Altered Functional Adaptation to Attention and Working Memory Tasks with Increasing Complexity in Relapsing-Remitting Multiple Sclerosis Patients

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Abstract: As attention, processing speed, and working memory seem to be fundamental for a broad range of cognitive performance, the present study on patients with mild forms of relapsing-remitting multiple sclerosis (RR-MS) focused on these domains. To explore subtle neuropsychological changes in either the clinical or fMRI domain, we applied a multistep experimental design with increasing task complexity to investigate global brain activity, functional adaptation, and behavioral responses to typical cognitive processes related to attention and working memory. Fifteen patients with RR-MS (mean age 38 years, 22–49 years, 9 females, mean disease duration 5.9 years (SD = 3.6 years), mean Expanded Disability Status Scale score, 2.3 (SD = 1.3) but without reported cognitive impairment), and 15 age-matched healthy controls (HC; mean age, 34 years, 23–50 years, 6 women) participated. After a comprehensive neuropsychological assessment, participants performed different fMRI experiments testing attention and working memory. In the neuropsychological assessment, patients showed only subtle reduction in learning and memory abilities. In the fMRI experiments, both groups activated the brain areas typically involved in attention and working memory. HC showed a linear increase or decrease in activation paralleling the changing task complexity. Patients showed stronger activation change at the level of the simple tasks and a subsequent saturation effect of (de-)activation at the highest task load. These group/task interaction differences were found in the right parahippocampal cortex and in the middle and medial frontal regions. Our results indicate that, in MS, functional adaptation patterns can be found which precede clinical evidence of apparent cognitive decline. *Hum Brain Mapp* 32:1704–1719, 2011. © 2010 Wiley-Liss, Inc.

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INTRODUCTION

Multiple sclerosis (MS) is a common cause of progressive neurological deficits in young adults [Compston and Coles, 2002]. Besides sensory and motor dysfunctions, cognitive deficits can be very disabling symptoms and affect about 45–65% of MS patients [Rao et al., 1991a]. Subtle cognitive changes may already be present early in MS [Achiron and Barak, 2003; Klonoff et al., 1991; Ruggieri et al., 2003; Schulz et al., 2006]. In contrast to physical

disability, these cognitive disturbances are more difficult to detect in the clinical setting, and the widely applied Expanded Disability Status Scale (EDSS) [Kurtzke, 1983] is not sensitive to cognitive changes. However, selective or global cognitive deficits mostly affecting memory, attention and executive functions, abstract reasoning, problem solving, and visuospatial skills are regularly detected in MS [Arnett et al., 1997; Pelosi et al., 1997; Rao et al., 1991a], whereas intellectual functions and language skills seem to remain broadly preserved [Bobholz and Rao, 2003; Ruggieri et al., 2003]. Once present, cognitive disturbances rarely stay stable and tend to progress in severity and to become more global [Amato et al., 2001] leading to problems in activities of daily living and employment [Rao et al., 1991b]. Although the patterns of cognitive impairment may vary, characteristic features include disturbances of memory and attention [Carroll et al., 1984; Elsass and Zeeberg, 1983; Fischer et al., 1994; Heaton et al., 1985; Rao, 1986; Rao et al., 1991a]. Attention as a basic cognitive function represents an essential premise for conscious perception and higher order cognitive functions and has a high impact on normal everyday functioning. Furthermore, working memory deficits and information processing capacity loss have been reported in MS patients [Kujala et al., 1994; Litvan et al., 1988; Rao et al., 1989] in a large number of studies that ascribe the extensive cognitive impairments in MS to a core deficit in working memory [D'Esposito et al., 1996; Lengenfelder et al., 2003; Pelosi et al., 1997; Rogers and Panegyres, 2007; Ruchkin et al., 1994]. To cope with the requirements of everyday life, working memory is important, as it enables a person to maintain information for a short period of time and to perform complex problem-solving tasks, language comprehension, and reasoning [Baddeley, 1992]. It has moreover been argued that working memory is the first step in encoding new information into long-term storage [Johnson, 1992] and is thus therefore essential for learning.

Several neurofunctional imaging studies support the assumption that the brain already in the early phase of the disease, when cognitive failures are clinically not yet detectable, recruits additional brain areas to compensate for potential cognitive deficits, which are clinically not yet detectable. In a study by Audoin et al. [2003], MS patients with clinically isolated syndrome showed greater activation in the right frontopolar cortex, the right and left lateral frontal cortex, and the right cerebellum while performing a Paced Auditory Serial Addition Test (PASAT). A study by Forn et al. [2006] investigated relapsing-remitting MS (RR-MS) patients with fMRI while they performed the PASAT. Comparable to the study by Audoin et al. [2003], MS patients did not perform worse than controls but showed a more widespread and stronger activation. Additionally, activated regions included the left middle and inferior frontal cortex.

Although the PASAT is an established test for assessing sustained attention, speed of information processing, and working memory, results are sometimes difficult to inter-

pret due to the involvement of different cognitive functions. For this reason, some groups used tasks that were either probing basic attention processes (alertness) or were testing pure working memory. In a study on alertness in mildly impaired MS patients, Penner et al. [2003], for example, found additional activation in a widespread network including the right dorsolateral frontal cortex, the right lateral cerebellum, the right superior temporal gyrus, the left angular gyrus, and the left and right inferior parietal cortex. Testing for working memory, Forn et al. [2007] contrasted an auditory 2-back task versus 0-back and found preserved performance compared to controls but greater activation in the inferior frontal cortex and the insula in MS patients.

All aforementioned studies were testing for group differences in neuronal activation, that is, for signal increase during task performance. In contrast, Raichle et al. [2001] identified a group of brain areas that consistently exhibit decreases from baseline state during a wide variety of goal-directed behaviors. In a study with mild cognitively impaired (MCI) subjects, Celone et al. [2006] found memory-related deactivation in medial and lateral parietal regions with greater deactivation in less pronounced MCI and loss of deactivation in more pronounced MCI.

In this study, we were interested in subtle neurofunctional modifications, represented both in activation and deactivation, in mildly impaired MS patients. We therefore examined patients without reported cognitive impairment and applied a multistep experimental design testing separately attention and working memory with increasing task complexity. With this multistep design, we aimed to investigate neuronal adaptation in the range of task load where deterioration of performance is supposed to occur first.

SUBJECTS AND METHODS

Participants

Patients were recruited from our MS outpatient clinic and healthy controls (HCs) by advertisements in the campus of the University of Basel. All participants gave written informed consent before study entry and underwent a comprehensive neuropsychological examination and an MRI investigation. Additionally, patients underwent a detailed clinical neurological assessment including EDSS scoring by an EDSS certified neurologist (<http://www.neurostatus.net>). Patients with a definite diagnosis of RR-MS according to the McDonald criteria [McDonald et al., 2001] with an upper EDSS limit of 3.5 were included in the study. A total of 16 patients (MS) and 16 age-matched HCs were examined. One of the patients was excluded from further analysis because of an acute relapse; in addition, a HC was excluded due to motion artefacts in the fMRI data. The remaining 15 patients neither had a relapse nor were treated with steroids for a minimum of 1 month preceding the assessment. The study was approved

TABLE I. Between subject effects (adjusted means, $df = 1$, two-tailed, uncorrected P -values)

Neuropsychological Tests and questionnaires	Patients	Controls	Std. error	F	p
Verbal memory					
Digit span forward	7.36	8.44	0.50	2.09	0.160
Long-term storage (SLTS)	58.79	66.41	2.38	4.60	0.041
Consistent recall (SCLTR)	53.96	64.38	3.15	4.92	0.035
Delayed recall (SRTDR)	11.52	11.82	0.26	0.60	0.444
Visual memory					
Blockspan forward	8.86	10.07	0.57	2.03	0.166
Visual short-term storage (SPAT)	23.19	26.14	1.19	2.77	0.108
Delayed recall (SPATDR)	7.70	9.30	0.51	4.48	0.044
Working memory					
Blockspan backward	9.09	9.45	0.44	0.30	0.590
Digit span backward	8.18	8.62	0.55	0.29	0.596
Paced Auditory Serial Addition Test (PASAT)	51.69	53.92	2.39	0.39	0.538
Attention and processing Speed					
SDMT	59.53	69.54	4.37	2.35	0.137
FST 90s	2.10	1.77	0.12	3.69	0.065
FST Total	2.12	1.74	0.13	3.88	0.059
Stroop Part C	19.35	20.41	1.98	0.13	0.723
Trail Making Test Part A	27.27	24.44	2.34	0.66	0.425
Trail Making Test Part B	69.16	53.73	6.18	2.81	0.105
Executive functions					
Verbal fluency	24.35	26.46	1.48	0.91	0.348
Stroop Quotient	1.52	1.44	0.08	0.41	0.527
Trail Making Test Quotient	2.64	2.26	0.24	1.16	0.292
Fatigue					
FSMC Subscore Cognition	29.26	16.07	2.47	12.82	0.001**
FSMC Subscore Motor function	32.11	14.49	2.45	23.22	0.000**
FSMC Total Score	61.37	30.56	4.71	19.18	0.000**
MFIS Subscore Motor function	16.19	2.95	2.41	13.55	0.001**
MFIS Subscore Cognition	13.81	4.39	2.32	7.43	0.011**
MFIS Subscore Psychosocial Fatigue	3.08	0.32	0.42	19.68	0.000**
MFIS Total Score	33.07	7.66	4.93	11.94	0.002**
Depression					
ADS	9.65	5.89	1.67	2.28	0.143
Neuropsychological Screening Questionnaire					
MSNQ self-report	22.49	13.98	1.92	8.86	0.006**
MSNQ informant	17.14	6.99	2.35	8.39	0.007**

**Significant after FDR adjustment ($P < 0.05$).

Digit Span and Block Span are part of the Wechsler Memory Scale Rev. SLTS, SCLTR, SRTDR, SPAT, SPATDR, and PASAT are part of the BRB-N [Härting et al., 2000].

BRB-N, Brief Repeatable Battery of Neuropsychological Tests [Rao, 1990].

SDMT, Symbol Digit Modalities Test [Smith, 1973].

FST, Faces Symbol Test [Scherer et al., 2007].

FSMC, Fatigue Scale for Motorics and Cognition [Penner et al., 2005].

MFIS, Modified Fatigue Impact Scale [Fisk et al. 1994].

ADS, General Depression Scale; german version [Hautzinger and Bailer, 1993].

MSNQ, MS Neuropsychological Questionnaire [Benedict et al., 2003].

Trail Making Test [Reitan, 1958].

by the Ethical Committee of the cantons Basel City and Basel Country.

Comprehensive Neuropsychological Assessment

Both patients and HC underwent a neuropsychological assessment of ~1.5-h duration. The neuropsychological test battery consisted of 10 tests assessing memory, attention,

and executive functions (for details see Table I). Furthermore, the patients completed self-assessment questionnaires for cognitive impairment [Benedict et al., 2003], fatigue [Fisk et al., 1994; Penner et al., 2005, 2009], depression [Hautzinger and Bailer, 1993], and handedness [Oldfield, 1971]. Premorbid verbal IQ was assessed using a multiple-choice vocabulary test [Lehrl et al., 1991].

Functional Imaging

Cognitive tasks

Two cognitive tasks were presented during functional image acquisition. Both were adapted from the test battery for attentional assessment by Zimmermann and Fimm [1992]. Tasks were presented block-wise. To assess basic attentional functions, an alertness task was administered. During this task, the digit “2” was presented visually at varying intervals. Each block contained 12 stimuli to which participants had to react as quickly as possible by button press. Reaction times and omissions were registered. Working memory capacity was assessed using an *n*-back task. Three levels of ascending difficulty and working memory load were administered. In this task, series of pseudo-randomised digits (1–9) were presented continuously on a screen. Participants had to react as fast as possible if the currently shown digit was identical with the last one (1-back task), the second last one (2-back task), or the third last one (3-back task), respectively. One block consisted of 10 stimuli with 20% being targets. Performance of the *n*-back tasks was evaluated registering reaction times as well as the number of omissions and commissions (wrong reactions) as accuracy indicators.

Apparatus

The cognitive tasks were presented using E-Prime for Windows (version 1.1; Psychology Software Tools, Pittsburgh, PA) on a dedicated notebook computer. Stimuli were projected onto a screen installed at the backside of the MR scanner. The participants viewed the screen by means of a mirror attached to the head coil. During functional image acquisition, white digits were presented on a black screen using bold 20-point Arial font. Because of back-projection techniques, the actual size of the digits was larger, but was kept constant for all participants. An MRI compatible key response box was connected to the notebook computer to monitor task performance.

Procedure

Before the fMRI session, the participants were instructed to the alertness and *n*-back tasks and did practice until they felt comfortable with the tasks. The alertness task contained four blocks of stimuli with 12 digits being presented for 500 ms each, separated by five resting blocks. The between-stimulus interval varied in a pseudo-randomized order between 1,200 and 2,800 ms in steps of 200 ms with an average interval of 2,000 ms per block. Block duration was 30 s, alternating with resting blocks of the same length. During resting, block participants had to look at a central white cross, which was presented for 500 ms with a between-stimulus interval of 2,000 ms according to the active blocks. Subsequently, the *n*-back experiment was performed. 1-back, 2-back, and 3-back tasks were pseudo-randomised resulting in four blocks containing each all

three of the *n*-back tasks in variable order. The stimulus duration was 500 ms with a between-stimulus interval of 2,500 ms. Before each *n*-back trial, an instruction about the next task to be performed was given visually. Instruction was presented for 1,500 ms, followed by a break of 500 ms black screen. At the beginning and at the end of the experiment and between each block, a resting block was inserted. As in the alertness task, resting blocks consisted of a central white cross being presented for 500 ms. The between-stimulus interval was 2,500 ms identical to the active blocks. The resting blocks had duration of 30 s; each active block lasted 90 s. To obtain more reliable behavioral data, the *n*-back experiment was repeated in a second run with different randomization of the three levels of difficulty.

Imaging protocol

The MR measurements were performed on a 3.0 T head scanner (Magnetom Allegra, Siemens Medical, Erlangen, Germany) using the manufacturer's circular polarized transmit-receive head coil. After positioning the subjects, the head coil was padded with foam cushions to restrict head motion. For the fMRI runs, a T2*-sensitive gradient-recalled single-shot echo planar imaging (EPI) sequence was used ($TR/TE/\alpha = 2\text{ s}/30\text{ ms}/90^\circ$) with an in-plane resolution of $4 \times 4\text{ mm}^2$. Per volume, 28 slices (3 mm thick, 1 mm gap) parallel to the inferior borders of the corpus callosum were scanned in interleaved order. Before the functional scans, repeated shimming was performed using the manufacturer's advanced 3D shim procedure to yield satisfactory B0 field homogeneity.

During the alertness task, 140 volumes were scanned in 4 min 40 s in each of the two *n*-back runs, 262 volumes were acquired in 8 min 44 s. Before each EPI data acquisition, three dummy volumes were acquired to minimize nonequilibrium T1 effects. In addition to the functional scans, one three-dimensional T1-weighted whole-brain data set was acquired (MPRAGE, $TR/TE/TI/\alpha = 1.9\text{ s}/3.5\text{ ms}/0.9\text{ s}/7^\circ$) with an isotropic resolution of 1 mm^3 (acquisition time: 7 min).

Data Evaluation

Behavioral data

Statistical analyses of behavioral data were computed with the Statistical Package for Social Sciences (SPSS, version 11; SPSS, Chicago, IL). As the IQ scores of the two groups differed significantly (see Table II), IQ was included as a covariate into a univariate analysis of covariance (ANCOVA). The resulting *P* values were controlled for false discovery rate.

Task performance

Reaction times of the fMRI paradigm were compared using a nonparametric test due to distribution

TABLE II. Demographic data, mean (SD)

	Patients		Controls	
Gender (<i>n</i>)				
Males	6		10	
Females	9		5	
Age (years)	37.6	(6.8)	33.9	(7.6)
Education*	3.9	(0.8)	4.8	(0.4)
Verbal IQ	115.7	(11.9)	128.8	(14.8)
Disease duration	5.9	(3.6)	—	
EDSS	2.3	(1.3)	—	

*0, Special School; 1, Primary School; 2, Secondary School; 3, Vocational School; 4, High School; 5, University.

characteristics. Accuracy, omissions, commissions, and outliers were compared in the same way. In the alertness task, accuracy was only dependent on the number of omissions, while in the *n*-back tasks, also the number of commissions reduced accuracy. Data processing of the within-group differences of the *n*-back tasks was done using the Wilcoxon test for dependent samples.

Postprocessing of the E-prime data was done using Microsoft Excel and SPSS. According to Zimmermann and Fimm [1992], reaction times, which lay above a predefined individual threshold (the individual mean across all trials of a task plus 2.35 times the individual standard deviation), were eliminated and marked as outliers.

Functional data

The MRI data evaluation was performed with AFNI [Cox, 1996]. First, all functional data sets were adjusted with respect to slice acquisition time. Each of the three fMRI time series of every subject (one series for the alertness task and two for the *n*-back tasks) were then motion corrected to the mid-volume of the respective series with the routine “3dvolreg” of the AFNI software package. In “3dvolreg,” it is possible to calculate the maximal displacement for brain voxels between original and corrected 3D volume. If an intraserial maximal displacement larger than 2 mm (absolute value) was detected the data of the respective subject were discarded, which was the case in one control. The functional data were then realigned to the individual high-resolution anatomical volume, spatially smoothed with a Gaussian filter (FWHM = 8 mm) and intensity normalized. For each subject and for each task, statistical maps were created by performing a multiple linear regression analysis (MLR). A stimulus response model was obtained by convolving the hemodynamic response function with a rectangular function describing the respective paradigm. In the MLR, the six-motion parameters and the whole-brain signal time course were treated as regressors of no interest. The resulting percent signal change maps were transformed to Talairach space [Talairach and Tournoux, 1988] using the transformation parameters of the respective anatomical volume.

For the alertness task, the intergroup contrast was calculated performing an unpaired *t*-test between patients and HC. Also, main task effect maps were created by contrasting the percent signal change maps of all subjects and in addition separately for HC and patients against the null hypothesis. The data of both *n*-back runs were pooled and underwent a three factor analysis of variance (ANOVA). Group (patients/controls) and task difficulty were treated as fixed factors and the subjects as the random factor. The following statistical maps were calculated for the *n*-back task: first, main effect maps for each task class (1-back, 2-back, and 3-back) over all subjects and separately for controls and patients; second, a contrast map between patients and controls for each task class. Third, we calculated separately for patients and controls, intertask contrast maps (3-back vs. 2-back, 3-back vs. 1-back, and 2-back vs. 1-back); and fourth, a difference map for the group/task interaction was created. The statistical *t*- and *F*-maps were thresholded at a corrected cluster significance level of $P < 0.01$ (single-voxel significance $P < 0.005$), except for the main effect maps over all subjects, which had a higher statistical power and were therefore thresholded at a corrected cluster significance level of $P < 0.001$ (single-voxel significance $P < 0.001$). Both positive and negative stimulus responses were considered.

Based on the group/task interaction map, the average percent signal change of specific brain areas was analyzed for the different *n*-back tasks. Regions of interest (ROI) were located in cortical areas where significant interaction differences were found. For each subject, the averaged percent signal change from baseline was calculated for each ROI and task. Separately for both patients and HC, mean regional percent signal change for each task class was calculated and paired *t*-tests were performed.

RESULTS

Demographic Characteristics

The 15 clinically stable patients were either untreated or treated with immunomodulatory medication (untreated $n = 4$; Interferon Beta 1b, $n = 4$; Interferon Beta 1a, $n = 4$; glatirameracetate, $n = 3$). The patients did not differ significantly in age from the HC. However, HC were higher educated ($P = 0.001$) and had a higher verbal IQ ($P = 0.007$). All controls were right handed; one of the 15 patients was left-handed, but performed the fMRI tasks with the right hand. Another patient preferred to perform the tasks with his left hand because of impaired fine motor skills of the right hand. Further information on demographic characteristics can be found in Table II.

Behavioural Data

In the neuropsychological testing, no significant group differences were found. However, trends toward reduced verbal long-term storage, consistent verbal recall, and

TABLE III. Reaction times in the fMRI-tasks

Paradigm	M (SD)	M (SD)	P value
	Patients (n = 15)	Controls (n = 13)	
Alertness			
Reaction time (ms)	354.3 (36.8)	319.8 (30.3)	0.014
Working memory 1-back			
Reaction time (ms)	488.3 (53.9)	455.0 (75.2)	n.s.
Working memory 2-back			
Reaction time (ms)	525.8 (113.0)	485.5 (112.3)	n.s.
Working memory 3-back			
Reaction time (ms)	593.5 (159.0)	539.2 (124.0)	n.s.

delayed spatial recall were observed in patients. The patients reported significantly higher fatigue scores than HC: FSMC ($F = 19.18$, $P = 0.000$); MFIS ($F = 11.94$, $P = 0.002$). Additionally, the MSNQ self-report score ($F = 8.86$, $P = 0.006$) as well as the informant version ($F = 8.39$, $P = 0.007$) were significantly higher in the patient group than in the control group, indicating more self-perceived neuropsychological impairment in the patient group. Depression scores did not differ between groups. For further information, see Table I.

Task Performance

The reaction times of the fMRI tasks are depicted in Table III. Because of technical problems, the performance data of two HC were lost. In the alertness task, patients had significantly longer reaction times than HC. A post hoc analysis using Spearman's rank correlation revealed a significant correlation between reaction times and FSMC total score ($\rho = 0.54$, $P = 0.004$) as well as between reaction times and both FSMC subscores (motor function: $\rho = 0.56$, $P = 0.002$; cognition $\rho = 0.50$, $P = 0.008$). In general,

patients made more omissions in the alertness task, but did not produce more outliers; details are shown in Table IV. The n -back tasks did not yield any significant group differences concerning reaction times or outliers. In the 2-back task, however, patients made more omissions and accordingly had a significantly lower accuracy than HCs. In the 3-back task, slightly more commissions for the patient group were observed (Table IV). Within-group comparisons of the n -back errors revealed differences in the characteristics of each group (see Fig. 1). Although patients showed a significant increase of the number of omissions from the 1-back to the 2-back task ($Z = -1.983$, $P = 0.047$), the difference between the 2-back and the 3-back task remained nonsignificant ($Z = -1.603$, $P = 0.109$). In HC, different characteristics could be observed. Their number of omissions was relatively stable in the 1-back and 2-back task ($Z = -0.447$, $P = 0.655$). However, in the 3-back task, their performance was worse ($Z = -2.539$, $P = 0.011$) with more omissions. Across both the alertness task and the n -back task, the overall performance level of patients and HC was high. Patients performed above an accuracy level of 97.1%, and HCs had a slightly higher accuracy not falling below 98.1%.

Functional Imaging

Concerning the task main effects, patients and HC showed both very similar activation patterns. In the alertness task, positive signal change in medial frontal areas, in right middle frontal, and in bilateral inferior parietal areas was observed. Negative signal change was observed in posterior cingulate cortex and cuneus and in the ventral anterior cingulate cortex. In the n -back tasks, both groups showed prominent positive signal change in medial frontal cortex and bilaterally in inferior parietal and middle frontal areas. Negative task response was found in the posterior cingulate cortex and in ventromedial areas. In addition, increasing task difficulty was accompanied by

TABLE IV. Error data and accuracy in the fMRI tasks (one-tailed P values)

	Alertness			1-back			2-back			3-back		
	Patients	Controls	P value	Patients	Controls	P value	Patients	Controls	P value	Patients	Controls	P value
Omissions												
Mean	0.800	0.210	0.027	0.200	0.150	n.s.	1.200	0.080	0.021	2.000	1.460	n.s.
Std. deviation	1.082	0.579		0.414	0.555		1.897	0.277		2.035	1.450	
Commissions												
Mean	—	—	—	0.070	0.150	n.s.	0.200	0.080	n.s.	0.330	0.000	0.047
Std. deviation	—	—		0.258	0.376		0.414	0.277		0.724	0.000	
Outliers												
Mean	1.330	1.210	n.s.	0.400	0.230	n.s.	0.600	0.540	n.s.	0.470	0.500	n.s.
Std. deviation	0.724	0.975		0.507	0.439		0.507	0.519		0.516	0.519	
Accuracy												
Mean	98.33	99.55	0.027	99.670	99.596	n.s.	98.250	99.808	0.024	97.083	98.173	n.s.
Std. deviation	2.26	1.21		0.572	0.814		2.535	0.469		3.122	1.813

Figure 1.

Omissions of patients and healthy controls at the different *n*-back tasks. Error bars indicate standard error.

more significant and more extensive activation change. The main task effects for the whole group of subjects are demonstrated in Figure 2 for an exemplary slice, and the areas of significant (de-)activation are listed in more detail in Tables V–VIII. In all four tasks, we found only minor intergroup differences (Fig. 3 and Table IX).

The contrast maps between the *n*-back task classes showed more prominent differences between the two groups. In patients, activation changes occurred mainly between 1-back and 2-back, whereas between 2-back and 3-back, only sparse additional signal in- or decrement was observed (Fig. 4a,b). In contrast, activation changes in HC were more continuous in parallel to the increasing task difficulty (Fig. 5a,b). In the 3-back to 1-back contrast, HC showed a significant signal decrement in medial parietal and occipital areas (Fig. 5c), which remained nonsignificant in patients (Fig. 4c).

Figure 2.

Task main effects for the group of all subjects ($N = 30$), depicting regions of significant change of activation ($P_{\text{cor}} < 0.001$) during the respective task; (a) alertness, (b) 1-back, (c) 2-back, and (d) 3-back. Positive *t*-scores represent positive signal change; negative *t*-scores represent negative signal change. Main effect maps are superimposed onto a Talairach anatomical template in radiological convention (right = left). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE V. Significant fMRI response in the Alertness task

Brain area	Patients				Controls			
	Talairach Coordinates			Max <i>t</i> -score	Talairach Coordinates			Max <i>t</i> -score
	<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>	
Right postcentral	−18	−37	60	−4.5				
Left paracentral	−38	−17	55	7.7	−41	−17	51	10.0
Medial frontal/anterior cingulate	−10	−13	56	8.8	−18	−12	46	13.6
Right inferior parietal	54	−45	40	10.2	55	−41	44	7.0
Left inferior parietal	−46	−37	36	10.4	−50	−29	36	6.9
Right middle frontal	46	23	27	6.8	38	31	24	6.2
Anterior cingulate/medial frontal	−2	47	20	−7.5	−5	40	−8	−5.9
Posterior cingulate/cuneus	6	−61	36	−8.5	−2	−44	20	−10.3
Right superior/middle temporal/hippocampus	62	−17	−8	−6.2				
Left superior/middle temporal/hippocampus					−62	−17	−8	−4.1
Right anterior insula	50	7	8	7.8	46	−5	18	11.5
Left anterior insula	−42	0	3	6.3	−30	19	12	6.5
Left basal ganglia	−18	−17	12	6.6	−26	−5	15	7.6
Cerebellum	6	−57	−16	8.3	2	−73	−16	6.7

Negative *t*-scores mean negative signal change in the Alertness task.

TABLE VI. Significant fMRI response in the 1-back task

Brain area	Patients				Controls			
	Talairach coordinates			Max <i>t</i> -score	Talairach coordinates			Max <i>t</i> -score
	<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>	
Right postcentral	15	-52	64	-6.2				
Right middle frontal	38	-4	51	7.7	34	-9	48	7.5
Left middle frontal	-34	-9	43	6.6	-50	-1	35	8.5
Medial frontal/anterior cingulate	-6	3	47	10.2	10	0	57	9.7
Right superior frontal					26	19	44	-4.8
Left superior frontal	-22	19	48	-6.2	-18	20	40	-6.1
Right inferior parietal	46	-45	44	9.1	42	-52	44	8.0
Left inferior parietal	-38	-45	32	14.0	-46	-49	43	12.2
Right middle frontal	38	36	23	8.8	38	31	27	5.0
Left middle frontal	-34	31	27	5.4	-42	14	33	5.5
Anterior cingulate/medial frontal	-6	43	19	-6.1	-5	31	20	-8.5
Posterior cingulate/cuneus	6	-61	16	-17.0	10	-61	16	-11.0
Right middle/superior temporal	42	-77	23	-6.5	50	-69	20	-7.7
Left middle/superior temporal	-46	-73	24	-7.7	-46	-76	20	-8.6
Right posterior insula					42	-17	20	-8.0
Left posterior insula					-50	-32	17	-7.2
Right anterior insula	34	21	2	9.1	43	7	7	6.0
Left anterior insula	-34	15	12	11.2	-29	16	13	6.6
Right basal ganglia	22	3	15	4.9	18	-17	8	7.6
Left basal ganglia	-18	-8	11	6.2	-25	-1	11	9.4
Right cerebellum	10	-61	-24	7.1	38	-48	-28	6.2
Left cerebellum	-34	-57	-24	6.0	-37	-60	-21	12.8

Negative *t*-scores mean negative signal change in the 1-back task.

TABLE VII. Significant fMRI response in the 2-back task

Brain area	Patients				Controls			
	Talairach Coordinates			Max <i>t</i> -score	Talairach Coordinates			Max <i>t</i> -score
	<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>	
Right postcentral	23	-49	64	-4.7	54	-24	47	-5.8
Right middle frontal	38	-9	46	10.4	30	-9	51	10.8
Left middle frontal	-30	-9	46	9.8	-50	-1	40	8.0
Medial frontal/anterior cingulate	-1	8	44	10.9	3	-5	56	12.5
Right inferior parietal	42	49	38	13.9	38	-53	39	12.0
Left inferior parietal	-42	-49	36	10.9	-29	-69	48	10.7
Right middle frontal	47	28	30	11.2	42	19	31	8.1
Left middle frontal	-33	35	27	6.7	-38	35	27	4.5
Anterior cingulate/medial frontal	10	39	44	-11.1	7	39	17	-7.7
Posterior cingulate/cuneus	6	-53	28	-14.3	14	-57	16	-17.9
Right middle temporal/occipital	39	-81	8	-5.5	22	-80	19	-10.5
Left middle temporal/occipital	-43	-68	24	-8.3	-42	-81	16	-7.8
Right sup. temporal/posterior insula/hippocampus	38	-24	11	-9.0	47	-25	19	-8.0
Left sup. temporal/posterior insula/hippocampus	-34	12	-10	-13.0	-25	-33	-10	-13.5
Right anterior insula	35	15	3	12.0	34	12	7	7.6
Left anterior insula	-29	15	10	13.8	-34	12	7	7.4
Right basal ganglia	15	-4	20	7.9	23	-1	16	8.4
Left basal ganglia	-18	-12	24	9.3	-17	-5	12	7.7
Right cerebellum	30	-53	-28	7.4	42	-53	-28	9.7
Left cerebellum	-34	-56	-25	7.3	-42	-57	-22	8.3

Negative *t*-scores mean negative signal change in the 2-back task.

TABLE VIII. Significant fMRI response in the 3-back task

Brain area	Patients				Controls			
	Talairach coordinates			Max <i>t</i> -score	Talairach coordinates			Max <i>t</i> -score
	<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>	
Right postcentral	23	-49	58	-6.9	22	-46	58	-7.1
Right middle frontal	50	1	38	10.4	31	-4	52	11.4
Left middle frontal	-30	-8	48	11.0	-33	-12	59	8.2
Medial frontal/anterior cingulate	-10	15	36	12.9	11	-1	56	12.3
Right inferior parietal	46	-45	40	15.7	42	-49	40	16.9
Left inferior parietal	-46	-48	39	11.4	-42	-57	47	11.6
Right middle frontal	42	28	28	11.6	47	23	32	9.9
Left middle frontal	-34	36	27	6.8	-42	27	27	5.3
Anterior cingulate/medial frontal	-2	35	0	-11.2	-2	28	11	-8.1
Posterior cingulate/cuneus	-6	-57	28	-12.5	-9	-65	20	-21.3
Right middle temporal/occipital	38	-81	8	-8.3	42	-73	3	-13.7
Left middle temporal/occipital	-46	-69	20	-7.7	-46	-65	24	-8.3
Right sup. temporal/posterior insula/hippocampus	42	-24	11	-8.7	46	-24	20	-12.4
Left sup. temporal/posterior insula/hippocampus	-38	7	-17	-10.5	-26	-37	-8	-15.3
Right anterior insula	35	16	3	10.0	42	8	11	8.6
Left anterior insula	-29	15	7	11.6	-30	11	7	8.3
Right basal ganglia	23	-16	8	7.7	14	-13	7	8.2
Left basal ganglia	-22	-8	19	7.4	-13	-4	8	9.4
Right cerebellum	30	-53	-28	9.0	46	-48	-28	11.1
Left cerebellum	-37	-57	-25	8.2	-42	-60	-20	8.5

Negative *t*-scores mean negative signal change in the 3-back task.

Group/task interaction differences were found in the right parahippocampal cortex, right inferior, and bilateral middle frontal cortex as well as in the medial frontal and anterior cingulate cortex (see Fig. 6 and Table X). The ROI analyses of the respective areas shed more light on these differences (see Fig. 7). In right parahippocampal and right inferior cortex, similar characteristics were observed as in the between-task contrasts: a deactivation saturation effect was detectable in patients but not in HC. This saturation effect was observable for all three working memory tasks in right inferior cortex. However, in right parahippocampal cortex, this effect was only seen at high-task load, and the absolute signal decrease was larger in patients. In the medial frontal and the bilateral middle frontal areas, patients showed signal increase in the 2- and 3-back tasks, whereas HC showed signal decrease for all three task classes.

DISCUSSION

The present study on patients with mild forms of RR-MS was focused on attention, processing speed, and working memory. To explore subtle neuropsychological changes in either the clinical or fMRI domain, we applied a multistep experimental design with increasing task complexity to investigate brain activity, functional adaptation,

Figure 3.

Group differences between patients and controls. Positive *t*-scores represent higher signal in patients, negative *t*-scores represent higher signal in controls ($P_{\text{cor}} < 0.01$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE IX. Significant activation differences between patients ($N = 15$) and controls ($N = 15$)

Task	Talairach Coordinates			Max t -score	Brain area
	x	y	z		
Alertness	-14	-17	44	-4.4	Left supplementary motor
1-back	-34	-5	24	3.8	Left insula/paracentral
	-34	-45	24	4.1	Left inferior parietal
2-back	6	27	40	4.0	Medial frontal
	-18	-85	28	-4.6	Left cuneus
3-back	-6	27	44	3.5	Medial frontal

and behavioral responses in the range of task load where deterioration of performance is supposed to occur.

The results section could raise concerns regarding constitution of the two groups with reference to verbal IQ and gender. We could show that patients differ significantly from HC in education and verbal IQ. However, we do not expect any significant impact onto the fMRI results, as the patients demonstrate an above-average verbal IQ with only one subject with an IQ just below 100 (98) but all within a narrow range of normal distribution. Nevertheless, in the evaluation of the performance data, the IQ was controlled as it was included into the analysis as a covari-

ate. Patients and HC were also not gender-matched, but since our activation paradigm did not contain any lateral specific task (e.g., verbal vs. nonverbal), we also do not expect any gender specific effects.

Evaluating the performance data, we found significantly longer reaction times for patients in the alertness task, but only a weak trend in the n -back tasks. In the alertness task, reaction times in all four active blocks were significantly different between the two groups as were the number of omissions. This suggests an overall reduction of processing speed in our MS patients, which is probably associated with the higher fatigue scores. Surprisingly, this

Figure 4.

Contrast between the different n -back task classes for patients ($N = 15$). First line: 2-back versus 1-back; second line: 3-back versus 2-back, third line: 3-back versus 1-back. Positive t -scores represent positive signal change; negative t -scores represent negative signal change ($P_{\text{cor}} < 0.01$). Please note the relative lack of

functional contrast in line b indicating little change of activation between the 2-back and 3-back tasks (also compare to line b in Fig. 6). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 5.

Contrast between the different *n*-back task classes for healthy controls ($N = 15$). First line: 2-back versus 1-back; second line: 3-back versus 2-back, third line: 3-back versus 1-back. Positive *t*-scores represent positive signal change; negative *t*-scores represent negative signal change ($P_{\text{cor}} < 0.01$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

reduction did not correspond to other neuropsychological outcome measures recorded in our study. Presumably, the alertness task was most sensitive to detect subtle differences between the two groups. One reason for this sensitivity may be of mere statistical nature: in the alertness task,

subjects had to react on 48 valid events, whereas each *n*-back task consisted only of 16 valid events. However, the significantly reduced reaction-time latencies, as expressed in the alertness-reaction, reflect a reduced preparatory stamina in the patient group. This finding is

Figure 6.

Areas of significant differences in group/task interaction (ParaHip, parahippocampal cortex; InfFC, inferior frontal cortex; MidFC, middle frontal cortex; MedFC, medial frontal cortex) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE X. Significant differences in group/task interaction between patients and controls

Talairach Coordinates			Max <i>F</i> -score	Brain area
<i>x</i>	<i>y</i>	<i>z</i>		
−14	15	52	13.5	Medial/superior frontal/anterior cingulate
18	15	52	11.7	Right middle frontal
−30	7	44	12.1	Left middle frontal
58	23	16	11.9	Right inferior frontal
30	3	−12	11.7	Right parahippocampal

further corroborated by behavioral (increased fatigue scores) as well as functional alterations (activation changes in frontal motor-related and inferior parietal areas). These results are in line with earlier findings [Archibald and Fisk, 2000]. This study also showed that patients with secondary-progressive MS had an additional decrement in

working memory capacity, whereas RR-MS patients did not show such memory impairments. The authors speculated that speed of information processing may be slowed early in the disease process, whilst deficits in working memory capacity may appear only later in the course of MS, which is in line with our observations.

Figure 7.

Regional mean percent signal change for areas that show significant differences in the group/task interaction. Error bar depicts standard error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

For both patients and HC, we found increasing bilateral middle frontal and bilateral inferior parietal brain activation in parallel to the increasing task load, indicating that the applied tasks challenged as expected both alertness and working memory. For the attentional task, our results support the assumption of a frontoparietal network underlying sustained attention, as it had been suggested by Büchel and Friston [1997]. For all *n*-back tasks, we found the typical activation pattern for working memory tasks with signal increase in medial frontal areas and bilaterally in inferior parietal and lateral frontal cortex [Cabeza and Nyberg, 2000]. The pattern of signal decrease, including posterior cingulate cortex, cuneus, bilateral superior temporal cortex, and anterior medial regions of frontal cortex was also more pronounced parallel to increasing task difficulty. Its localization is consistent with the “default mode network” first described by Raichle et al. [2001], which has been assumed to be active at rest and to be suspended during cognitive tasks.

In all *n*-back tasks in our study, patients showed similar brain activation patterns compared to HC. The intergroup differences were subtle: patients demonstrated consistently higher positive task response in a part of anterior medial frontal cortex in both the higher demanding 2- and 3-back. The comparison of the task main effect maps of both groups revealed an anterior expansion of signal increase in patients. Similar spatial expansions of either signal increase or decrease could be observed in the left cuneus in 2-back and in left precentral gyrus and left inferior parietal cortex in 1-back. Such spatially expanded or shifted regions of activation had been reported in other fMRI studies in patients with mild forms of MS. These modifications were reported on motor tasks [Rocca et al., 2002], on a visual attention task [Staffen et al., 2002], and also in auditory *n*-back tasks with increasing task load (0-back–2-back) [Wishart et al., 2004]. In the latter work, these shifts in activation were most prominent when working memory demands were high, which parallels our observations. Although not significant in the main intergroup contrasts, we also found evidence for altered activation patterns: In the ROI analysis of medial and middle frontal areas, we found deactivation in HC for all *n*-back tasks, whereas patients demonstrated signal increase at least in the higher demanding tasks.

In contrast to the present study where only minor differences between HC and patients were found, two previous studies detected increased and additional activation of brain areas in cognitively mild disabled MS patients by applying 1-, 2-, and 3-back tasks [Sweet et al., 2006], respectively, a 2-back task alone [Penner et al., 2003]. The respective *n*-back tasks in these experiments were more complex than the task adopted in the current study by either choosing consonants of random case [Sweet et al., 2006] or letters similar in appearance and phonetics (in our previous study), which, in turn, elicited longer mean reaction times for both patients and HC. This higher task

load could at least in part explain the greater activation differences found in both studies mentioned. Another reason for the more prominent activation differences could be the significantly longer mean disease duration of 11.4 years [Penner et al., 2003] and 21.3 years [Sweet et al., 2006] compared to 5.9 years in our actual study. That leads to the speculation that such an altered activation pattern might be a compensation for tissue damage accumulated over time.

Contrasting the functional maps between the different *n*-back task classes, we found stronger activation change (both positive and negative) in patients at the level of the simple working memory tasks and a subsequent saturation effect of activation at the highest task load. HC, however, showed different activation patterns; in this group, the activation change was more linear parallel to task difficulty. This pattern was confirmed by the ROI analysis of right inferior frontal cortex and right parahippocampal gyrus, in which both groups showed deactivation. In MS patients, this may be one possible response pattern to compensate at a functional level for structural damage: simple tasks seem to stay functionally compensated with increased levels of activation or deactivation, which results in a lower capacity for further increase and demonstrate a form of early ceiling effect already at the level of simple task difficulties in MS patients. An exhausted functional reserve [Cader et al., 2006] in turn could lead to a deteriorating task performance. Similar results were found in the study by Penner et al. [2003], in more severely impaired MS patients: they showed reduced activation compared to MS patients with mild impairment. In another fMRI study with subjects performing PASAT, RR-MS patients showed significantly greater brain activation than controls and recruited additional brain areas [Mainiero et al., 2004]. Again in this study, task-related functional changes were more significant in patients whose performance matched that of controls than in patients with a lower performance. Very similar effects were observed by Maruishi et al. [2007] in a study of patients with diffuse axonal injury conducting a Paced Visual Serial Attention Test. Considering our results of a saturation effect of (de-)activation at high task load, one could speculate that the patients in the aforementioned studies with deteriorated performance could be beyond their limit of additional functional compensation. Additionally, in our work, we could demonstrate that not only the working memory circuit but also cortical areas belonging to the default mode network of the brain may show impaired functional reserve in MS patients. Beyond the saturation effect, we found that patients had a larger signal decrease in right parahippocampal cortex at high-task load. This could be an indication of a compensatory higher resting state activation of the parahippocampal cortex in MS to maintain normal brain function.

Our results indicate that not only changes in brain activation patterns occur, but also altered functional

adaptation patterns can be found that precede apparent cognitive decline in MS. Similar observations have been made in CNS neurodegeneration, namely, Alzheimer disease (AD) and its preclinical stages of MCI where some of the activation and adaptive strategies are very similar to those in MS patients [Celone et al., 2006; Greicius et al., 2004]. In fact, our finding that activation changes in patients were only observed at more basic task demands while saturation effects occurred at more complex task levels could reflect a reduced “fine-tuning” due to neuronal rarification within the networks subserving these specific cognitive resources. Given that cognitive functioning requires integration of neuronal subpopulations between networks, these changes in dynamic adaptation might precede structural changes as visualized by altered brain activation patterns. This latter notion is supported by comparative studies using design-based stereology to measure the postmortem volume of neuronal cell bodies in individuals with and without cognitive impairment during lifetime. By using this technology, significant hypertrophy of cell bodies, nuclei, and nucleoli was described in individuals without cognitive impairment though high-neuronal pathology. This finding bears two implications: first, a compensatory enlargement of the cell body could be an adaptive mechanism of neurons to expand their dendritic arborization and postsynaptic structures to warrant neuronal connectivity despite high-lesion load. This assumption is corroborated by some findings showing paradoxical upregulation of presynaptic boutons and presynaptic markers in MCI and AD individuals [Bell et al., 2007]. Second, irreversibly damaged neuronal circuits could induce alternative neuronal networks to become operative based on different stages of disease [Grady et al., 2003; Woodard et al., 1998]. This might help task-related circuits of the cerebral cortex to remain functionally active despite the presence of pathology. In both cases, it is assumed that these compensatory mechanisms (both upregulation and functional adaptation) might be responsible for maintaining effective cognition at the expense of fine tuning. In fact, besides higher scores in both motor and cognitive fatigue subscales and in total scores (FSMC, MFIS) and self-perceived neuropsychological impairment, patients did not show significant differences in the neuropsychological tests.

In conclusion, our observations support the concept of early brain activation changes that allow mitigating the effects of tissue damage in MS patients and compensating cognitive functioning.

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