COGNITIVE REHABILITATION MODIFIES FUNCTIONAL CONNECTIVITY OF THE ANTERIOR CINGULATE CORTEX IN MULTIPLE SCLEROSIS

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Introduction. In a previous study [1], following cognitive rehabilitation, patients with relapsing remitting (RR) multiple sclerosis (MS) showed a change of recruitment of several fronto-parietal regions at functional MRI (fMRI).

Objective. Aim of this study was to investigate modifications of the functional connectivity (FC) at resting state (RS) of the anterior cingulate cortex (ACC) following cognitive rehabilitation in clinically stable RRMS patients.

Methods. RRMS patients with an Expanded Disability Status Scale score $\leq$ 4 and selective deficits at the Paced Auditory Serial Addition Test (PASAT) and Wisconsin Card Sorting Test (WCST) were assigned randomly to treatment (TG) or to serve as a control (CG) group. All patients underwent a standardized neuropsychological assessment and RS fMRI at baseline and after 12 weeks. During this period, TG patients underwent intensive computer-assisted cognitive rehabilitation of attention/information processing and executive functions. FC was assessed using a voxel-wise analysis [2], selecting the ACC as seed region and calculating the correlation coefficient between it and any other area in the brain. Within-group and between-group comparisons of FC at the different time points of the study were assessed using SPM8 (paired t test and ANOVA, respectively). Multiple regression models were used to assess correlations between FC and cognitive performances at neuropsychological tests.

Results. Ten patients were randomized to each group. After rehabilitation, the TG showed a significant improvement at tests of attention/information processing and executive functions. In both groups, at the two study time points, the ACC was significantly correlated with the bilateral middle frontal gyrus (MFG), bilateral inferior frontal gyrus, bilateral basal ganglia (including the thalamus), posterior cingulate cortex (PCC), cerebellum, precuneus, as well as several regions of the temporal and parietal lobes (Figure).
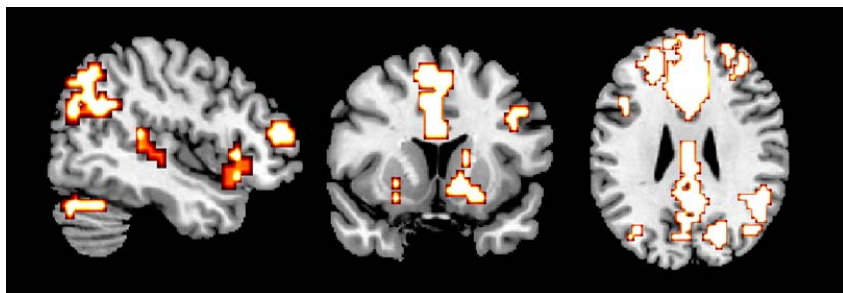
Figure legend.
Brain regions showing significant FC with the ACC (average of the two groups across the two timepoints, ANOVA model thresholded for positive values, p<0.05 family-wise error corrected for multiple comparisons).

At follow up, compared to baseline, the TG showed an increased FC between the ACC and the right (R) MFG [MNI coordinates: 36, 9, 44; p<0.001, t=9.3] and R inferior parietal lobe (IPL) [MNI coordinates: 69, -33, 32; p<0.001, t=12.1], while the CG showed a decreased FC between the ACC and the R cerebellum [MNI coordinates: 27, -36, -40; p<0.001, t=6.4] and R inferior temporal gyrus [MNI coordinates: 36, 3, -44; p<0.001, t=9.7]. In the TG, the increased FC between the ACC *vs*. the R MFG and R IPL were significantly correlated with improvements of performances at PASAT2 (r=0.88, p<0.001) and PASAT3 (r=0.76, p<0.001).

Conclusion. After cognitive rehabilitation, FC changes among brain regions subserving the trained functions were detected in MS patients, suggesting that fMRI might contribute monitoring the effects of therapeutic interventions in this and other neurological conditions.

References [1] Filippi M et al., Radiology 2011 *In press*. [2] Biswal B et al., Magn Reson Med 1995;34:537-541.