ALTERED DEFAULT MODE NETWORK FUNCTIONAL CONNECTIVITY AND WHITE MATTER INTEGRITY IN PARKINSON'S DISEASE AND RELATION WITH COGNITIVE FUNCTIONS

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Target audience: Researchers and physicians who work in the field of neuroscience, especially with movement disorders including Parkinson Disease.

Purpose:

To investigate functional connectivity (FC) of posterior cingulate cortex (PCC) and other default-mode-network (DMN) structures separately by resting state functional MRI (RS-fmri), and also white matter integrity by using diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS) in Parkinson's Disease (PD). A correlation was searched between cognitive functioning, functional connectivity and white matter integrity.

Material and Methods:

IRB was obtained for this study and all the participants gave signed consent form.

Subjects: Eighteen patients with idiopathic Parkinson Disease (PD) (M/F: 10/8; 65.72±7.69 years) and 10 healthy controls (HC) (M/F: 6/4; 66.90±7.58years) (t-test; p>0.5) were included in the study. All patients were diagnosed on basis of clinical findings.

Image Acquisition: All imaging data of the brain were obtained on a 3T MR scanner (Magnetom, Trio TIM system, Siemens, Germany) equipped with a 32-channel phase-array head coil. A T2* weighted gradient echo spiral pulse sequence (TR /TE: 2000/35 msec, FA 75°, FOV: 230 mm, matrix: 64 x 64, in-plane spatial resolution of 3.6 mm) was used with the subjects without a specific concentration. All participants also underwent 3D T1-weighted high resolution images (magnetization prepared rapid gradient echo-MPRAGE) (TR/TE: 1900/3.4 msec; FA: 90; FOV: 256mm; matrix: 224x256; distance factor: %50) and isotropic high resolution DTI of the whole brain (single-shot EPI; TR/TE: 8020 /83 msec, max. b factor: 1000s/mm^2, 60 independent directions, FOV: 256 mm, matrix: 128×128, 64 axial sections with 2 mm thickness without intersection gap, voxel size: 2x2x2 mm).

Data Processing and Analysis

-Preprocessing of the fMRI data: The RS-fmri scans were preprocessed using SPM8 [1]. Preprocessing of the RS-fMRI data included realignment, slice-timing correction, coregistration and normalization (to Montreal Neurological Institute template (MNI)), and spatial smoothing with an 6 mm³ isotropic Gaussian kernel.

-Functional Connectivity Analysis: Using the CONN toolbox in MATLAB R2008a [2], we identified principal components associated with segmented white matter (WM) and cerebrospinal fluid (CSF) for each subject and entered WM, CSF and realignment parameters as confounds in a first-level analysis. The data were band-pass filtered to 0.008 Hz–0.09 Hz. For group analysis, we then used seed-voxel analysis, and specified connectivity patterns for one 6 mm spherical clusters seed ROI located in posterior cingulate cortex (PCC). Using the specified seed ROI in PCC, temporal correlations were computed between the seed and all the other voxels in the brain. Seed-to-voxel results were reported as significant at a voxelwise threshold of level of p<0.001 uncorrected and cluster-level threshold of p<0.05 FDR corrected. t-test and Fisher's Z-transformed correlations were used to compute differences in FC between the patients with PD and HC. For the individual seed-based connectivity, we applied psychophysiological interaction (PPI) analysis to examine functional coupling respectively between the PCC and other seven specified ROI located in DMN regions. Volumes of interest (VOI)s were defined as spheres with 6 mm radius. To form a sphere mask around a voxel of interest, we used the fslmaths commands. The time-series was extracted from the voxel that was at the center of the activation cluster from the normalized fMRI file by using fslmeants command. We used FEAT toolbox [3] with the seed time-series file and calculated Z score values for each subject.

-Diffusion Tensor Imaging Analysis: For comparative DTI analysis of the groups, we used tract-based spatial statistics (TBSS), a part of FSL. Preprocessing of the diffusion weighted data including head motion and eddy current correction, and diffusion tensor fitting (FSL DTIFit) were performed. Fractional anisotropy (FA), and mean diffusivity (MD) maps were computed. FA maps were registered and aligned to the average space as input for TBSS, and the thinned mean FA skeleton was computed. Then voxelwise statistics were performed using the permutation-based inference with 500 permutations. The resulting TFCE output was corrected for multiple comparisons by controlling the family-wise error rate and thresholded at significance level p < 0.05. We used standard cluster-based thresholding corrected for multiple comparisons with a t threshold of 1.5 and obtained the contiguous clusters of supra-threshold voxels using 26-neighbour connectivity.

General cognitive functioning was measured by minimental test scores.

Results:

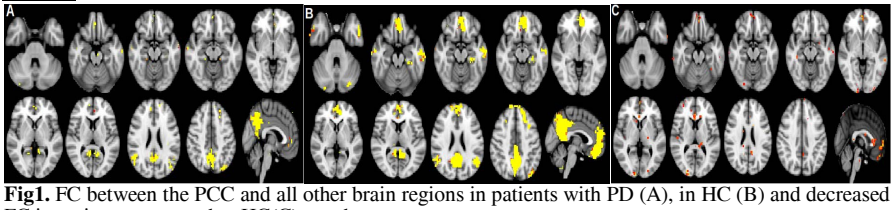

Fig1. FC between the PCC and all other brain regions in patients with PD (A), in HC (B) and decreased FC in patients compared to HC(C) are shown.

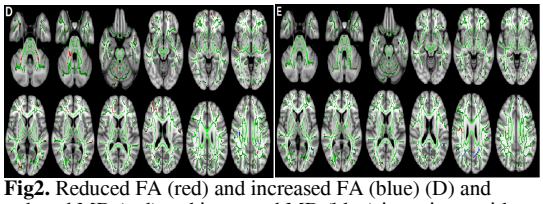

Fig2. Reduced FA (red) and increased FA (blue) (D) and reduced MD (red) and increased MD (blue) in patients with PD (E) compared to HC.

Seed-to-voxel analysis for the functional connectivity revealed marked reduction in the connectivity between PCC and all the other brain region in patients with PD. The HC group showed significantly stronger connectivity between PCC and MPFC (t=13.43, p=0.034). When we compared the patients and HC groups, there were significant reductions in FC of specified regions, especially between PCC-MPFC (t=16.67, p=0.0001), PCC-Superior frontal gyrus (t=12.91, p=0.048), PCC-right parahippocampal gyrus (t=17.79, p=0.003) in patients (Fig.1). We also explored the white matter integrity using DTI-TBSS analysis. Bilateral anterior thalamic radiation, superior frontal gyrus, left anterior corona radiata, genu and splenium of corpus callosum, left cingulum are seen as reduced FA regions in patients with PD compared to HC (Fig.2).

General cognitive functioning measured by minimental test scores was similar in patients with PD and HC. But, in parallel with the reduced FC between PCC and MPFC, patients with PD performed worse than HC in cognitive tests measuring attention and executive functions (trail making A test: 155.6±28.1 vs 66.8±9.6, p<0.05; trail making B test: 274.7±20.1 vs 144.0±26.0, p<0.05).

Discussion and Conclusion:

As revealed by RS-fmri and TBSS-DTI analyses, patients with Parkinson's Disease display reduced connectivity and white matter changes relevant to cognitive dysfunction.

References:

1. (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/)
2. (www.nitrc.org/projects/conn)
3. (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT)