Resting State Functional Connectivity Abnormalities Are Associated With Cognitive Impairment in Patients With Pediatric Multiple Sclerosis

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Introduction. Previous active functional MRI (fMRI) studies showed only minor functional abnormalities in patients with pediatric multiple sclerosis (MS) *vs.* controls [1]. Resting state (RS) functional connectivity (FC) in these patients has never been explored.

Objective. Aim of this study was to explore abnormalities of FC and functional interaction among cognitive networks (RSNs) in patients with pediatric multiple sclerosis (MS), as well as their correlation with cognitive impairment and T2 focal lesions.

Methods. Brain dual-echo and RS fMRI scans were acquired from 34 pediatric MS patients, and 18 age-matched controls. T2 lesion volume (T2LV) was assessed on dual-echo images. Independent component analysis (ICA) [2] and a template-matching procedure were used to identify the default mode network (DMN), the executive control network (ECN), the salience network (SN) and the attention network. Within-group and between-group FC comparisons were performed with SPM8. The functional network connectivity (FNC) toolbox [3] was used to assess changes of interactions among RSNs. In MS patients, correlations between network abnormalities, cognitive impairment and structural damage were also assessed.

Results. The spatial patterns of the DMN, ECN, SN and of the attention network are shown in the Figure.

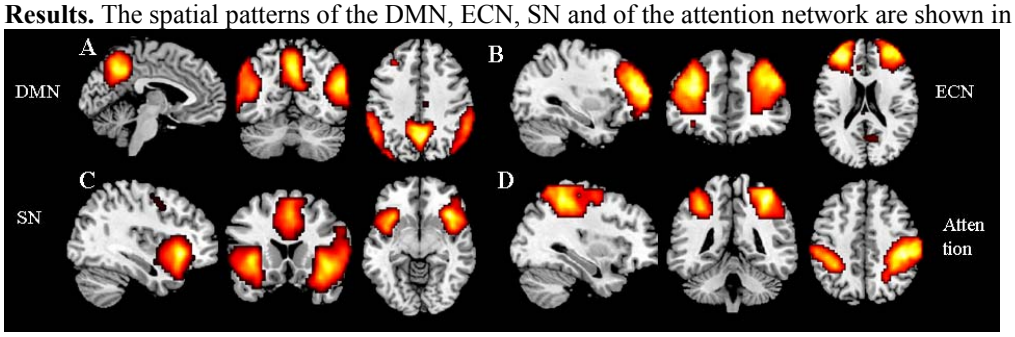

Figure legend. *Cognitive RSNs detected in our study subjects (ANOVA model, t test thresholded for positive values, p<0.05 family-wise error corrected for multiple comparisons): A: default mode network (DMN); B: executive control network /ECN); C: salience network (SN); D: attention network.*

Significant RS FC changes were detected in all RSNs of pediatric MS patients *vs.* controls. A decreased FC was found in regions of the posterior lobes, as well as in the cerebellum of the attention, SN and ECN. Conversely, an increased FC was found in frontal regions of the SN and DMN (see Table for further details).

	DMN	**ECN**	**SN**		**Attention network**
Region [MNI space coordinates]	R superior frontal gyrus (SFG) [9 54 14]	Posterior cingulate cortex (PCC) [0 -55 30]	L cerebellum [-33 -76 -38]	R inferior frontal gyrus (IFG) [39 20 -6]	L superior occipital gyrus [-33 -91 30]
P (ANOVA)	0.008	0.01	0.04	0.04	0.007
Healthy controls	0.60	1.06	0.67	1.63	0.96
Pediatric MS	0.90	0.61	0.50	1.77	0.59

Table. *Abnormalities of RS FC(expressed as Z score) in pediatric MS patients vs. healthy controls.*

FC decrease in the PCC was higher in cognitively impaired *vs.* cognitively preserved patients (p=0.01), whereas FC increase in the R SFG and R IFG were higher in cognitively preserved than in cognitively impaired patients (p=0.01 and 0.02, respectively). Patients with lower T2LV had a higher FC increase in the IFG (r=-0.36, p=0.04). Confirming the results of previous studies [4], the DMN and the attention network were significantly anticorrelated in healthy controls (r=-0.12, p=0.03), but they were disconnected in pediatric MS patients (r=-0.02, p=0.72).

Conclusion. Significant RS FC abnormalities occur in cognitive RS networks of pediatric MS. A decreased FC is associated with cognitive impairment, whereas increased FC seems to be related with a preserved functional reserve.

References. [1] Rocca MA et al., Hum Brain Mapp 2009;30:2844-51. [2] Calhoun V et al., Hum Brain Mapp 2001;14:140-151. [3] Jafri M et al., Neuroimage 2008;39:1666-81. [4] Fox P et al., PNAS 2005;102:9673-78.

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