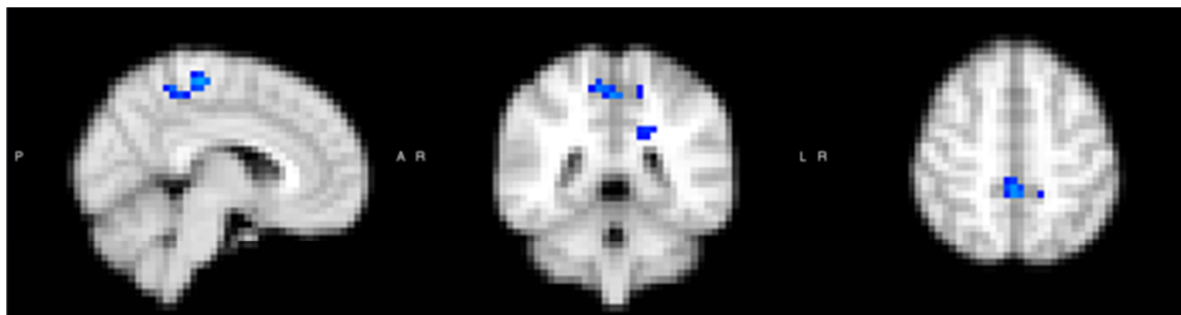


Fig 1: Reduced connectivity in the area of precuneus resulting from dual-regression analysis with corrected  $p < 0.05$  (blue) overlaid on template.

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