Reduced resting-state connectivity in the brain's default mode network in patients with mild forms of relapsing-remitting MS

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Introduction

In neurofunctional MRI, signal decreases have been observed in a cluster of brain regions during many different cognitive tasks. This cluster, including bilateral posterior regions of the brain, namely posterior cingulate cortex (PCC)/precuneus (preCun) and bilateral frontal regions like ventral anterior cingulate cortex (vACC) and an adjacent part of medial frontal gyrus (MFG), has been referred as the brain's default mode network and has been suggested to be more active at rest [1]. Recently, correlations have been found between the strength of resting state connectivity between MFG/vACC and PCC/preCun in an individual and his performance on a working memory task [2] and it has been speculated that resting state connectivity between these regions is a physiological marker of cognitive function. As cognitive impairments are highly prevalent even at early stages of multiple sclerosis (MS), we investigated the resting state connectivity in the default mode network of the brain in order to see whether altered connectivity may be present in patients with mild forms of relapsing-remitting multiple sclerosis (RR-MS) without overt cognitive impairment.

Methods

15 patients with RR-MS (median age 39y, range 22y-49y, 9 female) and 15 age-matched healthy controls (HC; median age 35y, range 23y-50y, 6 female) participated in our study. The MS patients had a mean disease duration of 5.9 years (SD=3.6) and were mildly affected with a mean Expanded Disability Status Scale score (EDSS) of 2.3 (SD=1.3), but without overt cognitive involvement. The MR measurements were performed on a 3.0 T head scanner (Magnetom Allegra, Siemens Medical, Erlangen, Germany) using the manufacturer's transmit-receive head coil. To locate task specific neuronal deactivation, the participants performed a visual N-back task. In the respective fMRI experiment, 1-digit numbers were presented and memory load was varied between 1-back, 2-back, and 3-back. Further details of the fMRI paradigm can be found in [3]. After the fMRI experiment, resting state functional connectivity MRI (fcMRI) was performed using a single-shot, T2*w EPI sequence (TR/TE/α = 700ms/30ms/30°) with an in-plane resolution of 4x4 mm^2. Each volume had 11 slices (3 mm thick, 1 mm gap) parallel to corpus callosum and covering both MFG/vACC and PCC/preCun. For each subject, 450 fcMRI time frames were acquired in 5min 15s. The fMRI and fcMRI data sets were post-processed using AFNI [4]. The post-processing included slice timing and motion correction and spatial smoothing with a Gaussian filter (FWHM = 8 mm). For the fMRI runs, statistical maps were created for each subject by performing a multiple linear regression analysis. After transformation into Talairach space, group analysis was performed with the fMRI data. In the resultant group statistical maps, a reference region for the subsequent fcMRI analysis was defined by the nine most significantly deactivated voxels in PCC/preCun (seed ROI). Similarly, a second region (target ROI) was defined by the nine most deactivated voxels in MFG/vACC. The resting state data sets of each subject were low-pass filtered in time (cut-off frequency 0.08 Hz) and a correlation analysis was performed to the averaged signal time course of the PCC/preCun ROI. In the analysis, signal time courses of the whole brain and of the CSF were treated as regressors of no interest. The resulting correlation maps were then transformed to z-scores of the standard normal distribution [5]. Differences in connectivity to PCC/preCun were calculated in two different ways: First, the z-score maps underwent voxel based statistical analyses: t-tests against the null hypothesis for each group and for differences between the groups were carried out. Second, for each subject, strength of the MFG/vACC to PCC/preCun correlation was calculated by averaging the z-scores of the voxels in the MFG/vACC ROI. A double-sided t-test between MS patients and HC was performed for this averaged MFG/vACC to PCC/preCun connectivity. Additionally, a linear regression was calculated between EDSS and MFG/vACC mean z-score for the MS patients.

Results

The resulting PCC/preCun connectivity maps are shown in Fig. 1. Both in HC (left column) and patients (middle), positive correlation was observed in brain areas typically belonging to the default mode network: MFG/vACC, parts of bilateral middle frontal cortex and bilateral superior temporal cortex (see also Tab.1 and Tab.2). Only one significant ($p_{cor} < 0.05$) between-group difference was found: patients showed reduced connectivity in MFG/vACC (Fig. 1, right). Independently, ROI analysis of the fMRI-defined MFG/vACC region revealed also significant decreased z-scores (p=0.02), indicating reduced connectivity in patients (mean ± SD: 1.28 ± 0.77) compared to HC (2.26 ± 1.33). No significant correlation was found between mean z-score and EDSS (r=0.35, p=0.2) in patients.

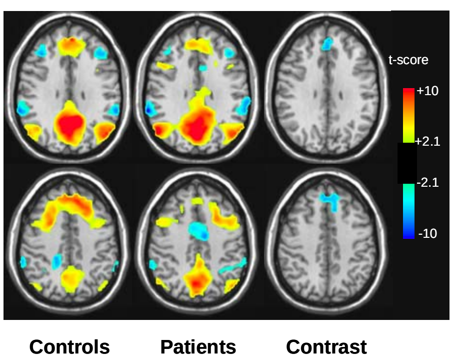

Fig.1: t-score maps showing resting state correlations with PCC/preCun (p<0.05). Right column: significant differences between patients and controls.

Talairach Coordinates				
x	y	z	Max t-score	Brain area
6	-61	28	20.1	PCC /preCun
2	39	35	9.3	MFG /vACC
26	7	39	7.9	r. middle frontal
-18	31	36	11.6	l. middle frontal
34	31	32	-6.4	r. middle frontal
-42	35	24	-7.2	l. middle frontal
62	-37	36	-8.0	r. inf. parietal
-58	-41	32	-8.1	l. inf parietal
38	-61	24	8.4	r. sup. /r. mid. temporal
-46	-57	24	10.4	l. sup. /l. mid. temporal
62	3	16	-8.6	r. insula /r. inf. frontal
-34	11	12	-7.7	l. insula/l. inf. frontal
10	3	16	7.3	r. caudate
-10	3	16	4.1	l. caudate

Tab.1: Brain regions correlating significantly (p<0.05) with PC/preCun in controls. Negative t-scores indicate anti-correlation.

Talairach Coordinates				
x	y	z	Max t-score	Brain area
-2	-69	28	16.1	PCC /preCun
-6	47	11	7.8	vMFG /ACC
43	11	32	6.0	r. middle frontal
-22	15	36	8.1	l. middle frontal
38	31	28	-4.8	r. middle frontal
-38	27	28	-5.8	l. middle frontal
62	-41	28	-10.0	r. inf. parietal
-58	-33	28	-8.0	l. inf. parietal
52	-65	32	14.2	r. sup. temporal
-46	-60	19	14.4	l. sup. temporal
39	3	11	-8.5	r. insula /r. inf. frontal
-42	-1	20	-7.7	l. insula /l. inf. frontal

Tab.2: Brain regions correlating significantly (p<0.05) with PC/preCun in patients. Negative t-scores indicate anti-correlation.

Discussion

In our study, we found reduced resting state connectivity between MFG/vACC and PCC/preCun in MS patients independently both in voxel based statistical analysis and also in the ROI analysis. The aforementioned brain regions play a pivotal role in the default mode network, which has been proposed to facilitate or monitor cognitive tasks. In the corresponding n-back fMRI experiment of our study, we did not find any significant performance deterioration in the MS patients. One may therefore speculate that a reduction of default mode network connectivity might be a preclinical manifestation of cognitive impairment. Similar results have been reported on patients with Alzheimer's disease who also show weaker connectivity in the default mode network even in the earliest stages of the disease [6].

References

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