Reduced functional adaptation to working memory tasks with increasing complexity in patients with early stages of relapsing-remitting multiple sclerosis

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Introduction

In multiple sclerosis (MS), cognitive impairments are highly prevalent but often clinically difficult to detect. The most commonly affected abilities are attention, speed of information processing and memory. Impairments in these skills may be reflected in altered and/or reduced functional activation and connectivity [1]. In this ongoing study, we investigate functional differences between patients with early stages of relapsing-remitting MS and controls with respect to a basic attention task and to working memory tasks with increasing complexity. Further, we evaluated if there is any indication of altered resting state connectivity in MS patients.

Methods

Six patients with relapsing-remitting MS (2 female, median age 39, range 30-43; median EDSS 2.5, range 0-3; median disease duration 5 years, range 3-8) and six controls (1 female, median age 35, 27-39) were recruited and participated in this study. Written informed consent was provided before examination and the study was approved by the local ethical committee. To measure attention and working memory performance, the participants performed an alertness task and three N-back tasks with increasing difficulty (1-back, 2-back, and 3-back). Subjects had to react on single-digit numbers which were projected onto a screen mounted at the scanner's bore. Performance was recorded by a response monitor unit. During the first fMRI run, attention was tested with an alertness task. In this task, participants had to press a button if a predefined number appeared in variable intervals. This task was altered with a baseline condition where a fixation cross was presented. Five baseline blocks altered with four task blocks. In the second fMRI run, surveying working memory with the N-back tasks, subjects had to react whenever the current presented number coincides with the number 1, 2, or 3 steps before. In this run, all three N-back tasks were nested, so that five baseline blocks (fixation cross) were altered in random order with four blocks of each N-back task, resulting in overall 17 blocks. In both fMRI runs, each task and baseline block consisted of 15 time frames.

The MR scans were performed on a 3 T head scanner (Magnetom Allegra, Siemens Medical, Germany). One T1w whole brain data set was acquired (MPRAGE, TR/TE/TI/α = 1.9s/3.5ms/0.9s/7°) with an isotropic resolution of 1 mm^3. For the fMRI runs, a T2*w EPI sequence was used (TR/TE/α = 2s/30ms/90°) with an in-plane resolution of 4x4 mm^2. Per volume, 28 slices (3 mm thick, 1 mm gap) parallel to the inferior borders of the corpus callosum were scanned in interleaved order. Resting state functional connectivity MRI (fcMRI) was performed with an adapted EPI sequence (TR/TE/α = 700ms/30ms/30°, slice thickness and orientation as in the fMRI scans). 450 volumes with 11 slices were acquired, with the most inferior slice 4 mm superior to the inferior borders of corpus callosum.

The fMRI and fcMRI data sets were post-processed using AFNI [2]. The post-processing included slice timing and motion correction, spatial smoothing with a Gaussian filter (FWHM = 8 mm), intensity normalization and realignment to the high resolution anatomical volume. For the fMRI runs, statistical maps were created for each subject and for each task by performing a multiple linear regression analysis. The ideal function was a boxcar function convolved with the hemodynamic response. The whole brain signal time course and motion parameters were treated as regressors of no interest. The resulting percent change maps were transformed to Talairach space using the transformation parameters of the anatomical data set.

For the alertness task, group analysis was applied performing a t-test between patients and controls. Data of the N-back tasks underwent a three factor analysis of variance (ANOVA). Group (patient/control) and task difficulty were treated as fixed factors and the subjects as the random factor (AxBxC(A) ANOVA). Following statistical maps were created: first, a main effect map for each task class; second, a contrast map between patients and controls for each task class; and third, contrast maps between the different task classes, separately for patients and controls. All statistical t-maps were thresholded at a corrected significance level of $p<0.01$. For the fcMRI analysis, a seed ROI in the medial frontal gyrus (MFG) was defined by the patient-control contrast found in the 2-back and 3-back tasks. The resting state data set was low-pass filtered in time (cut-off frequency 0.08 Hz) and a correlation analysis was performed to the average signal time course of the MFG [3].

Results

The task main effects showed normal patterns of alertness and working memory functions. Both groups showed increase in functional response parallel to increasing difficulty of the presented tasks, especially in bilateral frontal and pariental areas (Fig. 1). Significant differences between patients and controls were only found in 2-back and 3-back, where patients had higher activation in MFG (Fig. 2). Considerable differences in activation change were found in the contrast of higher to lower demanding working memory tasks (Fig. 3). In controls, the contrast between 3-back and 1-back showed a significant and widely distributed change of activation. By comparison, patients showed only sparse signal increase and no signal decrease was found. The fcMRI analysis revealed no significant difference between patients and controls, although a minor trend ($p_{cor}<0.25$) of decreased connectivity of superior temporal gyrus to MFG was found in patients.

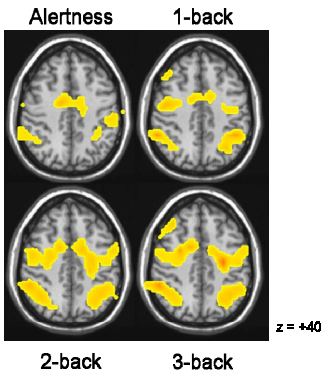

Fig.1: Group main effect for the different tasks (controls, t-scores, $p_{cor}<0.01$).

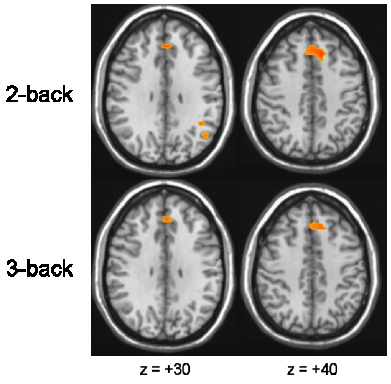

Fig. 2: Group difference between patients and controls ($p_{cor}<0.01$).

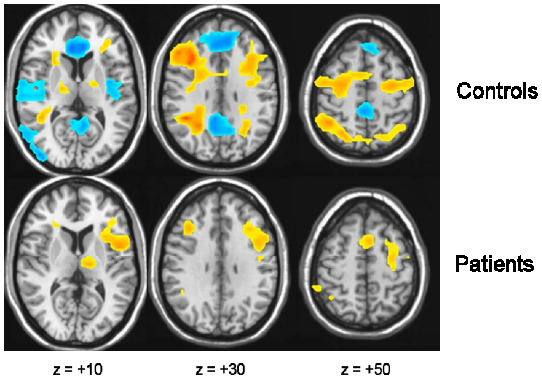

Fig.3: Contrast between 3-back and 1-back task. Yellow to red: signal increase; blue: signal degrease ($p_{cor}<0.01$).

Discussion

Although obtained from a small number of MS patients at this point, our results strongly indicate an altered functional adaptation to higher demanding memory tasks (2-back and 3-back) in patients with early stages of relapsing-remitting MS despite the lack of obvious clinical cognitive impairments. Compared to healthy controls, patients showed significant reduced change of activation parallel to task difficulty. In contrast to these results, fcMRI analysis reveals only a potential difference between patients and controls in regard to resting state connectivity that may need a larger cohort to become apparent.

References

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