

REVIEW

Structural and Functional MRI Techniques in Multiple Sclerosis Related Cognitive Dysfunction

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Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the central nervous system that is prevalent in young adults and therefore with significant social impact. Cognitive impairment occurs in 40% to 70% of patients with MS and has a weak correlation with disease duration. Neuropsychological assessment is a standard method in the detection of cognitive dysfunction. However, in order to understand the etiology and evolution of cognitive dysfunction, several elaborate magnetic resonance techniques have been developed. Their aim is to measure structural changes in the CNS that are considered main substrates in cognitive function such as whole brain and gray matter atrophy, cortical lesions and changes in subcortical gray matter. Evidence shows that the clinical manifestations of multiple sclerosis are complex interactions between tissue damage, tissue repair and cortical reorganization. In order to study this heterogeneity, structural magnetic resonance analysis of brain morphology and functional magnetic resonance imaging are essential. This review summarizes current techniques in structural MRI and the value of functional MRI in understanding the link between cognitive deficit and cortical activation and reorganization.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the CNS that is prevalent in young adults and therefore with significant social implications.¹ The etiology of MS is still unknown, although it is believed that a complex interplay between genetic and environmental factors may have a role. Cognitive impairment (CI) occurs in 40% -70% of patients diagnosed with MS, and has weak correlation with disease duration. Even in the early stages of the disease, neuropsychological assessment may show deficits of mental processing speed, memory and attention.² For a long time MS was regarded as a white matter disease, but in the last decade, gray matter involvement has been widely proven in both histopathological and MRI studies.¹ The development of neuroimaging techniques increased our understanding of structural and functional changes in white and grey matter.³ More information regarding the link between dis-

ease duration, cognitive impairment and functional MRI changes in order to visualize possible cortical reorganization is necessary in the development of new and effective methods of cognitive rehabilitation and improving quality of life in patients with MS. The aim of this review is to summarize current techniques in structural MRI which best detect grey matter lesions and the value of functional MRI in understanding the link between cognitive deficit and cortical activation and reorganization.

GRAY MATTER PATHOLOGY IN MS

In the process of inflammatory demyelination of axons the involvement of both white and gray matter was acknowledged in early studies, however, the lack of advanced neuroimaging techniques and myelin immunohistochemistry did not put in perspective gray matter lesions, making MS a classically regarded white matter disease.¹

The abnormality in gray matter can mainly occur

in two ways, primary and secondary. The primary gray matter (GM) lesion occurs within GM as focal and diffuse demyelination, the secondary changes are a result from continuing white matter damage adjacent to GM (e.g. Wallerian degeneration).^{1,4} Since the introduction of myelin immunohistochemistry a classification of cortical grey matter lesions was proposed by Bø et al. (2003) which includes four types of GM lesions: type I – mixed white matter-grey matter, type II intracortical lesions surrounding a blood vessel, type III subpial lesions which start at the pial surface and never reach the white matter-gray matter boundary, and type IV lesions that affect the entire width of cerebral cortex but not the adjacent white matter.⁵

PATHOGENESIS OF GRAY MATTER LESIONS.

Histopathologically, GM lesions are very different from white matter lesions, T cell inflammation, blood-brain-barrier disruption and foamy macrophages are present in the latter but not found in cortical changes. The question of how this discrepancy arises in the course of this disease is still uncertain, but a couple of mechanisms have already been proposed.

Primary pathogenic mechanisms occur without intervening effects from white matter lesions. Magliozzi and co-workers, suggest that meningeal inflammation may cause cortical demyelination that eventually results in neuroaxonal degeneration. The ‘use-it-and-lose-it’ principle is another possible primary pathological development. In functional and cortical thinning studies investigating default mode networks show that areas that are constantly active are more likely to be subject to neurodegeneration.¹

Secondary pathogenic mechanism – inflammatory process in WM lesions causes axonal transection and redistribution of Na⁺ channels and mitochondrial dysfunction resulting in virtual hypoxia that eventually results in neuroaxonal degeneration in gray matter. In addition glutamate excitotoxicity also pathogenic factor in WM lesions can aggravate the neuroaxonal damage in GM.¹

STRUCTURAL MRI ASSESSMENT OF COGNITIVE IMPAIRMENT

Cognitive impairment (CI) affects between 40% to 70% of patients diagnosed with MS. Various neuropsychological deficits can occur even in the early stages of the disease and tend to worsen over time. Studies show evidence of CI even in patients with clinically isolated syndrome.^{2,3} Working memory, information processing speed, attention, processing efficiency and visual learning are the most frequently

affected domains in MS. Cognitive deficit results in daily life disturbances and decreased quality of life. Patients may complain about decreased efficiency in their work, difficulties in concentrating and less active participation in their social life.³

The best method to evaluate CI is neuropsychological testing (NP). Symbol Digit Modality Test (SDMT) and Paced Auditory Serial Addition Task (PASAT) are investigating processing speed, the domain in which MS patients tend to fail more often than others, thus making the two tests a sensitive tool in the detection of cognitive deficits in patients with relapsing remitting MS (RRMS).² In order to better understand the evolution of cognitive impairment NP test results have been correlated to structural MRI findings. Conventional MRI is fundamental in diagnostics and assessment of disease activity however more elaborate techniques are used in order to investigate the heterogeneity of the pathological process in MS.⁶

Fluid Attenuated Inversion Recovery (FLAIR), T2-weighted and gadolinium enhanced T1-weighted sequences are basic in diagnostics and follow-up in disease activity.^{2,6} T2 hyper intense lesions are the result of inflammation, demyelination, edema, gliosis and axonal damage in various degrees.² T1 hypointense lesions are a subset of T2 and FLAIR lesions, their level of hypo intensity can differ and is proportional to the degree of pathological severity, these lesions are commonly called ‘black holes’ (BH). Persistent BH indicates irreversible axonal loss and demyelination.^{2,6}

Cortical lesions and brain atrophy are primary substrates in the etiology of cognitive deficit but they cannot be detected by standard MRI methods, therefore a number of quantitative MRI techniques have been developed to increase our understanding of tissue damage and the pathogenesis of GM. Calabrese et al. studied the correlations between cortical lesions, cortical atrophy and cognitive impairment in patients with RRMS, and concluded that volume of cortical lesions (CL) and tissue loss are the most important structural changes associated with CI. The study also stated that CL number and volume are higher in patients with CI than those who are cognitively preserved.⁷ Double-inversion recovery (DIR) sequence has highly improved the ability to detect cortical lesions in MRI, making it possible by suppressing the signal from CSF and WM. Three-dimensional (3D) DIR is standard method in investigating cortical changes even in early onset MS and CIS.^{6,8} Geurts et al. compared 3D DIR

with 3D FLAIR and T2-weighted spin-echo (SE) MR imaging in their ability to depict intracortical lesions, the results showed that the DIR sequence gives a better definition of mixed white matter-gray matter lesions since it gives a better contrast between the lesion and the surrounding tissue.⁹ However, the concern with DIR remains the high number of false positive findings.⁶

Brain atrophy is usually a marker for disease burden. The rate of whole-brain atrophy is between 0.5 and 1% per year in MS patients.⁶ The techniques used must be sensitive to small changes. The primary requirement is image analysis software.^{6,10} Semi-automated and automated programs generate a rapid assessment of atrophy, and are commonly used to calculate whole and partial brain atrophy.¹⁰ Measurement approaches that are able to distinct GM from WM and calculate the GM and WM volumes separately are of crucial value in the research of cognition in MS. Registration-based and deformation-based methods are used to differentiate brain tissue into white and gray matter, both methods use anatomic and intensity information to classify voxels in their appropriate tissue type. SIENA (structural image evaluation using normalization of atrophy) and its adaptation SIENAX for cross-sectional measurements of normalized brain volume are registration based approaches. Voxel-based morphometry (VBM) belong to the deformation-based approach and subjects can be assessed on a voxel-by-voxel basis using a common software package - SPM. Despite the existing sophisticated software techniques MS lesions can still be problematic and segmentation errors can occur.¹⁰ Derakhshan et al.¹¹ evaluated GM segmentations of several commonly used automated software methods for the detection of brain atrophy in MS patients compared to manual segmentation by trained expert readers (e.g. radiologists, neuroradiologists and neurologists). Their study concluded that the automated software and the manual segmentation perform equally in the segmentation of cortical GM but severe shortcomings were observed in deep GM segmentation. Most of the established software packages did not recognize all subcortical GM as such thus analyzing the regions as WM.¹¹ In light of this the choice of appropriate segmentation software in future research is essential especially when the focus of research is deep GM.

The correlation between cortical atrophy and CI is confirmed by several studies. In a recent study Kunchev T et al. studied the relation between global cortical atrophy (GCA) and cognitive performance

in patients with RRMS, proving a significant correlation between cognitive dysfunction and GCA. Another interesting aspect of this study is the measurement of medial temporal lobe atrophy (MTLA) that was significantly more prominent in cognitively impaired patients.^{12,13} Other research confirms that cortical atrophy is not the sole factor in cognition deficit.^{14,15} Benedict et al. studied the relation between neocortical atrophy, third ventricular width and cognitive dysfunction, one of the objectives of this research was to determine whether neocortical volume (NCV) would be the only factor to determine cognitive changes. The authors stated that even though NCV correlates significantly with NP test results, the measurement of third ventricular width (TVW) gave the same outcome, concluding that both central and cortical atrophy contribute equally in the development of cognitive deficit in MS patients. The width of the third ventricle is in relation to the thalamic volume, atrophy of the latter may cause ex vacuo enlargement of the third ventricle.¹⁵ In consequence the thalamus is one of the central substrates in the development of CI. Schoonheim M et al. studied the thalamic structure and the severity of CI in MS. In result the thalamic volume was significantly lower in CI patients, the lowest volumes were observed in severely cognitively impaired patients. This study also shows that lesion volume and whole brain volume are not significant predictors in CI.¹⁶ Other subcortical GM structures have shown involvement in MS patients with cognitive dysfunction, the hippocampus crucial to memory function is a substrate of interest. Roosendal et al. investigated the structure and functional hippocampal changes in MS patients and found that the right hippocampal volume is significantly lower than in the control group, even though memory function was intact.¹⁷ This evidence supports the thesis that hippocampal involvement may precede memory dysfunction.

More elaborate techniques have been developed to investigate the microstructure of tissue. Magnetization transfer-MRI (MT-MRI) is based on the magnetization exchange between protons in the brain tissue and the surrounding 'free' water. This generates information about very subtle tissue changes that are impossible to be seen with standard MRI methods.² The pathological processes such as inflammation, leading to an increased amount of unbound water initiate MTR changes. The information is expressed as magnetization transfer ratio (MTR), low MTR indicates tissue damage.¹⁸ Van Waesberghe

et al. found strong correlation between MTR and the degree of demyelination.^{18,19} MT-MRI is the primary technique when the focus of research is normal-appearing brain tissue. Post-mortem studies detected changes in normal-appearing white matter (NAWM) in MS patients such as diffuse astrocytic hyperplasia, patchy edema and abnormally thin myelin among others. In this regard GM is not spared. Changes in normal-appearing grey matter are also found.¹⁸

Diffusion tensor imaging (DTI) evaluates the random movement of water molecules in brain tissue, the measures describing this movement are mean diffusivity (MD) and fractional anisotropy (FA). DTI is sensitive in detecting WM demyelination.⁴ In this regard some authors suggest that DTI is better suited in the research of WM rather than GM.²⁰ However, Ceccarelli et al. found GM DTI abnormalities in brain area (thalami, right insula) associated with cognition.^{2,21} A study by Bester M et al. showed that impaired executive functions and verbal learning were associated with decreased FA in corpus callosum, the same study also showed correlation between fatigue and increased MD of the thalamic tracts measured by DTI.^{2,22} In consequence DTI may not be as limited to the investigation of WM as presumed.

FUNCTIONAL MRI IN MULTIPLE SCLEROSIS

Several techniques for functional imaging have been developed to study brain function, some of them by measuring glucose metabolism, receptor binding or cerebral blood flow. SPECT (single photon emission computed tomography) and PET (positron emission tomography) are the earliest functional imaging techniques. They are dependent on the use of radioactive tracer. The functional magnetic resonance imaging (fMRI) uses a strong magnetic field (1.5 or 3 T), and is dependent on the ratio of oxyhemoglobin to deoxyhemoglobin that increases as a result of hemodynamic response during neuronal activation. This response is detected as the blood oxygen level dependent (BOLD) signal. The use of fMRI does not involve exposure to radioactive substances and has a superior spatial resolution compared to SPECT and PET, therefore this technique has been well established in the last two decades. A major disadvantage to fMRI is the relatively long acquisition time and the fact that data is highly susceptible to movement in the scanner. Other variables may also affect the BOLD response such as caffeine intake, lack of

sleep and circadian rhythm. The use of fMRI in MS patients faces some specific challenges, focal lesions and atrophy may cause misalignment thus reducing statistical power. The use of medications or disease-modifying therapies may change neural activity or the hemodynamic response. In spite of these challenges a large number of studies have applied fMRI in MS populations and have successfully revealed significant differences from healthy controls.²³ The investigation of cognition in MS patients with fMRI has the potential to provide useful data about brain connectivity and cortical reorganization.²⁴ The methodology in investigating cognition with fMRI techniques includes task dependent design with an on/off paradigm to localize brain activity. Three main areas have been investigated: working memory, attention and executive functions using several paradigms.³ The PASAT has been applied in fMRI studies to investigate attention and working memory, a version of this test, specially developed for fMRI research is the PVSAT (paced visual serial addition test). Lazeron RHC et al. proved that PVSAT is suitable for research of cognitive functioning in patients with widespread brain damage such as MS.²⁵ The N-back test and word recall have been successfully applied in fMRI studies. Another technique that is able to analyze brain connectivity and reorganization is resting state fMRI, this method is preferable in severely impaired patients since no stimulus is required, the subjects are only asked to relax and not fall asleep for about 5 to 10 minutes. The resting state fMRI shows basic brain activity and a pattern of default mode networks (DMN) is revealed. In result information about resting state networks and their possible functional reorganization is acquired.^{23,24}

CORTICAL REORGANIZATION

In recent years evidence shows that the clinical manifestations of multiple sclerosis is not only a result from the extent of tissue damage but rather a complex balance between tissue damage, tissue repair and cortical reorganization. In light of this, fMRI can provide important information about the plasticity of the human brain. In the investigation of cognitive systems fMRI changes have been described in all MS clinical phenotypes. Several fMRI studies have used active paradigms in order to investigate patterns of activation of cognitive networks. Working memory and attention have been widely studied by PASAT and its visual analogue PVSAT.²⁴ Research shows that even patients in the

very early stage of the disease - clinically isolated syndrome (CIS) demonstrate cortical reorganization. Audoin et al. conducted a study in which patients with CIS were subjected to an fMRI evaluation with PASAT as cognitive paradigm. The main areas of activation were assessed and compared to healthy controls. Patients showed significantly greater activation in several areas - the right frontopolar cortex, the bilateral lateral prefrontal cortex and the right cerebellum, meanwhile the two groups performed equally during the PASAT. Thus the authors concluded that their study argues in favor of the existence of compensatory cortical activations even in the earliest stages of the disease.²⁶ Staffen W et al. studied the cognitive function and fMRI activation patterns in patients with RRMS within 3 years of diagnosis and a group of matched healthy volunteers. They performed the PASAT test prior to the fMRI evaluation and in the scanner its visual analogue PVSAT was used as paradigm. Although PASAT scores of patients and controls were not significantly different, the fMRI analysis revealed different activation patterns for patients compared to the control group. The main activation in healthy controls was detected at the frontal part of the right gyrus cinguli - Brodmann area (BA) 32, in patients the main activation was found in the right hemispheric frontal cortex (BA 6, 8 and 9), and in addition the left BA 39 was activated. The authors interpret the different patterns of activation accompanied with intact performance in PASAT scores as the consequence of compensatory mechanism and expression of neuronal plasticity.²⁷ In a similar research Mainero C et al. studied brain reorganization in fMRI of patients with RRMS. 22 patients and 22 matched healthy controls were scanned during PASAT and a word recall test. Patients exhibited a greater extent of brain activation than healthy controls and recruited additional brain areas for the same performance of the cognitive tasks. Of interest is another insight the authors made that brain activation was more significant among patients whose performance matched that of the controls in both PASAT and the recall test. Conversely several patients who performed worse showed less extensive brain activation. The authors suggest that impaired cognitive task performance could be a result of decreased function of task-specific areas in the absence of compensatory strategies.²⁸ In consequence this supports the thesis that compensatory functional reorganization of the cortex precedes cognitive decline in MS. In a multicenter study Rocca M et al. applied

fMRI to define functional correlates of cognitive dysfunction in patients with MS. The subjects, a group of patients with RRMS and a control group were scanned during the performance of the N-back test (to assess working memory), prior to the fMRI acquisition a number of NP tests were conducted to assess the cognitive status of all participants. As a result during the N-back load condition cognitively preserved (CP) patients had increased recruitment of the right dorsolateral prefrontal cortex compared to controls and cognitively impaired (CI) patients. However when increasing task difficulty CI patients showed reduced activations located in the fronto-parieto-temporal lobes compared to the two other groups.²⁹ This result is in line with the thesis that compensatory mechanisms are depleted when cognitive impairment arises. Baltruschat et al. conducted an fMRI study with PASAT in patients with RRMS with a different point of view, their research focused on the location of GM atrophy and its influence on cortical reorganization in cognitively preserved patients. After patients performed an fMRI adapted version of the PASAT, brain parenchymal fraction (BPF), GM and WM volumes were obtained for each participant. When assessing the fMRI results no statistically significant differences were found between MS patients and healthy controls (HC). However, the authors observed that localized brain atrophy in patients occurred at the same anatomical sites where they showed stronger functional connectivity than HC. In patients bilateral GM atrophy was found, localized in the PCG (posterior cingulate gyrus) and the adjacent precuneus area. In HC PASAT performance was inversely related to connectivity between the left PCG / precuneus and the left pre/postcentral gyri and left occipital gyrus. According to the authors this negative relationship means that compared to patients, healthy controls needed less resources because they did not show GM volume loss that interfered with cognitive effectiveness.³⁰ In light of all study results future fMRI investigation should be focused in both CP and CI patients and brain atrophy and its location is to be considered essential part of the etiology in cognitive dysfunction.

CONCLUSIONS

Functional magnetic resonance imaging has opened a new chapter in the future research of cognition in MS patients in all stages of the disease. This method has the potential to reveal the role of neuronal plasticity in the evolution of cognitive

functions. Even though several studies successfully proved cortical reorganization in patients with intact cognition many questions remain. Evidence show that gray matter atrophy precedes cognitive decline. On the other hand cortical reorganization is associated with intact cognition. The evolution of brain reorganization in relation to cognitive and clinical disability is an aspect that should be studied with functional MRI in order to reveal predictive markers for cognitive impairment and to develop future cognitive rehabilitation methods that will improve quality of life in MS patients.

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Структурные и функциональные методы МРТ при когнитивной дисфункции у пациентов с рассеянным склерозом

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Рассеянный склероз (РС) является воспалительным демиелинизирующим и нейродегенеративным заболеванием центральной нервной системы, которое преобладает у более молодых пациентов и, следовательно, оказывает значительное социальное воздействие. Когнитивные нарушения наблюдаются у 40% до 70% пациентов с РС и в незначительной степени коррелируют с продолжительностью заболевания. Нейропсихологическая оценка является стандартным методом выявления когнитивной дисфункции. Однако, чтобы понять этиологию и эволюцию когнитивной дисфункции, были разработаны несколько сложных методов магнитного резонанса. Их цель - измерить структурные изменения ЦНС, которые считаются основными субстратами для когнитивной функции, такими как атрофия всего мозга и серого вещества, кортикальные поражения и изменения подкоркового серого вещества. Данные показывают, что клинические проявления рассеянного склероза представляют собой сложные корреляции между повреждением тканей, восстановлением тканей и кортикальной реорганизацией. Чтобы исследовать это многообразие, первостепенное значение имеют структурный магнитно-резонансный анализ морфологии мозга и функциональная магнитно-резонансная томография. В этом обзоре обобщены современные методы структурной МРТ и ценность функциональной МРТ в осмыслении взаимосвязи между когнитивным дефицитом и кортикальной активацией и реорганизацией.