Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task

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Summary
Mild cognitive impairment has frequently been reported for patients in the early stages of multiple sclerosis. The aim of the present study was to measure whether altered cortical activation during a sustained attention task occurs along with limited extent of neuropsychological problems. Expanded brain activation of multiple sclerosis patients with normal motor function compared with healthy controls during a finger tapping paradigm has previously been reported. Compensatory brain activation in patients with multiple sclerosis compared with normal controls may also be observed when the subjects are performing cognitive functions. In 21 patients with clinically definite relapsing–remitting multiple sclerosis, a psychometric assessment was performed using the Wechsler Memory Scale (WMS) and the Multiple Sclerosis Functional Composite Score (MSFC). In addition, functional MRI was performed during a Paced Visual Serial Addition Task (PVSAT), a visual analogue of the Paced Auditory Serial Addition Task (PASAT). All patients were within 3 years of diagnosis and were not suffering from a relapse at the time of investigation. The multiple sclerosis patients were compared with a control group of 21 healthy volunteers matched for handedness, age, years of education and sex. With regard to psychometric results, the WMS general memory score showed statistically significant differences between patients and controls. We did not find differences for either the MSFC or the PASAT scores. A group analysis of the functional imaging data during the PVSAT revealed different activation patterns for patients compared with control subjects. In healthy volunteers, the main activation was found in the frontal part of the right gyrus cinguli (Brodmann area 32). In patients, the main activation was detected at the right hemispheric frontal cortex (Brodmann areas 6, 8 and 9). In addition, the left hemispheric Brodmann area 39 was activated. We interpret the different patterns of activation, accompanied with intact performance in a sustained attention task of our multiple sclerosis sample compared with healthy controls, as the consequence of compensatory mechanisms. This is an expression of neuronal plasticity during early stages of a chronic disease.

Keywords: fMRI; multiple sclerosis; cognition; brain plasticity

Abbreviations: fMRI = functional MRI; MSFC = Multiple Sclerosis Functional Composite Score; PASAT = Paced Auditory Serial Addition Task; PVSAT = Paced Visual Serial Addition Task; WMS = Wechsler Memory Scale

Introduction
Multiple sclerosis is the most common non-traumatic neurological illness of young adults. It has a progressive course and affects multiple anatomic areas of the central nervous system. After the appearance of neurological symptoms, it is diagnosed by means of cerebrospinal fluid analysis, MRI and evoked potential recordings (Farlow et al., 1986; Paty et al., 1988; Staffen et al., 1993). Diagnosis during the early stages of the disease, when minor symptoms and only mild cognitive impairment occur (Rao et al., 1984, 1986; van den Burg et al., 1987; Gilchrist et al., 1994; Amato et al., 1995), has become important for the effective use of recently developed treatments (Jacobs et al., 1996; Hohlfeld et al., 1997; Achiron et al., 1998).

It is well known that in early stages of multiple sclerosis, patients and healthy controls differ in cognitive test performance. In particular, memory deficits can be demonstrated...
(Rao et al., 1991), whereas attentional processes are less compromised as long as the cognitive load of the attention task remains relatively low (Dujardin et al., 1998).

Before functional MRI (fMRI) was available, conventional MRI data (i.e. plaque volume, plaque localization and brain atrophy) were compared with neuropsychological test scores to relate structural lesions to cognitive function (Rao et al., 1989; Breteler et al., 1994; Comi et al., 1995). In contrast to conventional MRI, fMRI has a sufficient anatomical resolution for the localization of cerebral functions (Rao et al., 1995; Van Oostende et al., 1997; Gelnar et al., 1998; Ogawa et al., 1998; Poldrack et al., 1998; Yousry et al., 1997; Di Salle et al., 1999). Recent research with multiple sclerosis patients reports fMRI activation patterns of the motor and visual system (Kim et al., 1993; Wexler et al., 1997; Yousry et al., 1998; Gareau et al., 1999). In the fMRI study of Reddy et al. (2000), the authors could demonstrate that multiple sclerosis patients with normal motor functions showed increased activation in the ipsilateral sensorimotor cortex during finger tapping compared with healthy controls. They suggested that compensatory cortical adaptive responses account for the limited relationship between conventional MRI measures of lesion burden and clinical measures of disability.

However, since Cabeza et al. (2000) showed that fMRI can also be used for the representation of cognitive functions, we hypothesized that the limited cognitive deficits during the early stages of multiple sclerosis are also accompanied by additional brain activation during task performance. To demonstrate changes in activated cerebral areas, a sustained attention test [Paced Visual Serial Addition Task (PVSAT) Diamond et al., 1997] served as the paradigm during the fMRI measurements. This test requires information processing speed demands, working memory and arithmetic abilities, and thus can be referred as a test of dual processing. The PVSAT does not lead to substantial performance difficulties in either multiple sclerosis patients (in early stages of disease) or healthy controls.

**Patients and methods**

Our sample included 21 patients between the ages of 16 and 43 years (mean 33.5 years, SD = 7.5) who were diagnosed according to the criteria of Poser et al. (1983) and had suffered from definite multiple sclerosis with a relapsing–remitting course for <3 years. They were compared with 21 healthy volunteers who were matched according to handedness, age, years of education and sex. The volunteers were between 20 and 45 years of age (mean 31.8 years, SD = 7.4). All subjects signed a written consent form.

All patients were assessed using the expanded disability status scale (EDSS) developed by Kurtzke (1983). Before functional neuroimaging, all subjects were inter-

in a summary score, and additionally with the specific Multiple Sclerosis Functional Composite Scale (MSFC; Fischer et al., 1999), with the Paced Auditory Serial Addition Task (PASAT; Gronwall and Sampson, 1974; Gronwall, 1977) as an integral part. The MSFC is an outcome measure for multiple sclerosis clinical trials and assesses the dimensions ambulation/leg function, arm/hand function and cognition. A PASAT-version as the cognitive test part included the acoustic presentation of 60 randomized numbers between one and nine. The subject is asked to add each presented number to the previous one. We performed a 3 s paradigm (a new stimulus was presented every 3 s, one trial) and used the total number of correct answers as the test score. The test assesses several neuropsychological functions aside from sustained attention including speed of information processing, speed of information retrieval from memory stores, working memory and dual processing.

Conventional MRI [axial FLAIR T2 weighted slices, TE (echo time) = 80 ms, TR (repetition time) = 6000 ms] was performed for all patients. As with PASAT procedures, an equivalent visual version of a PVSAT served as attention paradigm for the fMRI examination. During the activation phase, arabic digits (black numbers on a white background) were presented via a projection mirror system for 1 s. There was a 2 s break after each number. The presentation size guaranteed good readability for all participants. Subjects had to look at the screen and add the presented digit to the previous one. They were instructed to calculate, but not to spell the numbers or results. During the rest condition, subjects were instructed to fixate on the empty screen in a relaxed state.

All experiments were performed on a 1.5 T whole body scanner (Gyrosan ACS-NT Powertrak 6000, Philips, Best, The Netherlands) with an echo-planar capable gradient system (rise time 200 μs, 23 mT/ms) and a circular polarized head coil [FOV (field of view) = 250 mm]. For fMRI, we employed T2*-weighted gradient-echo sequences [PRESTO, TR = 48 ms, TE = 56 ms, matrix = 128 × 128, voxel dimension = 1.8 × 1.8 × 3.5 mm, DF (degrees of freedom) = 0]. We acquired 15 slices parallel to the bicommissural plane, with a slice thickness of 3.5 mm. Previous studies (Posner et al., 1990; Fletcher et al., 1995; Pauls et al., 1996) revealed that attention and working memory processes show significant brain activation in the cingulate cortex. Therefore, we selected the supratentorial area for our investigation: alternating series of 10 images during the performance (A) of the sustained attention task (PVSAT) (three blocks); and 10 images during resting (B) (three blocks) were acquired (ABABAB). The temporal resolution was 5 s and up to 60 images were taken in 300 s.

Image analysis was performed offline on a Compaq workstation (Compaq Computer Cooperation, Houston, TX, USA) using Matlab (Version 5.3) (The Mathworks inc) and statistical parametrical mapping (SPM99/Wellcome Department of Neurology, Institute of Neurology, London). Sixty volume images were realigned automatically to the first
image of the time series to correct for head movements. The functional data sets from each subject were smoothed (6 × 6 × 6 mm) to a small extent using a Gaussian filter and normalized. The alternating periods of rest and activation were modelled using a simple fixed response (box car) wave reference vector in order to take the delayed cerebral blood flow changes after the stimulus into account. Significantly activated voxels were identified by using the ‘General Linear Model’ approach for time-series data (Friston et al., 1995a, b, c). For this, we defined a design matrix that contrasts the test for significant activations during the PVSAT-activities versus resting. Significant activation of voxels was identified by calculating individual analysis for each single subject and a random effects group analysis (one-tailed t-test) within multiple sclerosis patients and within controls. The activated voxels surviving this procedure were superimposed on a functional mean image. The anatomical location of the activated foci was identified with the aid of the atlas of the human brain produced by Talairach and Tournoux (1988).

According to the results of the random effects analysis, regions of interest were defined in Brodmann areas 6, 8, 9, 32 (right hemispheric) and 39 (left hemispheric). For individual statistical comparison between patients and controls, a single subject analysis was performed using SPM. Activated voxels were counted in regions of interest (P = 0.01; threshold cluster size 20).

Statistical group comparisons were computed with SPSS 10.0 (SPSS Inc., Chicago, Ill., USA) by using the $\chi^2$ test for nominal data and non-parametric analysis [Mann–Whitney U-test (two-tailed) for ordinal data] due to the variability of the data.

Results
The conventional MRI data showed small plaque volumes for all patients and singular plaques in the white matter of the frontal lobe in 33% of the patients. Expanded disability status scale scores for the multiple sclerosis patients did not exceed 2.5 (median = 1.5, range = 0–2.5).

Behavioural data
Both the MSFC scores and PASAT scores of patients and healthy controls were not significantly different. With respect to memory, multiple sclerosis patients scored significantly lower on the WMS ($P = 0.001$) as well as on sub-tests of logical memory ($P = 0.028^*$), digit span ($P = 0.019$) and visual reproduction ($P = 0.005$) (see Table 1).

Neuroimaging data
Random effects group analysis in controls and patients
In control subjects, significant activation (cluster size: K = 77, $P = 0.01$) was seen in the anterior part of the right gyrus cinguli (Brodmann area 32) ($Z = 5.05$) during the PVSAT (Fig. 1). In contrast, patients showed activated regions in Brodmann areas 6, 8 and 9 (right hemispheric) ($Z = 4.07$) and 39 (left hemispheric) ($Z = 4.3$) during PVSAT (Fig. 2). The results of statistical group comparison following single subject analysis (cluster size: K = 20, $P = 0.01$) are shown in Table 2. With the exception of Brodmann area 8, significant differences between the two samples could be shown for all activated areas.

Discussion
The multiple sclerosis-specific MSFC did not show any significant differences between our patients suffering from recently diagnosed remitting–relapsing multiple sclerosis and a control group matched for age, sex and years of education. The PASAT-version performed as an integrated part of the MSFC did not differentiate between the two groups. This finding is in agreement with the results of Fisk et al. (2001),

### Table 1 Patient and control characteristics and results in neurological and cognitive scales

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>Z-score</th>
<th>Significance (U-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (females/males)</td>
<td>21 (13/8)</td>
<td>21 (14/7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>33.5 (7.5)</td>
<td>31.8 (7.4)</td>
<td>−0.958</td>
<td>0.34</td>
</tr>
<tr>
<td>MSFC, median (range)</td>
<td>0.24 (3.1)</td>
<td>0.21 (2.7)</td>
<td>−0.149</td>
<td>0.882</td>
</tr>
<tr>
<td>PASAT (Z-score)</td>
<td>0.031 (1.04)</td>
<td>−0.027 (1.07)</td>
<td>−0.095</td>
<td>0.924</td>
</tr>
<tr>
<td>WMS-subtests, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>information</td>
<td>4.9 (1.1)</td>
<td>5.4 (0.7)</td>
<td>−1.46</td>
<td>0.146</td>
</tr>
<tr>
<td>orientation</td>
<td>4.9 (0.3)</td>
<td>5 (0)</td>
<td>−1.432</td>
<td>0.152</td>
</tr>
<tr>
<td>mental control</td>
<td>8.1 (1.2)</td>
<td>8.5 (0.8)</td>
<td>−0.915</td>
<td>0.36</td>
</tr>
<tr>
<td>logical memory</td>
<td>9.9 (3.3)</td>
<td>12.3 (3.1)</td>
<td>−2.193</td>
<td>0.028*</td>
</tr>
<tr>
<td>digit span</td>
<td>10.1 (2.3)</td>
<td>11.7 (1.6)</td>
<td>−2.354</td>
<td>0.019*</td>
</tr>
<tr>
<td>visual reproduction</td>
<td>8.5 (3.8)</td>
<td>11.5 (2.2)</td>
<td>−2.825</td>
<td>0.005*</td>
</tr>
<tr>
<td>associative learning</td>
<td>15.7 (3.5)</td>
<td>17.5 (3.2)</td>
<td>−1.743</td>
<td>0.081</td>
</tr>
<tr>
<td>general memory score</td>
<td>62.5 (10.9)</td>
<td>71.9 (5.9)</td>
<td>−3.183</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Asymptotic significance (two-tailed, corrected for ties), significance level: *$P < 0.05$; **$P < 0.01$. 

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who described a similar group of 20 patients with remitting–relapsing multiple sclerosis. Fisk et al. (2001) could not find

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**Fig. 1** Controls: activation in the anterior part of right gyrus cinguli (Brodmann area 32) during PVSAT.

**Fig. 2** PVSAT activation pattern in the multiple sclerosis patients group: Brodmann area 6, 8 and 9 in the right hemisphere, area 39 in the left hemisphere.
differences between these patients and healthy controls with respect to the given correct answers in the PASAT.

We found significant differences in memory abilities, measured by WMS general memory score and WMS sub-tests of logical memory, digit span and visual reproduction. These findings correspond with the results of a meta analysis of 36 studies investigating the memory deficits of multiple sclerosis patients carried out by Thornton et al. (1997). Their analysis suggests a global memory disorder with indices for short-term memory, working memory (in particular the simultaneous retention and internalization of information) and long-term memory of multiple sclerosis patients differing significantly from those of the controls. Although PASAT and PVSAT (as well as digit span scores) require working memory abilities (Fos et al., 2000), DeLuca et al. (1993) failed to find high correlations between PASAT and digit span scores. The higher memory load during digit span tasks (up to nine units) compared with the PASAT memory demands (two units) could serve as explanation for the differences described above. Fisk et al. (2001) claim that a chunking strategy (building comprehensive units of information for lowering mental effort) may be common in the PASAT (particularly as task demands increase) and that this may mask actual performance differences.

Combining functional imaging with psychological tests offers new insights for the understanding of chronic diseases such as multiple sclerosis. Motor, visual and language systems (Kim et al., 1993; Rao et al., 1995; Wexler et al., 1997; Gareau et al., 1999) as well as cognitive abilities (Spitzer et al., 1995; Le Bihan et al., 1997; Courtney et al., 1997; Rao et al., 1997; Beason-Held et al., 1998; Clark et al., 1998; Carpenter et al., 1999; Chee et al., 1999; Peterson et al., 1999; Cabeza et al., 2000) have been recently analysed. Our PVSAT paradigm requires intact capabilities for information processing and sustained attention (i.e. simultaneous focusing on more stimuli or actions). In addition to visual information processing, it engages number recognition, attention based on working memory and the recall of semantic information (additive associations).

One could argue that the PASAT performance which we measured during behavioural testing is not indicative for PVSAT performance during functional imaging, but Fos et al. (2000) showed that the PVSAT was easier to perform than the PASAT in healthy subjects and attribute the lower difficulty level of the PVSAT compared with the PASAT to the reduction of interference between output and input modalities. Diamond et al. (1997) found that patients with multiple sclerosis performed PVSAT better than PASAT. If patients do not show difficulties performing the more difficult task, we do not expect group differences for performing the easier version of the task; this approach was used during the fMRI measurements.

Control subjects showed a significant activation in Brodmann area 32 (right hemisphere) during PVSAT. This can be interpreted as related to attentional demands according to the importance of Brodmann area 32 for problem solving (Bush et al., 2000; Cabeza et al., 2000; Duncan et al., 2000; Menon et al., 2001) and attention focusing during the processing of an arithmetical task (Posner et al., 1990). This suggests that solving a simple addition problem is primarily associated with heightened attention in healthy subjects.

In contrast, the multiple sclerosis patient group showed significant activation in Brodmann area 39 (left hemisphere) and the prefrontal regions 6, 8, 9 (right hemisphere). The left hemispheric area 39 is involved in the perception of written language, recognition of printed symbols and later recall of them as well as in problem solving. Damage may cause acalculia (Goldberg et al., 1998; Dehaene, 2000).

Brodmann area 6 usually is activated during decision processes based on working memory referring to verbal or numeric stimuli as well as during the construction of motoric concepts, attention focusing and sustained attention (Coulou et al., 1996).

Oculomotoric function and attention for visual stimuli have been localized to Brodmann area 8 while Brodmann area 9 has been shown to be typically involved in working memory tasks (Passingham, 1997), in tasks of sustained attention and (bilaterally) in tasks demanding problem solving (Cabeza et al., 2000).

Working memory, providing executive control and active maintenance during problem solving have an important role as a component of our attention paradigm (PVSAT). This activation pattern agrees with the regions exhibiting significant activity during the sequential-letter working memory task performed by Cohen et al. (1997). We interpret this pattern of activation of our multiple sclerosis patient sample as an expression of assumed higher requirements of attention.

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### Table 2 Differences of activation of specific Brodmann areas for patients and controls

<table>
<thead>
<tr>
<th>Brodmann area</th>
<th>Patients mean rank</th>
<th>Controls mean rank</th>
<th>Z-score</th>
<th>Significance (U-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>18.83</td>
<td>12.17</td>
<td>-2.144</td>
<td>0.032*</td>
</tr>
<tr>
<td>8</td>
<td>17.17</td>
<td>13.83</td>
<td>-1.333</td>
<td>0.183</td>
</tr>
<tr>
<td>9</td>
<td>18.87</td>
<td>12.12</td>
<td>-2.17</td>
<td>0.03*</td>
</tr>
<tr>
<td>39</td>
<td>19.07</td>
<td>11.93</td>
<td>-2.415</td>
<td>0.016*</td>
</tr>
<tr>
<td>32</td>
<td>11.63</td>
<td>19.37</td>
<td>-2.541</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

Asymptotic significance (two-tailed, corrected for ties), significance level: *P < 0.05.
and working memory for PVSAT solving for our patients in comparison with the normal sustained attention and dual processing function shown by the controls. Therefore, these measurable consequences of cerebral pathology seem to be indicative of a mechanism to preserve or compensate specific functions. In our case, the recruited areas have a functional connection as integrated parts of the systems of error processing, response inhibition and competition (Menon et al., 2001).

As an additional explanation, one could interpret the brain activation in the frontal lobe as a consequence of shifting the activated area to cerebral tissues adjacent to those activated in controls. This altered brain function occurred, although the psychometrically assessed attention capacity (PASAT) did not differ significantly between patients and controls. Similar relocalization has been reported in stroke patients using PET and fMRI (Cramer et al., 1997; Cao et al., 1998, 1999; Karbe et al., 1998, 1999; Carpenter et al., 1999). Adaptive modifications of motoric areas have recently been described in multiple sclerosis patients (Reddy et al., 2000).

The widespread differences in cerebral activation in our sample of multiple sclerosis patients compared with control subjects suggest that their cerebral efforts are raised when solving cognitive problems. This may be a consequence of their relatively reduced working-memory capacity as revealed by reduced WMS scores.

In conclusion, we interpret the different patterns of activation that accompany intact performance in a sustained attention and dual processing task of a multiple sclerosis sample compared with healthy controls as the consequence of compensatory mechanisms (Weiller et al., 1993; Witte, 1998; Lee et al., 2000)

These findings provide further evidence for the adaptive capacity of neuronal systems and the plasticity of the brain during early stages of multiple sclerosis.

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Received May 31, 2001. Revised November 5, 2001. Accepted January 10, 2002