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Review article

# FMRI in multiple sclerosis

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**Abstract**

In multiple sclerosis (MS) conventional, structural and modern functional MRI (magnetic resonance imaging) techniques have been extensively used for studies and to understand its mechanism responsible for the accumulation of irreversible disability. Multiple sclerosis (MS), is a disease in which physical and cognitive deficit not only reflect structural damage, but also functional damage between the brain networks. Cognitive dysfunction in MS occurs during several stages of disease duration. MS with severity of cognitive manifestation is not closely related to indicate structural brain damage. Brain network and neuroplasticity may contribute to maintain the normal performances despite of the brain lesion. Most of the fMRI studies reported, changes in functional reorganization of cerebral cortex is seen in MS and hence provides to understand how brain networks and reorganization changes in MS. Resting-state functional magnetic resonance imaging allows to investigate intrinsic, synchronized brain activity across the whole brain, and to measure the degree of functional correlation between different cortical regions. This functional reorganization of the brain might be help full for the studies of the effect of rehabilitation and pharmacological therapy of the brain plasticity especially in different stages of the disease. In this study we try to focus on what kind of brain activity have been reported during the fMRI in MS of different phenotypes. This review describes the major findings obtained in MS patients at different clinical stages using resting state fMRI and discusses how the use of fMRI techniques may improve our ability to identify novel biomarkers useful in the context of the diagnostic work-up, establishing prognosis and monitoring treatment.

**Keywords:** Multiple Sclerosis (MS), Functional magnetic resonance imaging (fMRI), Resting state functional magnetic resonance imaging (RS-fMRI), Cognitive Impairment (CI), Clinical isolate syndrome (CSI), Information processing speed (IPS).

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## Introduction

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disease of central nervous system affecting most of the young adults. MS is one of the most common autoimmune disease affecting central nervous system in which the myelin producing oligodendrocyte of the central nervous system are the target of recurrent cell mediated auto immune attackand subsequent neuroaxonal damage [1]. Previously studies focused on white matter (WM) which is most responsible and extensive for demyelinating and degenerative process but in recent studies gray matter (GM) involvement is also familiar and GM lesion involvement is solely related to the physical disability, cognitive deficit and fatigue [2].

As known already magnetic resonance imaging (MRI) is the most sensitive tool for assessment of multiple sclerosis (MS).Whereas Structural magnetic resonance imaging (MRI) is the most sensitive for ruling out focal abnormalities of white matter lesion in patient with MS [3].New magnetic resonance imaging technique such as T2-Weighted, Fluid-Attenuated Inversion Recovery and post-contrast T1-Weighted Sequences are already established techniques which provides objective information about subclinical disease activity, in which the chances of the lesion being seen is 5 to10 times higher than that of clinical observations. Recent studies have shown that functional MRI can be used as a diagnostic tool for the work-up and monitoring the stage of evolution of MS. The rate of brain atrophy in MS is about 0.5% to 1% per year thus atrophy measurement technique is highly sensible for tiny changes. Techniques for future routine research acquisition are Double-Inversion Recovery Sequences, Magnetization Transfer–MRI, Diffusion Tensor–MRI, and Proton MR Spectroscopy, Functional MRI [4].

Brain being largest network every region has different function and their own task which are sharing information with each other. Recent studies provides incredible amount of information about functional neuroimaging which have provided new tools to measure and examine functional interactions between brain regions. A functional MRI is a method to detect the areas of brain using tasks-specific blood flow and their neuronal activity provides information about the functional organization, by comparing between the cases and healthy control. These method has widely been used to detect functional reorganization of brain in MS. Previously these Studies have been widely used in MS phenotypes staging for its functional reorganization

during motor [5, 6] sensor [7, 8] and cognitive task [9-13].The advance technique of fMRIcompliments structural MRI in such a way that provides information about brain activity followed by tissue injury [14].

Functional MRI (fMRI) of MS phenotype visual, cognitive and motor systems shows constant changes in its cortical function, with vivid activation of areas during task performance and or additional area recruitment in comparison with healthy control [15]. Functional magnetic resonance imaging (fMRI) shows adaptive functional changes which is related to tissue structural damage such as T2 lesion load [10, 16, 17] intrinsic lesion [18, 19], gray matter [20] and normal appearing white matter [21, 22] injury in MS. However, these adaptive changes in mechanism are not only because of these cortical recruitments but also other factors which are potentially responsible for the clinical evolution of the diseases staging [23].

One of the main caveats that influence the fMRI during task or active stage is the intersubjective variability during task performance; hence these days other techniques such as resting state fMRI are being widely used. As the word itself suggests, resting state fMRI, is a technique that is performed during the resting state of the brain.

## fMRI: A brief principal

fMRI is also based on the same technique as magnetic resonance imaging (MRI), a noninvasive technique that uses a strong magnetic field and radio wave to create images of the body. But instead of creating images of organ and tissue like MRI, fMRI looks for the blood flow in the brain to detect the activity area .These changes in blood flow are captured on screen which helps to understand the brain network and its activity. fMRI uses a specific signal (BOLD = blood oxygenation level dependent) as a contrast. Depending upon this technique fMRI can be performed in two different ways: task stage and resting stage.

Functional magnetic resonance imaging is also called blood oxygenation level-dependent MRI. Functional magnetic resonance imaging, images neuronal activity through blood flow (oxyhemoglobin delivery) which increases with brain activity and measures activity in the sensorimotor cortex, such aslanguage, sensory, and motor function. Functional magnetic resonance imaging uses the MRI platform to generate functional images of the brain.

## fMRI in task stage in MS

Optic neuritis (ON) is the first clinical manifestation in about 20% of patients with multiple sclerosis (MS). The inflammation and demyelination of the optic nerve are characterized by symptomatic visual impairment and retro bulbar pain, and associated with decreased visual acuity, decreased color and contrast sensitivity, delayed visual evoked potentials and visual field defects. Visual evoked potential (VEP) is a method used to investigate the visual system in MS and other disease where 8 Hz photic stimulations is used. VEP refers to the electric potential, initiated by visual stimuli, which are recorded from the scalp overlying visual cortex. VEP is a potential bio marker of disease progression in MS (24).

## fMRI and optic neuritis in MS patients

In some studies, patient having history of acute optic neuritis with documented loss of visual acuity at presentation show recovered normal visual acuity and color vision. Four patients had VEP records at presentation in which three were abnormal VEPs and now had normal latencies. Werring et al, has compared with control, in which it shows exclusive activation of visual cortex with asymmetrical visual impression in activation pattern between left and right eye. The unaffected eyes of the patients shows activation in right insula-claustrum but showed a significantly larger response in visual cortex in control. The generic activation maps of unaffected eye and the left eye maps from controls, conformed greater activation especially in the orbitofrontal cortex, anterior insula bilaterally, and the corpus striatum of patients but significantly greater activation in visual cortex in controls [24].

In the ON group, both brain atrophy and MRI brain new lesions correlated with lower VEP amplitudes was found only in the right eye. But didn't find any significant association of VEP latency and brain atrophy or new brain lesions in MRI. In patients without a history of ON and non ON, VEP parameters showed even stronger association with both MRI new brain lesions and brain atrophy than in ON group. We found a significant but moderate relationship of new brain T2 lesions with longer latencies of VEP in the left and right eyes. We also found correlation of VEP amplitudes and MRI new brain lesions. VEP latency delay correlated significantly with duration of disorder. Both brain atrophy and new MRI brain lesions have shown stronger correlation with VEP results than with GDx RNFL measures [25].

In ON VEP amplitude is decreased in the acute phase and it typically increases in the recovery phase, whereas the VEP latency may/may not recover or remain prolonged as it is in the acute phase [26]. The reduced activation of the lateral geniculate nucleus (LGN) in the acute phase is probably caused by

reduced neuronal input to the LGN due to inflammation, edema and demyelination of the optic nerveconsistent with reduced VEP amplitudes and prolonged VEP latencies. The persistently delayed VEP latencies suggest that remyelination is not the primary mechanism of recovery of the LGN activation.

## Motor system

Studies have found that MS patients with motor weakness experienced larger motor activation than controls while patients with optic neuritis experienced smaller visual activation than controls. Motor disability in MS is commonly assessed by the Expanded Disability Status Scale (EDSS). Categorical rating scales are limited by subjective error and inter-rater variability. Therefore, objective and quantitative measures of motor disability may be useful to supplement the EDSS in the setting of clinical trials. Most of the studies conducted for motor system are based on the analysis of simple motor task using the dominant part of the body. The right hand is studied in most of the cases. It has previously been shown that grip-force-variability (GFV) is increased in MS [27] with the use of DTI imaging. The role of fMRI in GFV and its result may be of help in further evaluating the disease condition.

Patterns of activation consistent with motor execution and planning were observed in patients and controls during the performance of right and left hand movements [28]. Group comparison during right hand movements showed that patients increased activation of the ipsilateral primary motor cortex (BA4) as well as bilateral activation of regions associated with the sensorimotor network (BA5–7, 31). Consistent with our findings, similar fMRI motor studies in MS patients with low disability have reported increased activation of bilateral sensorimotor regions during right hand movements [23, 29].

While increased ipsilateral motor cortex activation in patients compared to controls may represent an adaptive mechanism, recent evidence suggests that it is also related to reduced task-associated deactivation [30] and loss of trans-callosal inhibitory fibers [31]. An increase in activation of regions outside of the classical motor network has also been described during right hand movements. However, the patients in these studies had greater disability [32] or were in the progressive stage of the disease [33]. Interestingly, when patients performed the same motor task with the non-dominant hand, additional areas not typically activated in simple motor tasks, including the bilateral ACC and the right DLPFC, were recruited. These findings may be related to increased cognitive effort that patients may require for performing non-dominant hand movements. While most motor fMRI studies in MS have involved right hand movements, a recent fMRI study by Rico et al. [34] examined bilateral movements in patients with clinically isolated syndrome [35].

## Cognitive system

Cognition refers to the processes involved in thinking, concentrating, planning, solving problems, learning, analyzing sensations and remembering. A person's cognitive status is the extent to which they can use their brain to undertake these processes. Cognitive dysfunction is also one of the main important symptoms in MS. Cognitive impairments is usually present in 65% of the patient suffering from MS. It includes memory impairment, executing functioning, working memory [36]. The severity of cognitive manifestation in MS is not only related to structural brain damage but also functional changes in the cerebral cortex which is also reported in fMRI.

Working memory: Memory is one of the most consistently impaired cognitive function in MS. Patients with MS may show impairments across all memory domains. 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.

Functional MRI is widely used to assess cognitive impairment (CI) in MS. Sweet et al. was the first to evaluate verbal working memory (VWM) that showed the higher functioning shifting towards the higher activity in the region which is associated with the sensorimotor function [37]. Filippi et al. has revised that fMRI has great potential to know, the inside and the cortical reorganization of the brain followed by tissue injury in MS. fMRI provides lots of information about the cognitive impairment pathology [38]. To identify cortical areas involved in working memory, the widely used N-back task was implemented [39, 40]. Chiaravalloti et al. using the modified Paced Auditory Serial Addition Test (PASAT) confirmed that working memory dysfunction in MS is associated with cerebral activation patterns in accordance with CI. Although fMRI provides a better understanding of cognitive constructs determining pathology in CI, the most common paradigms used, do not evaluate varying degrees of working memory nor have they been validated by neuropsychological testing within the study reported.

The application of the immediate memory task/delayed memory task (IMT/DMT) fMRI paradigm in MS is a novel concept, since it has never been used to assess MS related CI. This paradigm has the potential to be more sensitive than fMRI paradigms used for evaluation of working memory in MS like the N-back test. The IMT/DMT paradigm is similar to N-back paradigm because longer working memory delay period (DMT) and a shorter delay period (IMT) is analogous to N-back letter memory test. N-back and IMT/DMT paradigm are similar sequential letter memory test but the difference is, 2-back vs 1-back analogous to longer working memory delay period (DMT) and a shorter delay period (IMT). IMT/DMT, a fMRI working memory paradigm, is associated with BOLD activation in areas of the brain related to cognitive function in patients with MS.

The MACFIMS is designed to quantify cognitive function with psychometric testing, it includes these component assessments: processing speed and working memory assessed by Paced Auditory Serial Addition Test (PASAT) and Single Digit Modality Test (SDMT).

The 3-digit as well as the 5-digit wmem showed significant fMRI BOLD activation. The 3-digit wmem, activation was found in portions of the bilateral superior and mid frontal cortex, supplementary motor area, pre and post central gyrus, bilateral superior and inferior parietal lobule, inferolateral pre-frontal cortex, cuneus, insula and cingulate regions. The 5 digit wmem activation was seen in the inferior medial frontal and medial orbitofrontal cortex.

IMT/DMT behavioral scores were within normal range and consistent with MACFIMS. IMT/DMT, a novel fMRI working memory paradigm, is associated with BOLD activation in areas of the brain related to cognitive function in patients with MS. Both MACFIMS and IMT/DMT scores were in agreement and supported intact cognitive function [41].

## Information processing speed

Information processing speed (IPS) is a problem of speed which occurs in all the sub types of MS with progressive disease condition. The computerized test of the information processing (CTIP) is a relatively new measurement of IPS [42]. CTIP measurements were based upon the reaction time (RT) and its three error tasks: simple RT, choice RT and semantic search RT with increased cognitive impairments. CTIP results show significant difference between the MS and control patients. During the task stage, RT is slower in the MS group than control however reaction time increases during the tasks process.

Despite of slower performance by the MS group as compared with the healthy controls,reactive time in both the groups are same, however patients with brain injury required relatively more reaction time to complete cognitive related task [42]. MS and control both show increased RT with increased task complexity, however error is not significantly different between two groups. But the results of semantic search condition shows significant difference between the MS and controls. MS groups shows compensatory increase activation in prefrontal cortex and right temporal gyri as compared with healthy individuals and also shows decrease activity in left temporal gyri [43].

## Resting state fMRI

One of the new trends in functional neuroimaging study is ‘resting-state fMRI. This approach focuses on spontaneous, rather than task-induced, fluctuations in the blood oxygenation level-dependent (BOLD) signal. Resting state fMRI allows investigating the brain function without the active involvement of the brain. At rest stage the brain is organized into multiple active sub-systems, resembling the specific brain networks.

Clearly, one of the main caveats when interpreting the results derived from active fMRI paradigms in disabled people is to define if and how much they are influenced by inter-subjective variability in task performance. Resting state fMRI is different from active fMRI in a way such that it avoids the performance related activity and its activation level of the brain so that the studies becomes easier to be acquired and standardized, may be very effective and convenient to understand and it also analyses the abnormality associated with MS. Recent advanced techniques of RS fMRI also provide to investigate intrinsic brain activity of the whole brain and are also able to functionally communicate and correlate the cortical activity of different reason or RS networks (RSN). RSN abnormalities have been studied in the patients with MS [15, 44-50]. Roosendaal et al. investigated RSN in CIS patient having MS and relapsing remitting multiple sclerosis (RRMS). It shows there is higher functional connectivity in CIS then in RRMS, including DNM. It also shows increase functional connectivity in the sensory motor networks, attention and executive system, the right and left fronto-pariatal networks [50]. These studies show theses difference in cortical activation pattern in RSN in early stage of MS may also be compensated by the progression of brain damage phenomenon. Faivre et al. investigated patients having early stage RRMS and found connectivity in RSN in all major network

regions: motor, cognitive, and sensory as compared with healthy controls [15]. Recently the main principal of the RSN was assessed in large sample of RRMS patients and healthy controls which shows the decrease in RS connectivity in some region such as working memory, sensory motor, visual networks, default network mode (DNM) and increase connectivity in the region such as executive control and auditory during RSN [49]. These decrease connectivity in RSN signifies that it may be due to disability and T2 lesion volumes. The studies also analyses the functional networks connectivity (FNC) to understand the interaction of functional connectivity networks during RSN in RRMS patients and healthy controls. It shows that there is increase connectivity between the regions that is executive control networks and salient networks and also shows the decrease connectivity with DNM. Abnormal connectivity was also noted between working memory network and sensory network. The study signifies that functional abnormality between these global networks in patient with RRMS may be due to the severity of disability and the extent of T2 lesions [49]. While in case of longitudinal studies the functional abnormality is due to the disease progression and the onset of the clinical deficits [47].

Several studies have been done to assess the pattern of functional connectivity of DNM in patients with different phenotypes and progressive form of the disease. Rocca et al. found different activation patterns in different stages of disease. They found significant inhibition of the DMN activity in ACC in patient having MS in both the stages; primary progressive MS (PPMS) and secondary progressive MS (SPMS) as compared with the healthy control [48]. This inhibition of functional connectivity of ACC in DNM in progressive MS related to cognitive impairment was assessed by the Paced Auditory Serial Attention Test and word list test. The studies also show the severity of structural damage of corpus callosum and cingulum measured by diffusion tensor MRI. These studies signified that anterior components of DNM may be the factor responsible for the cognitive deficit in MS patient.

The modified Story Memory technique was used in patients with RRMS to evaluate the efficiency of the behavior. After 5-weeks treatment, the behavior was found to be improved and the connectivity also increased in the cortical region and hippocampus (the regions involved visual imaginary and memory process respectively). The connectivity is also increased in core DNM [51]. These studies show the alteration in RSN connectivity is due to the effect of cognitive rehabilitation process.

## Conclusion

In MS cognitive impairment plays a vital role and effects daily routine of an individual's life, including memory, personal relationship, lack of completing work, and up to significant decrease in the efficiency of performing even simple activities of daily life. These advanced technologies have provided huge opportunities to view and understand the functioning of brain and its activity. fMRI in MS helps to understand the different activation pattern of the brain at different stages and hence plays a vital role in helping us to understand the diseases pathophysiology. These studies provide the information about active and resting stage of the brain and how it works. fMRI and its technique RS fMRI may be valuably useful in clinical setting to understand and classify disease stage of individual MS patients, with the ultimate goal to identify the disease condition and the context of the diagnostic work-up. All these positive factors can be used as a guide for the management of the disease. Despite so many studies that have been conducted there still remains a lot to be explored and understood about the disease and its treatment. In depth studies of fMRI can be used as a tool in achieving this goal of ways and means for stopping the progression of the disease, treating the disease or maybe even curing people of the disease.

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