

Functional MRI in investigating cognitive impairment in multiple sclerosis

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There is increasing evidence that the severity of the clinical manifestations of multiple sclerosis (MS) does not simply result from the extent of tissue destruction, but it rather represents a complex balance between tissue damage, tissue repair, and cortical reorganization. Functional magnetic resonance imaging (fMRI) provides information about the plasticity of the human brain. Therefore, it has the potential to provide important pieces of information about brain reorganization following MS-related structural damage. When investigating cognitive systems, fMRI changes have been described in virtually all patients with MS and different clinical phenotypes. These functional changes have been related to the extent of brain damage within and outside T2-visible lesions as well as to the involvement of specific central nervous system structures. It has also been suggested that a maladaptive recruitment of specific brain regions might be associated with the appearance of clinical symptoms in MS, such as fatigue and cognitive impairment. fMRI studies from clinically (and cognitively) impaired MS patients may be influenced by different task performances between patients and controls. As a consequence, new strategies have been introduced to assess the role, if any, of brain reorganization in severely impaired patients, including the analysis of resting-state networks. The enhancement of any beneficial effects of this brain adaptive plasticity should be considered as a potential target of therapy for MS.

KEYWORDS

multiple sclerosis, functional mri, cognitive impairment, plasticity, adaptation, maladaptation

1. | INTRODUCTION

Cognitive impairment occurs in 40%–70% of patients with multiple sclerosis (MS), and it is known to have a significant impact on the quality of life. Most frequently cognitive impairment in MS presents as impaired information processing speed, as well as impaired immediate and delayed recall or memory.^{1,2} Verbal fluency and executive function can also be involved.³

Over the past decade, magnetic resonance imaging (MRI) has demonstrated a valuable role for investigating MS pathophysiology in vivo and monitoring disease evolution.⁴ The application of functional MRI (fMRI) has led to the exploration of the role of brain plasticity and functional reorganization in contrasting cognitive dysfunction in MS.^{5,6}

This report summarizes the major contributions of fMRI in exploring brain plasticity mechanisms and in individuating adaptive or maladaptive changes underlying cognitive functioning in MS. In addition, examples of fMRI application as a tool in monitoring treatment response are provided.

2. | ACTIVE COGNITIVE TASKS

Several fMRI studies have adopted active paradigms in order to investigate the patterns of recruitment of the principal cognitive networks in patients with MS. Working memory has been the most extensively studied domain by means of the Paced Auditory Serial Addition Test (PASAT) or the Paced Visual Serial Addition Task.^{7–13} In patients with

a clinically isolated syndrome (CIS) suggestive of MS, an altered pattern of cortical activations has been described during PASAT performance, confirming the presence of cortical reorganization at the earliest clinical stage of disease.¹⁰ An increased recruitment of several cortical areas during PASAT has also been shown in patients with relapsing-remitting (RR) MS and mild cognitive impairment,¹¹ suggesting that an impaired cognitive task performance in these patients could reflect a decreased function of canonical task-specific areas in the absence of adequate compensatory strategies.

Using a 3-T scanner, more significant activations of several areas of cognitive network involved in Stroop test performance have been demonstrated in cognitively preserved (CP) patients with benign (B) MS when compared to matched healthy controls (HC).¹⁴ Patients with BMS also showed an increased connectivity between several cortical areas of the sensorimotor network with right inferior frontal gyrus and cerebellum, as well as a decreased connectivity between other areas, including the left secondary sensorimotor, prefrontal cortices, and right cerebellum, with anterior cingulate cortex. These results suggest an altered interhemispheric balance in favor of right hemisphere recruitment in patients with BMS.

3. | CORRELATIONS BETWEEN BRAIN FUNCTIONAL REORGANIZATION AND STRUCTURAL DAMAGE

In addition to an abnormal pattern of functional activations, the majority of previous studies described the variable relationships between fMRI abnormalities and several measures of tissue damage.^{8,11,15–22} An increased recruitment of several brain areas with increasing T2 lesion volume (LV) has been shown in patients with RRMS^{9,11,23} and primary progressive (PP) MS. Also, the severity of intrinsic T2 lesion damage, measured using T1-weighted images,²⁴ magnetization transfer (MT), and diffusion tensor (DT) MRI,¹⁹ has been found to modulate the activity of some brain areas.

The severity of normal appearing brain tissue (NABT) injury, measured using proton MR spectroscopy,¹⁸ MT MRI,^{8,15,19,21} and DT MRI,^{15,18} is another important factor associated with an increased recruitment of motor- and cognitive-related brain regions. A seminal study²¹ found significant correlations between functional activation in the lateral prefrontal cortices during PASAT execution in patients with CIS and the severity of NABT damage, quantified using MT MRI. By combining fMRI with DT MRI tractography, other authors^{14,25} found a relationship between structural damage to strategic WM tracts, such as the superior longitudinal fasciculus (SLF), and a more bilateral pattern of fMRI recruitment during the performance of a cognitive task.

4. | ADAPTIVE AND/OR MALADAPTIVE FUNCTIONAL REORGANIZATION

The results from several studies suggest that an increased cortical recruitment might not always be beneficial for patients with MS,

representing, in some cases, a maladaptive phenomenon. A study²⁶ including 14 cognitively impaired (CI) MS patients and seven HC, undergoing three different cognitive tasks (tonic alertness, focusing attention, and working memory), showed that CP MS patients had a higher recruitment of frontal lobe regions, while CI MS patients had a higher recruitment of posterior brain regions, individuating in functional integration of the frontal and parietal associative areas and in the involvement of multimodal cortical structures, a compensatory mechanism to contrast cognitive impairment. Rocca et al.²⁷ performed a fMRI study of verbal working memory in patients with PPMS showing the decreased activation of prefrontal cortex and the increased recruitment of cerebellum, insula, and secondary sensorimotor cortex in CI MS patients. In consideration of the correlations found between the pattern detected with fMRI and brain tissue damage, the over-recruitment detected in CI MS was interpreted as a maladaptive response related to severe tissue injury.

When interpreting the data on cognitive impairment, results from studies on patients performing active tasks can be biased by the patients' ability to match task performance with HC. This can be overcome by analyzing connectivity within the resting-state network (RSN), particularly in CI or clinically disabled populations.

The analysis of brain RS functional connectivity (FC) has shown increased FC of the majority of RSNs in patients with CIS,²⁸ including the default-mode network (DMN) and sensorimotor network. These changes were found in the absence of cognitive impairment and are likely to reflect the recruitment of reserve capacity to compensate for structural damage. Consistent with the hypothesis of an early but finite reorganization process, RS FC modifications were not found in patients with RRMS in whom cognitive impairment was indeed present.

Better cognitive performance in patients with MS has been associated with increased FC among several regions of the attention network, thus supporting the adaptive role of RS FC modifications.²⁹ In CI MS patients, other authors have described a reduced RS FC of anterior regions of the brain, mostly located in the frontal lobes,^{30,31} which was related not only to the severity of cognitive impairment, but also to structural disruption of connecting cognitive-related WM tracts.³⁰

It is worth mentioning that findings from other studies^{32–34} seem to contradict the adaptive/compensation hypothesis because a correlation between increased RS FC and worse cognitive performance was found. A recent study³⁵ conducted in patients with RRMS explored the integrity of principal brain RSNs showing a distributed and complex pattern of RS FC abnormalities. This was characterized by the co-presence of regions with increased and decreased RS FC, which was correlated with T2 LV and the severity of disability. Another study³⁰ of patients with progressive MS (PPMS and secondary progressive [SP] MS), in whom fMRI results with active tasks would inevitably be lacking in information, explored the clinical relevance of DMN abnormalities. A reduction in RS FC in several DMN regions was found. Specifically, the dysfunction of anterior regions of the DMN contributed to characterize progressive MS patients with CI. Other authors,³⁶ analyzing less explored RSNs such as the left and right frontoparietal networks (FPN) and salience network, observed that CI MS patients display reduced RS FC among different brain areas belonging to these

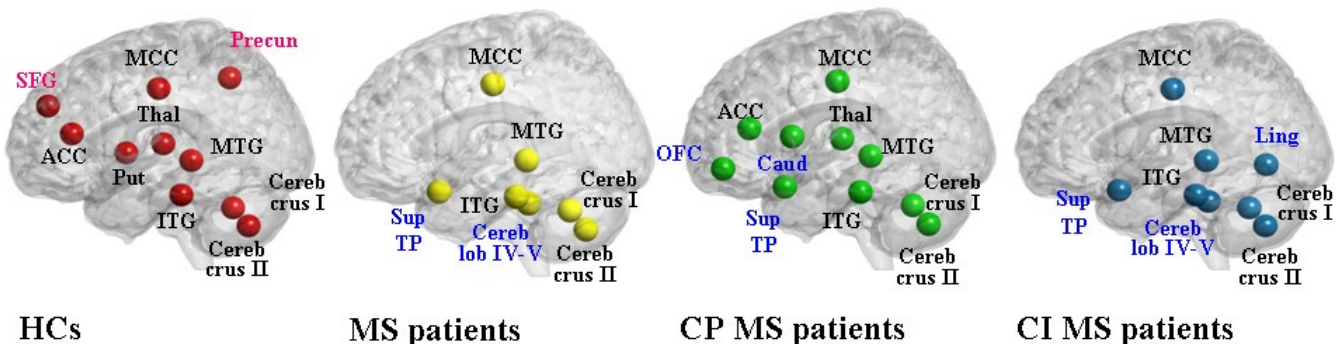
RSNs, thus supporting the notion that RSN alterations could play a global role in MS cognitive disturbances. Some associations between PASAT scores and RS FC within dorsal FPN and right ventral FPN, generally involved in attentional and working memory processes, have been detected in patients with MS. Similarly, an association between 9-hole Peg test scores and connectivity within the left dorsal FPN network, which is involved in motor preparation,³³ has been found.

Graph analysis represents the state-of-the-art methodology to assess brain FC and is contributing to characterize functional disconnection and efficiency loss in several neurological conditions.³⁷ This interesting approach allows the brain to be depicted as a set of nodes connected by edges, and to identify the so-called hubs that are nodes with high degree (high number of connections) and with an overall central position in network topological organization. A recent study applying graph theory in 246 patients with MS and 55 matched controls found that regional redistribution and impaired functional integration of network properties in patients with MS contributed to cognitive status and phenotypic variability.³⁸ These findings suggested that the loss of "critical" hubs and functional incompetence of alternative hubs may contribute to a progressive disease course. This indicates that the capability to maintain functional integrity and specialization of specific brain

regions over time might be among the main factors responsible for the preservation of clinical and cognitive functions. Hub distribution was relatively intact in CP MS patients, whereas CI MS patients lost hubs in the thalamus and left frontal lobes. As previously discussed, several previous studies have suggested that increased FC between frontal regions may represent a compensatory mechanism contributing to a preserved cognitive performance in patients with MS,^{7,27,39} but this was one of the first studies showing that functional loss of the thalamic connector is also associated with cognitive impairment. Notably, regional modifications of network organization correlated with phenotypic variability had only partial overlap with those associated with cognitive impairment, indicating the importance of functional abnormalities at a regional level in explaining the various MS clinical manifestations (Fig. 1).

Currently, fMRI is being recognized as a promising tool even when studying pediatric patients with MS. In this rare condition, the main objectives are (i) to improve the understanding of the mechanisms responsible for the better clinical course compared with adult patients with MS and (ii) to define the factors associated with the presence of cognitive impairment, which characterizes a high number of these patients. A multiparametric study⁴⁰ that combined structural and functional MRI techniques in 35 pediatric patients with MS and 16

A Left



B Right

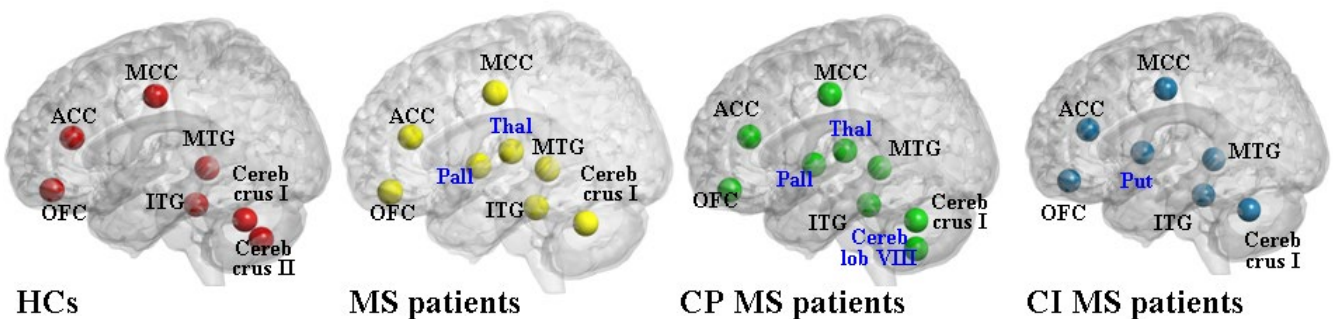


FIGURE 1 Brain hubs (A left hemisphere, B right hemisphere) of the functional networks of healthy controls (HC) and patients with MS as a whole in accordance with the presence/absence of cognitive impairment. Hubs present in HC only are reported in **red**. Hubs present in patients with MS only are reported in **blue**, and hubs present in all groups are reported in **black**. CP cognitively preserved, CI cognitively impaired, ACC anterior cingulate cortex, Caud caudate nucleus, Cereb cerebellum, ITG inferior temporal gyrus, Ling lingual gyrus, MCC middle cingulate cortex, MTG middle temporal gyrus, OFC orbitofrontal cortex, Pall pallidus, Precun precuneus, Put putamen, SFG superior frontal gyrus, Sup TP superior temporal pole, Thal thalamus. From³⁸ with permission

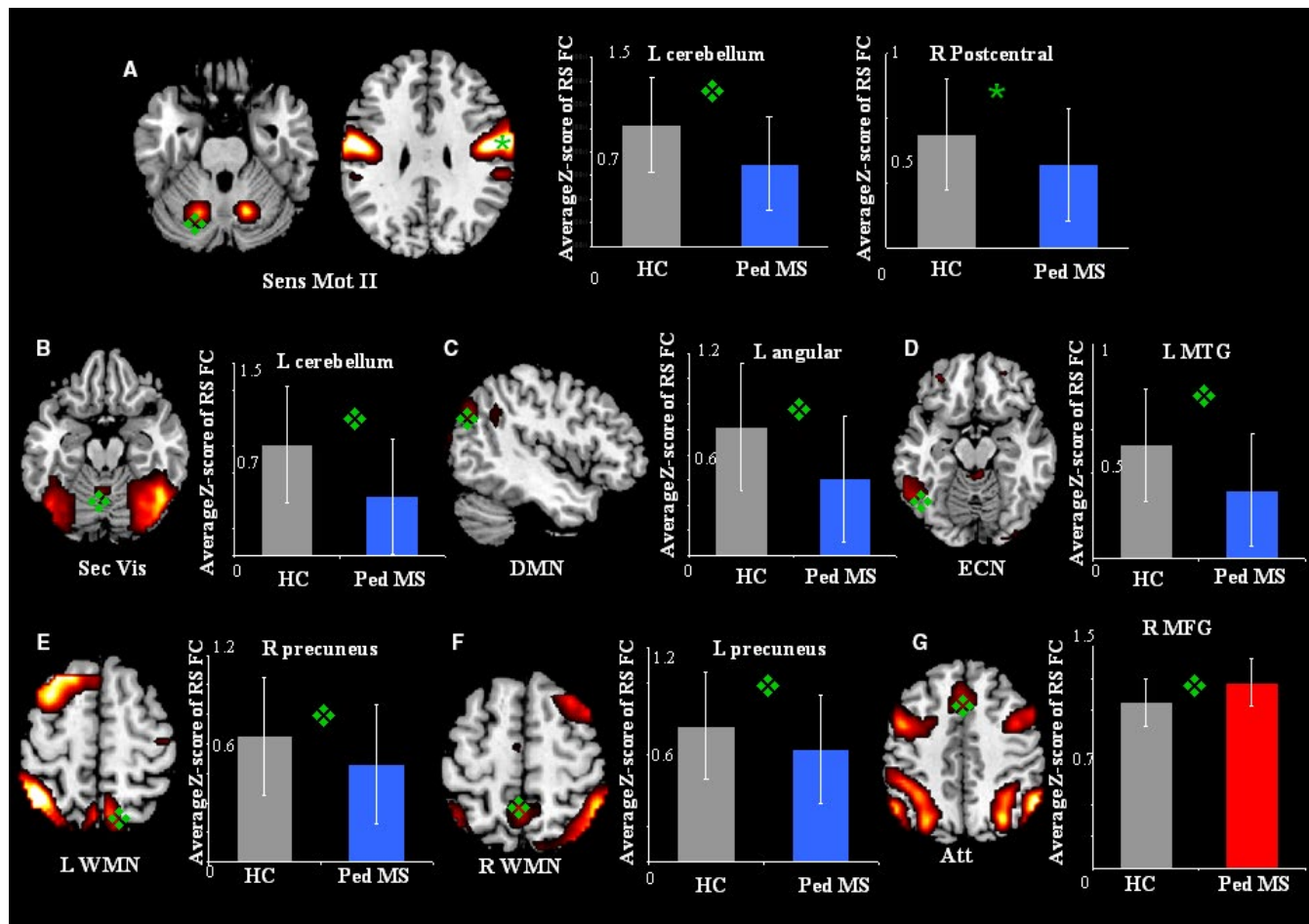


FIGURE 2 Illustrative examples of the spatial patterns of resting-state (RS) functional connectivity (FC) from healthy controls (HC) and pediatric (Ped) multiple sclerosis (MS) patients ($P < .05$, familywise error corrected). Bar plots showing average Z-scores and standard deviations of each significant cluster of between-group difference. A) Sensorimotor network II; B) secondary visual network; C) default-mode network (DMN); D) executive control network (ECN); E) left (L) working memory network (WMN); F) right (R) WMN; G) frontoparietal attention (Att) network. Blue bars represent clusters of decreased RS FC in pediatric patients with MS vs controls, and red bars represent clusters of increased RS FC in pediatric patients with MS vs controls. Abbreviations: L=left; R=right; MTG=middle temporal gyrus; MFG=medial frontal gyrus. From⁴¹ with permission

age-matched controls detected the structural and functional abnormalities of core regions of the posterior DMN as substrate of cognitive dysfunction in these patients. Another study quantified RS FC abnormalities within and between the principal RSNs in pediatric patients with MS and found diffuse RS FC abnormalities of large-scale neuronal networks (Fig. 2)⁴¹ Specifically, compared with pediatric controls, pediatric patients with MS showed the decreased RS FC of several areas of sensory- and cognitive-related RSNs, mainly located in posterior brain regions. They also experienced increased RS FC of the medial frontal gyrus, which was more pronounced in patients with CP MS and was inversely related to T2 LV.

5. | THALAMIC CONNECTIVITY

Histopathologic and neuroimaging studies have suggested that MS pathologic findings significantly involve the gray matter (GM),^{42,43} with diffuse microscopic damage found in deep GM nuclei, even in

the absence of macroscopic MS lesions. Due to its central position and extensive connections, the thalamus is known to play an important role in cognitive functions. In line with this, RS FC abnormalities of thalamo-cortical network have been demonstrated in patients with MS and have been correlated with cognitive performance.⁴⁴ Increased RS FC of the thalamic network was correlated with reduced cognitive performance and was enhanced by increasing cognitive demand, suggesting that such an increased thalamic RS FC could be unable to compensate for tissue damage and prevent cognitive dysfunction in MS.

These results have been confirmed by another study³⁴ that showed increased thalamic FC with areas mainly located in frontoparietal and occipital brain regions in CI MS patients.

6. | HIPPOCAMPAL CONNECTIVITY

Memory deficits develop in 40%–65% of patients with MS and can lead to problems in daily life activities.¹ The hippocampus plays an

essential role in memory function and is therefore a target structure to understand neurobiological substrates of memory impairment in MS. By studying hippocampal FC in relation to structural integrity measures, a decreased RS FC between the hippocampus and several cortical areas was found in MS patients with mild structural damage and intact spatial memory.⁴⁵ A fMRI study,⁴⁶ adopting an active episodic memory encoding paradigm, found an increased activity of hippocampal memory system in CP MS patients, possibly reflecting a functional adaptive process to prevent cognitive deficits. Combining several measures of hippocampal involvement, including task-induced activation, RS FC, volume and lesions, a decreased activation of the right hippocampus, and an increased RS FC of the left hippocampus with right posterior cingulate cortex, was significantly associated with impaired memory function in MS. In interpreting these results, it is important to consider that hippocampal activation in response to a given task is a local measure of hippocampal function, whereas functional connectivity is a more global measure that provides information on how well the hippocampus “communicates” with other brain regions.⁴⁷ Starting from this consideration, the increased hippocampal FC observed in patients with MS could be interpreted as a maladaptive response of memory network to pathology, possibly driven by disinhibition of the entire DMN. This hypothesis is at least in part supported by a more recent study that demonstrated a widely distributed association between reduced hippocampal RS FC with many DMN regions and high T2 LV. This suggests that the accumulation of focal WM lesions is likely to be one of the factors affecting the altered interaction between the hippocampal formation and other regions of the DMN. Hippocampal RS FC disruption also correlated with the severity of disability and depression.⁴⁸

7. | IMPAIRED FUNCTIONAL RESERVE

Despite the clear advantages of RS fMRI, it is important to note that there might be some mechanisms related to cognitive network function which are unlikely to be captured properly by the use of a non-task-active/resting paradigm. In details, it has been suggested that patients with MS might have a limited ability to optimize cognitive network recruitment with increasing cognitive load, which reflects an impaired cognitive functional reserve (i.e., the ability to match brain activity to increasing cognitive demand).^{49–52} Such an impaired functional reserve is likely to be a maladaptive mechanism contributing to MS clinical manifestations. It is present from the beginning of the disease, including patients with CIS,⁵¹ but is more pronounced in patients with SPMS⁵⁰ and those with cognitive impairment.⁵³

8. | LONGITUDINAL MODIFICATIONS OF COGNITIVE NETWORKS

Longitudinal modifications of cognitive networks' recruitment and their impact on patients' cognitive status have been marginally

explored to date. A 1-year longitudinal study in patients with early MS found an association between increased activation of the right dorso-lateral prefrontal cortex during a cognitive task and improved working memory and processing speed performance.⁵⁴ A 20-month longitudinal study⁵⁵ showed that worsening of Symbol Digit Modality Test performance in patients with RRMS was correlated with an increased activity of left inferior parietal lobule over time, probably reflecting a maladaptive mechanism.

9. | FMRI TO MONITOR TREATMENT

Only few fMRI studies have been performed to monitor the treatment effects in MS.^{22,56,57} Different patterns of brain response and modulation of FC to acute and chronic administration of rivastigmine have been demonstrated in patients with RRMS using cognitive tasks.^{22,57} Increased activation of the ipsilateral primary sensorimotor cortex and supplementary motor area has been observed after a single dose of 3,4-diaminopyridine, suggesting that this treatment may modulate brain motor activity in patients with MS, probably by enhancing excitatory synaptic transmission.⁵⁶

Active fMRI and RS fMRI have also been applied to assess the modifications of the patterns of activations and FC following cannabis consumption.⁵⁸ Compared to cannabis non-users, cannabis users had worse performance at cognitive demanding tasks, which was associated with more diffuse cerebral activation during a cognitive task and a higher number of errors. These results suggest that cannabis further compromises cerebral compensatory mechanisms, already faulty in MS.

One of the most interesting applications of fMRI in terms of treatment is assessing the modification of cognitive network recruitment following cognitive rehabilitation. A study that applied a 3-month computer-assisted cognitive rehabilitation in RRMS patients with selective deficits of attention and executive functions⁵⁹ detected an enhanced recruitment of brain networks subserving the trained functions in the rehabilitation group. Interestingly enough, changes in RS FC connectivity of cognitive-related networks helped to explain the persistence of the effects of cognitive rehabilitation in the patients several months after treatment termination and the patients improvement on depression and quality of life scales, suggesting that cognitive rehabilitation exerts a positive effect that is not limited to the trained function but extends to several additional domains.⁶⁰ Notably, the previous study⁵⁹ found no structural changes in the GM and NAWM following cognitive rehabilitation. Such a negative finding might reflect an impairment of structural plasticity in these patients, which is likely to be caused by the MS pathological process. Another study⁶¹ also provided proof of neuroplastic effect as assessed by active paradigm fMRI of a well-defined highly specific cognitive rehabilitation program in patients with MS and cognitive impairment. An innovative approach in the treatment for cognitive dysfunction may be the use of the results obtained from fMRI technique to guide the combined use of computer-based cognitive rehabilitation and non-invasive brain stimulation.⁶²

One of the main issues to properly apply fMRI tools in the context of treatment monitoring (either drug related or in the context of rehabilitation) is to prove the applicability of this technique in a multicenter setting. Recently, a European multicenter study applied fMRI to define the functional correlates of cognitive dysfunction in RRMS.⁵³ Consistent with previous single-center studies, the authors found the increased recruitment of the right dorsolateral prefrontal cortex in CP MS patients, whereas patients with CI had reduced activation of several areas located in fronto-parieto-temporal lobes as well as a reduced deactivation of regions that are part of DMN. Significant correlations were found between abnormal fMRI patterns of activation/deactivation and behavioral measures, cognitive performance, and brain T2 and T1 LV.

10. | CONCLUSIONS

fMRI studies in patients with MS have demonstrated the potential of this technique to provide important insights into the role of brain reorganization following structural CNS injury and to improve our understanding of the factors associated with cognitive impairment. Available fMRI data suggest that cognitive impairment in MS might be a function not only of tissue loss, but also of the progressive failure of the adaptive capacity of the brain with increasing tissue damage. Preliminary data in selected cohorts of patients indicate that interventions that drive neuroplasticity can promote functional restoration by inducing adaptive changes or by predisposing functional systems to adaptive plasticity. An improved understanding of recovery mechanisms may guide the development of new recovery-oriented strategies in patients with MS.

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CONFLICTS OF INTEREST

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