Functional Connectivity Abnormalities and Cognitive Impairment in Relapse-Onset Ms Patients: A Whole-Brain Functional Network Connectivity Analysis

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Introduction. Previous studies [1] showed abnormal functional connectivity (FC) at resting state (RS) of the default mode network (DMN) in patients with progressive multiple sclerosis (MS).

Objective. Aim of this study was to explore abnormalities of FC and of functional interaction among cognitive resting state networks (RSNs) in patients with relapsing remitting (RR) and secondary progressive (SP) MS, and their correlation with cognitive impairment and damage to selected white matter (WM) tracts.

Methods. RS fMRI and diffusion tensor (DT) MRI were acquired from 30 RRMS, 30 SPMS patients and 30 matched controls. Maps of the corpus callosum (CC) and cingulum were produced using DT tractography. Independent component analysis (ICA) [2] and a template-matching procedure were used to identify the DMN, the executive control network (ECN) and the salience network (SN). Within-group and between-group RS 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 and SN detected in our subjects are shown in Figure 1.

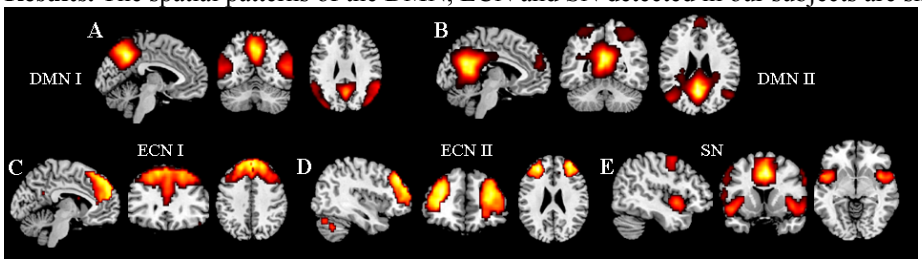

Figure 1.
Cognitive RSNs detected in our study subjects (ANOVA model, t test thresholded for positive values, p<0.05 family-wise error corrected for multiple comparisons): A,B: default mode network; C,D: executive control network; E: salience network.

Significant RS FC abnormalities, which were more pronounced in SPMS *vs*. RRMS, were detected in all RSNs, and were characterized by a decreased FC in frontal, temporal, parahippocampal and cerebellar regions, as well as an increased FC in the anterior cingulate cortex (see Table for further details). FC abnormalities were more severe in cognitively impaired *vs.* cognitively preserved patients (p ranging from 0.02 to 0.04), and were correlated moderately with DT MRI indexes of damage to the CC and cingulum (r ranging from -0.40 to 0.48, p ranging from 0.001 to 0.03).

	DMN I		**DMN II**		**ECN I**			**ECN II**		**SN**	
Region [MNI space coordinates]	R middle frontal gyrus [45 44 6]	R superior temporal gyrus [63 5 -6]	L para-hyppocampal gyrus [-30 -49 -14]	R superior temporal gyrus [57 5 -6]	Anterior cingulate cortex [3 50 46]	R cerebellum [30 -82 -30]	R orbito-frontal cortex [30 17 -22]	L cerebellum [-42 -61 -42]	R para-hyppocampal gyrus [33 -40 -22]	L cere-bellum [-18 -85 -26]	L inferior frontal gyrus [-39 47 6]
P (ANOVA)	0.01	p=0.003	0.03	0.04	0.004	0.03	0.007	0.03	0.05	0.002	0.05
HC	0.69	0.81	0.80	0.80	1.28	0.70	0.97	0.78	0.78	0.84	0.90
RRMS	**0.59**	0.62	**0.51**	0.65	1.33	0.75	0.75	0.63	0.72	**0.54**	0.77
SPMS	**0.54**	**0.37**	**0.46**	**0.56**	**1.41**	0.58	**0.58**	**0.50**	**0.57**	**0.40**	**0.62**

Table. *Abnormalities of RS FC (expressed as Z score) in RRMS and SPMS patients (highlighted in bold) vs. healthy controls (HC).*

FNC analysis detected a decreased connection between the DMN and ECN, and an increased connection between the SN and ECN in both RRMS and SPMS patients. SPMS also showed an increased FC between the SN and DMN (Figure 2). Altered connectivity among RSNs was moderately correlated with cognitive and structural MRI variables (r ranging from -0.36 to 0.34, p ranging from 0.003 to 0.03).

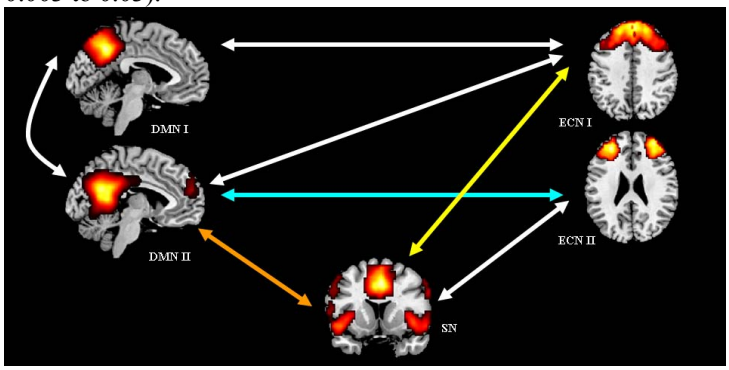

Figure2.
Diagram showing significant functional network connectivity (FNC) among cognitive RSNs in the three study groups.
White: significant FNC in all three study groups.
Light blue: significant FNC in healthy controls and RRMS.
Yellow: significant FNC in RRMS and SPMS.
Orange: Significant FNC in SPMS only.

Conclusions. Intra-network and inter-network dysfunction at rest is associated to more severe clinical disability and cognitive deficits in MS patients.

References: [1] Rocca MA et al., Neurology 2010;74:1252-59. [2] Calhoun V et al., Hum Brain Mapp 2001;14:140-151. [3] Jafri M et al., Neuroimage 2008;39:1666-81.

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