Functional correlates of cognitive impairment in PP-MS across multiple frequency bands.

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Background

Cognitive impairment occurs in approximately 47% of patients with PP-MS, affecting a wide range of functions[1]. A recent study has suggested that it is related to the disruption of brain functional connectivity (FC) of the default mode network (DMN) as measured by resting-state functional MRI (rs-fMRI)[2]. Recent advances in rs-fMRI analysis have shown that the investigation of FC in multiple frequency bands and the assessment of BOLD signal amplitude variability (SD) could provide a more comprehensive characterization of brain functional correlates of cognitive impairment. Indeed, while FC of slow frequency bands (slow-5: 0.01–0.027 Hz and slow-4: 0.027–0.073 Hz) may contribute to the characterization of deep gray matter (GM) and midline cortical regions[3,4], variability of BOLD signal amplitude across time might represent a more direct index of neuronal activity, with actively firing neurons showing high variability and with gray matter (GM) exhibiting higher variability than white matter (WM)[3,5,6].

Aims

1) identify the major domains of cognitive impairment in PP-MS through a principal component analysis (PCA) of neuropsychological (NPS) tests and select resting state networks (RSNs) of interest accordingly; 2) characterize, for the selected networks, FC and SD abnormalities associated with cognitive impairment in different frequency bands and, 3) investigate whether the presence of cortical lesions (CLs), which show a high prevalence in PP-MS patients[7,8], has an impact on specific FC and SD changes.

Methods

Twenty-five patients with PP-MS (M/F=12/13, mean age 51±10 yrs, median EDSS 4.0; range 1.5-6.0, disease duration 8.0±4.5yrs) and twenty sex- and age-matched (M/F=9/11, mean age 51±10yrs) controls (CTRLs) were consecutively enrolled. All subjects underwent MRI on a 3.0 T scanner with the following protocol: a) T2-weighted TSE (TR/TE:2500/90 msec; 46 3-mm thick contiguous slices); b) 3D T1- weighted turbo field echo (TR/TE/TI:7.5/3.5/900 msec; voxel size:1 mm3); c) T2* echo-planar imaging (TR/TE:2300/27 msec; 150 volumes; in-plane spatial resolution: 3 mm2; 46 3-mm thick contiguous slices) for rs-fMRI. Raw scores from MACFIMS battery were converted in z-scores. A PCA of the NPS tests was performed using SPSS (version 20.0, IBM, Chicago, Illinois). The first principal component was used to calculate a global cognitive (GC) score used to divide patients into cognitive impaired (CI) and cognitively preserved (CP) using a hierarchical clustering analysis. (Fig. 1)

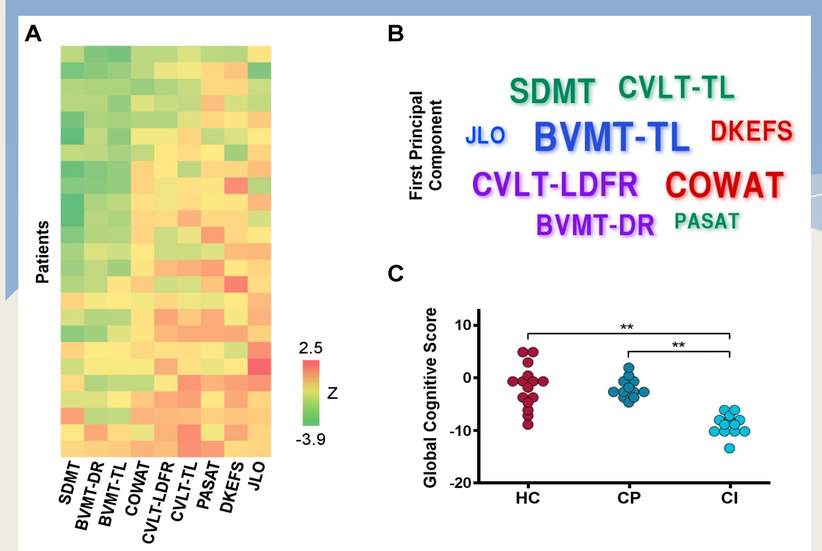

Fig.1 Cognitive status of PP-MS patients. Panel A shows results of the NPS tests for all patients. Rows represent individual patients and columns each test, both sorted by increasing mean z-score, indicated by the color code. Panel B presents the NPS tests used in the PCA analysis, with each name scaled by the loadings of the first principal component for the patient dataset. Colors indicate cognitive domain: executive functions (red), visuo-spatial ability (blue), short-term memory (purple) and working memory/processing speed (green). Panel C shows the global cognitive scores for CTRLs, CI and CP patients. Asterisks represent level of significance for Mann-Whitney test (p<0.001).

Structural damage was evaluated in terms of white matter (WM) and GM lesion loads and voxel-wise FA. (Fig. 2)

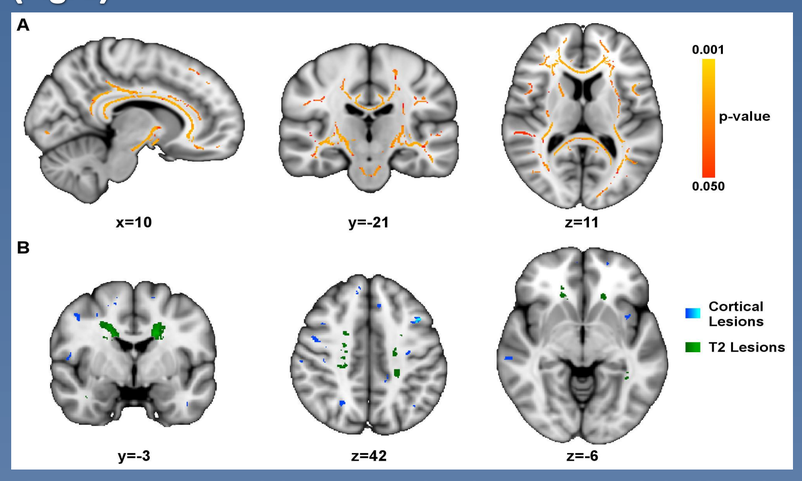

Fig. 2 PP-MS structural damage. Panel A shows regions of significantly higher FA in CP compared to CI patients (two-sample t-test, age corrected), displayed on white matter skeleton derived using a Tract-based Spatial Statistics (TBSS) analysis. The color bar represents the p-value of significant results (p<0.05). Panel B shows cortical lesions (in blue) and white matter lesions (in green) probability maps (thresholded respectively between 0.04-0.08 and 0.1-0.4). Results are overlaid on MNI T1-weighted template.

Processing of functional data were implemented in Analysis of Functional NeuroImages (AFNI) (http://afni.nimh.nih.gov/afni). The data were filtered and signals between 0.01 and 0.1 Hz, which are thought to reflect mainly neuronal fluctuations, were conserved. On the basis of recent findings in healthy subjects, we also focused on two separate bands within the standard range of 0.01–0.1 Hz: slow-5 (0.01–0.027 Hz) and slow-4 (0.027–0.073 Hz). A seed-based analysis of RS functional connectivity and variability was conducted for the dorsal attention network-DAN; right attentional network-RAN and executive control network-ECN, chosen as networks of interest corresponding to the cognitive domains found to be relevant in the PCA of the NPS tests.

Results

CI patients showed a significantly higher intracortical (IC) lesion count and volume (respectively 2.85±2.15 vs 0.54±0.69 and 0.09±0.06 vs 0.02±0.02ml, p<0.01) and a widespread significant decrease in FA compared to the CP group. Between group comparisons of SD in GM (global variability) seed ROIs and target clusters (regional variability) showed constantly higher SD in patients than CTRLs and in CI patients in comparison with CP patients (p<0.01).

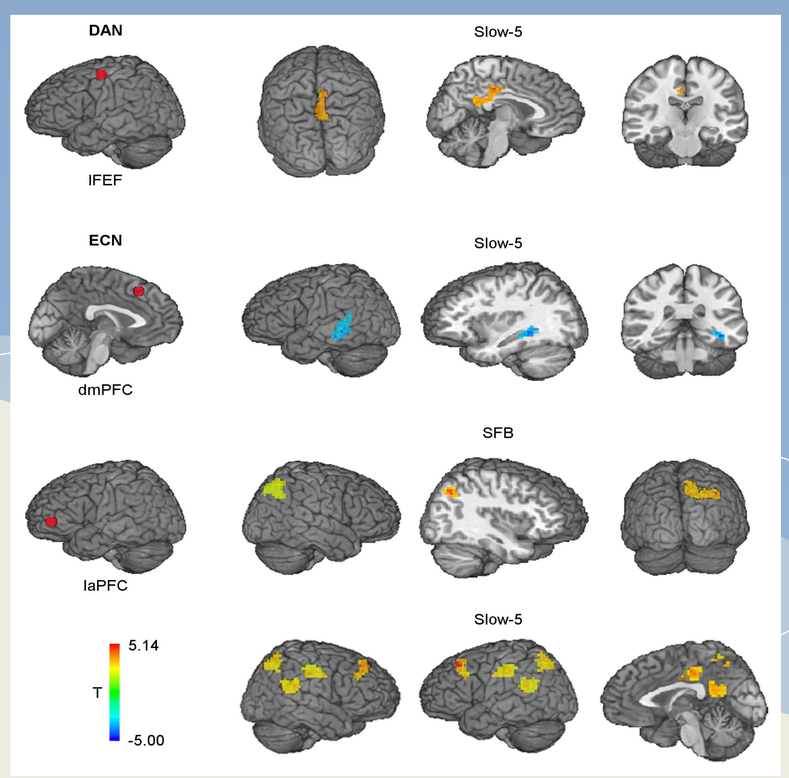

Fig.3 Clusters showing a significant difference in FC between PP-MS patients and CTRLs. Seed regions (first column) for the dorsal attention network-DAN (left frontal eye field-lFEF), and executive control network-ECN (dorsomedial prefrontal cortex-dmPFC and lateral anterior prefrontal cortex-laPFC) are shown. Significant results are shown for the standard frequency band (SFB; 0.01-0.1Hz), and Slow-5 (0.01-0.027Hz). All t-maps are thresholded at corrected p<0.01 (covariates: age and grey matter z-scores). The color bar shows voxel-wise T-values.

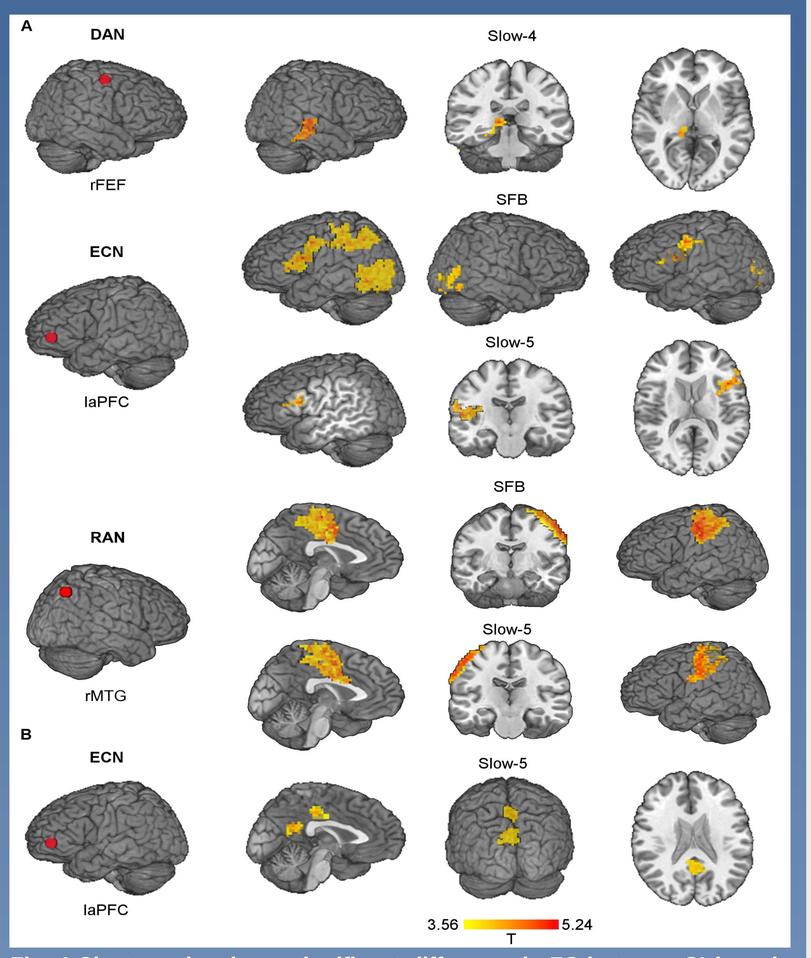

Fig. 4 Clusters showing a significant difference in FC between CI (panel A) and CP (panel B) patients and CTRLs. Seed regions (first column) for the dorsal attention network-DAN (right frontal eye field-rFEF), executive control network-ECN (lateral anterior prefrontal cortex-laPFC), and right attentional network-RAN (right middle temporal gyrus-rMTG) are shown. Significant results are shown for the standard frequency band (SFB; 0.01-0.1Hz), Slow-5 (0.01-0.027Hz) and Slow-4 (0.027-0.073Hz). All t-maps are thresholded at corrected p<0.01 (covariates: age and grey matter z-scores). The color bar shows voxel-wise T-values.

IC lesion volume was correlated with increased FC between RAN (rMTG) and left precuneus in the SFB. In slow-5, IC lesions volume was correlated with increased SD in rMFG.

Conclusions

We confirmed the presence of a widespread cognitive deterioration in PP-MS patients, with main involvement of visuo-spatial and executive domains and increased variability and inter-network connectivity between ECN, DAN, RAN and other RSNs responsible for cognitive control. IC lesion volume was higher in CI patients and was directly correlated with the increase in FC and variability.

Increased FC is usually regarded as a compensatory mechanism that limits the consequences of neurological damage[9-11], or as expression of maladaptive reorganization[12,13]. In our CI patients, similarly to what observed in chronic stroke patients, where the long term persistency of increased brain activation is related to a poor behavioral outcome[14], FC and SD increase do not reflect maintenance of an adequate cognitive status, suggesting a maladaptive reorganization, possibly depending both on the extent of WM structural damage and the presence of CLs. We demonstrate, for the first time, that a maladaptive hyper-synchronization of large scale networks and an abnormal pattern of neural activity underlie cognitive dysfunction in PP-MS, and that CLs possibly play a role in SD and FC abnormalities.

Acknowledgements

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