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Brain reorganization during attention and memory tasks in multiple sclerosis: Insights from functional MRI studies

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Abstract

Deficits in memory and attention frequently occur during the course of multiple sclerosis (MS). In patients with MS the severity of cognitive manifestations is not closely related to indices of structural brain damage on both conventional and non conventional magnetic resonance imaging (MRI). It is conceivable that the ability of the brain to compensate for tissue impairment or loss may contribute to the maintenance of normal performance despite scattered brain lesions. Accordingly, using functional MRI (fMRI), patients with multiple sclerosis showed a greater extent of brain activation during motors tasks than controls. Changes in functional organization of the cerebral cortex have also been reported by fMRI studies comparing the activation patterns during cognitive tasks in patients with MS and in healthy subjects. Differences in patients' selection, activation paradigm, experimental design and MR acquisition parameters make, however, the results obtained from fMRI studies difficult to be compared and may explain, at least partially, some discrepant findings. Nevertheless, fMRI studies provide a new interesting way of understanding how the brain can change its functional organization in response to MS pathology, and might be useful in the study of the effects of either rehabilitation or pharmacological agents on brain plasticity.

Keywords: Functional MRI; Neuroplasticity; Multiple sclerosis; Cognitive impairment; Memory; Attention

1. Introduction

Cognitive dysfunction is a frequent finding in patients with MS [1–3]. Deficits in memory, attention, and speed of information processing are typical, and about 30% to 70% of patients experience impairment in these cognitive domains during the course of the disease [2,4]. Cognitive impairment may be present in the earliest stages of MS, even in the absence of clinical disability [5,6].

Several studies have shown that the extent and severity of the macroscopic and microscopic brain changes seen on conventional and non-conventional MRI are related to neuropsychologic measures of cognitive performance in MS [7–11]. The correlation, however, is far from perfect, and the pathological mechanisms underlying cognitive dysfunction in MS are still largely unexplained. One explanation for the weak relationship between neuropsychological deficits and conventional measures of disease burden in MS is that neuroplasticity, the ability of the brain to respond to various insults, allows adaptive reorganization of cognitive functions to limit impairment, despite widespread tissue damage.

Blood oxygenation level dependent (BOLD) fMRI is a technique with relatively high spatial and temporal resolution that allows noninvasive mapping of brain activity related to specific cognitive tasks. fMRI has made possible the identification of large-scale activation patterns associated with higher-order cognitive processes in healthy subjects [12], as well as the monitoring of functional

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reorganization and its response to therapeutic interventions in different patients' populations, including patients with MS [13,14].

fMRI studies on motor function in MS have showed a strong correlation between the extent of changes in fMRI activation and the MRI lesion burden, suggesting that functional changes in cortical and subcortical motor-related areas can limit impairment secondary to brain damage in MS [15–18]. It has been shown, however, that there is a distinct effect of clinical disability and cerebral injury burden on changes in the patterns of movement-associated brain activation in patients with MS [17].

Here, we provide an up-to-date review of the main fMRI studies on patients with MS during tasks requiring memory and attention, with the purpose to show how the findings emerging from these studies are changing our view on the ability of the central nervous system to adapt to irreversible structural tissue damage.

2. Memory

Memory is one of the most consistently impaired cognitive function in MS. Patients with MS may show impairments across all memory domains [19]. Dysfunction during tasks involving working-memory is commonly observed while short-term memory remains mostly unimpaired. Long-term memory impairment is also frequently observed if spontaneous and free recall is required. Recognition memory is normal or less impaired than free recall. Some authors consider this special pattern in memory deficits in MS patients as evidence that their encoding of information is unimpaired, but that they have problems in retrieving the stored information. However, MS patients may also show deficits in learning [20].

Most of the fMRI studies during cognitive tasks in patients with MS have focused on working memory. According to Baddeley's model [21,22], working memory consists of three main components: a phonological loop for the maintenance of verbal information, a visuospatial sketchpad for the maintenance of visuospatial information, and a central executive for attentional control. Working memory abilities in MS are often evaluated in the clinical setting using the Paced Auditory Serial Addition Task (PASAT), a test that also requires sustained attention and information processing speed [23]. During the PASAT subjects are required to add up auditorily presented randomized single digits, adding each digit to the one immediately preceding it. Each new stimulus is typically presented every 3 or 2 s.

During execution of the Paced Visual Serial Addition Task (PVSAT), a visual analogue of the PASAT, 21 patients with early relapsing–remitting (RR) MS exhibited different activation patterns compared to a group of sex-, age-, and education-matched 21 healthy controls [24]. Task performance during fMRI was not assessed, but patients did not show any clinical evidence of cognitive dysfunction at neuropsychological evaluation. In healthy controls the main activation was found in the frontal part of the right anterior gyrus cinguli (Brodmann area, BA 32). In patients the main activation was detected at the right hemispheric frontal cortex (BA 6, 8, 9). Patients additionally activated the left BA 39. The authors interpreted their findings as expression of cortical plasticity during the early stages of a chronic disease.

We [25], using a modified version of the PASAT, studied during fMRI 22 RRMS patients with no or only mild cognitive impairment as assessed by the Rao's Brief Repeatable Battery [26] and 22 sex-, age-, and education-matched healthy controls. Neuropsychological testing showed that, of the 22 patients, only four had no cognitive dysfunction compared with healthy controls; 11 exhibited deficits in both memory and attention; five had an isolated impairment in memory; and two had an isolated deficit in attention. fMRI showed that, although the overall pattern of activation in patients with MS during the PASAT resembled that observed in the control group and reported by previous research on healthy subjects, patients with MS activated larger brain areas located in the bilateral prefrontal and inferior parietal cortex, in the bilateral but mainly right temporal cortex, and additional foci in the supplementary motor area (SMA) and anterior cingulate of the right hemisphere (Fig. 1AB). When the 22 patients were subgrouped according to their performance at the PASAT during fMRI, activation of the aforementioned areas in the frontal, parietal, and temporal areas of both hemispheres markedly increased in the 12 patients whose performance matched that of healthy subjects (Fig. 1B1). In the remaining 10 patients, who had lower scores than healthy subjects, this increased activation was less significant (Fig. 1B2). The same patients also underwent fMRI during a recall task of unrelated pairs of words, a task that typically engages the prefrontal, frontal–insular, temporal (mainly medial) parietal, anterior cingulate and cerebellar regions [12, 27]. Activation in the prefrontal cortex tended to be more extensive and less lateralized in patients than in controls (Fig. 2AB). Patients showed significantly greater brain activation in the bilateral middle and superior temporal cortex, and activation of additional foci were in the right lateral premotor cortex (PMC), left thalamus and in the bilateral basal ganglia. As for the PASAT, patients whose performance did not match that of healthy controls during the recall task at fMRI, showed less extensive brain activation (Fig. 2B1,B2). Moreover, we found that activation in the bilateral prefrontal cortex, left temporal cortex, right PMC and parietal cortex during execution of the PASAT, whereas activation in the prefrontal, parietal and temporal cortex bilaterally, and in the left PMC during the recall task, positively correlated with total lesion burden as assessed by T_2 lesion load. Interestingly, in our study, the brain areas significantly more activated in patients than in controls during both the PASAT and the recall task only