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# Changing the paradigm of multiple sclerosis characteristics: fact or fiction; Role of non-conventional MRI techniques in screening, prognosis, diagnosis, and following

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**Abstract**

Multiple sclerosis (MS) can be regarded as a common chronic demyelinating diseases of the white matter (WM). It is thought to be the mostfrequent cause of non-traumatic incapacity in young and middle-aged adults. The accuracy and precision of quantitative MRI scans in spotting longitudinal, MS-related changes should be made clear and individual large-scale, prospective studies are required. This is a central issue for aupcomingrequest of quantitative MRI to the monitoring of MS evolution in clinical trials.

**KEY WORDS:** MRI, white matter, DTI, MRS, MTI, cMRI, PWI, fMRI.

## 1. INTRODUCTION

**What is multiple sclerosis?** Multiple sclerosis (MS) is one of the common chronic demyelinating diseases of the white matter (WM). It is thought to be the most frequent cause of non-traumatic incapacity in young and middle-aged adults. According to statistics, more than 400,000persons in the United States and 2 million people worldwide are affected. MS is defined as relapsing remitting (RR) clinical course in about 85% of patients with episodic onset of symptoms followed by residual deficits or by a full recovery particularly in the initial stage of the illness. The precise etiology and original mechanism of progress of the disease are still not fully agreed, though numerous experimental proofs support the auto-immune pathogenesis. Magnetic resonance imaging (MRI) is an important tool, notonly in the diagnosis of MS but also for its follow up regarding the activity of the disease and responses to therapeutic trials (Fatehi, 2016). Conventional MRI (cMRI) images of patients with MS display numerous focal irregularities particularly on T2 and FLAIR sequences, which correspond to the histopathological changes in the WM lesions; though it is not so sensible to the related diffuse damage in normal looking white matter (NAWM) and normal appearing gray matter (NAGM). Also the limitations of the prolonged disability status scale (EDSS) andKurtzke practical system score (KFS-p), which is heavily weighted toward ambulatory dysfunction (Sospedra, 2005; Rahmani Tanha, 2016).

**Classification of MS patients:** MS as a chronic inflammatory-demyelinating and MRI studies are challenging the view condition affecting solely the WM of the central nervous system. Indeed, there is a growing body of evidence showing that a significant portion of MS-related damage affects virtually all the gray matter (GM) structures. Pathologically, cortical lesions have been distinguished in mixed WM-GM lesions (type I) and purely intracortical lesions (types II, III, and IV) (Fatehi, 2016). The latter may represent more than two-thirds of macroscopic cortical pathology in the disease, and the extent of cortical demyelination can exceed that occurring in the WM. Demyelination is seen not merely in the neocortex (especially in the cingulate cortex) but moreover in the GM of the thalamus, basal ganglia, hypothalamus, hippocampus, cerebellum, and spinal cord. Compared with WM lesions, GM lesions are characterized by a much milder lymphocytic infiltration, less microglial activation, and fewer perivascular cuffs. GM lesions also lack complement deposition and have only a modest increase in blood brain barrier permeability. In MS, GM pathology also includes neuronal injury, with neurotic swelling as well as dendritic and axonal transections. In addition to focal lesions, Wallerian and trans-synaptic degeneration of fibers passing through diseased WM areas can cause GM damage in MS. Consistent with pathologic observations, recent MRI studies have revealed a clear involvement of the GM in MS in terms of focal lesions, “diffuse” tissue abnormalities, and irreversible tissue loss (i.e., atrophy) (Fatehi, 2016). These studies have also revealed that GM injury marks the cerebral cortex, brain deep nuclei, and cerebellum and spinal cord; is present from the initial clinical stages of the disease; accumulates with time; and is at least partially, independent of the WM damage. In addition, the application of fMRI holds significant promise for improving our understanding of the role of GM changes in MS pathophysiology. This review summarizes the main results obtained from the use of conventional and nonconventional MRI based techniques for the assessment of GM pathology and dysfunction in patients with MS.

The implications of such outcomes in ameliorating the checking of the efficacy of new experimental treatment will also be discussed (Yamasaki, 1996).

**Diagnostic imaging methods:** MS is considered an inflammatory autoimmune neurologic disease that is characterized by pathologic changes, including demyelination and axonal injury. The first MR images of MS were shaped in the early 1980s, when MRI was presented into hospitals. The high conspicuity atypical signal intensities of MS lesions seen on MRI provided the best view yet of tissue damage, abrasion activity, and ailment accumulation compared with all other imaging modalities, including CT. Since then, MRI has become a routine scientific inspection in MS and is used to support the diagnosis and track the natural sequence of the disease. With the influx of novel nonconventional MRI techniques including volumetric MRI, magnetization transfer imaging (MTI), diffusion tensor imaging (DTI),perfusion weighted imaging (PWI) and MR spectroscopy (MRS) our ability to detect and characterize the disease burden, such as occult microscopic disease invisible when using cMRI techniques, has largely improved (Gharib Salehi, 2016). Today, MRI is the most significant paraclinical instrument for MS, and MRI–derived measures have been established as standard consequence markers to monitor the treatment response in various MS clinical trials. Structural MRI is the most frequently used neuroradiological tool in addition to clinical and laboratory data for diagnosis and monitoring of MS, and has emerged as a key surrogate measure for treatment outcomes in clinical trials. Because MS has been classically viewed as a provocative, demyelinating condition that chiefly touches WM tracts, the main focus of cMRI lies usually on WM plaques (lesions) that occur as signal hyper intensities on T2-weighted images. However, recent studies provide growing evidence of GM participation in MS, e.g. GM atrophy having a prognostic value for growth of MS after clinically isolated syndromes (CIS) (Batista,) It has been revealed, for instance, that selective GM atrophy is relevant in patients with CIS who change early to MS (Calabrese, 2011). Despite its high sensitivity in detecting MS abnormalities, conventional T2-weighted MRI is unable to depict the burden of GM lesions because these lesions are typically small, have poor contrast with the surrounding normal GM, and, in case of cortical lesions, have partial volume effects from the CSF. Fast FLAIR and gadolinium-enhanced T1-weighted sequences were the first used to surge the quantity of GM lesion detection in MS. More recently, DIR sequences have been developed and used to improve further the sensitivity of MRI in detecting such lesions (Rahmani Tanha, 2016). Despite the fast-paced growth of imaging techniques there is still a lack of healthy association between relapses, clinical symptoms, and sites of lesion location. Furthermore, devices to identify neurodegeneration or neuroprotection during the illness course in daily practice or clinical studies are still limited. The microscopic spatial sensitivity of DTI might be one method to bridge this gap due to its potential to quantitatively differentiate apparently normal brain tissue on cMRI (T1w, T2w, FLAIR) into tissue with normal and conspicuous water diffusion behavior. DTI has recently been applied successfully to quantify structural WM disintegration in a neuroprotection study and is capable to detect functionally relevant neurodegeneration even if cMRI is inconspicuous. These quantitative characteristics of DTI and the ability to detect functionally relevant microscopic alterations in “normal appearing” brain tissue (McDonald, 2001).

**Conventional MRI:** Longitudinal and cross-sectional MRI studies have shown that the formation of new MS plaques is nearly always associated with a focal area of contrast enhancement on T1-weighted images obtained after gadolinium injection, at least in patients with RR or SP MS.

This enhancement correlates with altered blood– brain barrier permeability in the setting of acute perivascular inflammation and enables differentiation between acute, active lesions and chronic, inactive ones. The Gadolinium enhancement varies in size and shape, and usually lasts from a few days to weeks, with an average duration of 3 weeks (97% of lesions enhance during less than 2 months) although this period is shortened by steroid treatment.

According to their pattern of contrast uptake on static MRI, lesions have been categorized as nodular or ring like (closed and open), though there are no clear histological differences between these two types [Davis, 1983). New contrast-enhanced lesions are almost always related with a hyperintense lesion in the same location on T2-weighted images. However, they can also be discovered before irregularities appear on T2-weighted scans, and can return in chronic lesions, with or without a concomitant increase in size. These new T2 hyperintense lesions regularly shrink over time (3–5 months) and their strength declines as edema resolves and some tissue repair occurs (extensive or partial remyelination), leaving a much smaller T2 permanent ‘footprint’ of the prior inflammatory event [Meier and Guttmann, Meier]. On unenhanced T1-weighted images, the recently formed lesions with contrast uptake show dissimilar signal patterns: 20% of the lesions appear isointense; while 80% appear hypointense in comparison with the normal appearing WM (wet black holes). Once contrast enhancement ends, more than 40% of these wet or acute black holes become isointense. This change mainly reflects a progressive repair process (remyelination), although resorption of edema may also play (Miller, 2005).

**Nonconventional magnetic resonance techniques:** Because of the high sensitivity of cMRI derived metrics for detecting MS plaques, these techniques are now the most important paraclinical tool for diagnosing MS, for understanding the natural history of the disease, and for monitoring the efficacy of experimental

treatments with a predominantly anti-inflammatory effect. However, the correlation between the extension of lesions observed on cMRI and the clinical manifestations of the disease is weak and underlines the fact that cMRI techniques do not suffice to explain the entire spectrum of the disease process. This clinical–radiological mismatch or paradox may be partly clarified by numerous limits of cMRI: limited specificity for the various pathological substrates of MS; incapability to quantify the extent of damage in NAWM; inability to detect and quantify the extent of GM damage; variability in the clinical expression of MS plaques in dissimilar anatomical sites (e.g. spinal cord and optic nerve); and inability to assess the effectiveness of reparative mechanisms in MS (Barkhof, 2005). In recent years, substantialenergy has been done to conver these restrictions with nonconventional MR-derived metrics that can selectively measure the more critical aspects of MS pathology and monitor the reparative mechanisms (Giacomini and Arnold, Barkhof, 2005). These nonconventional metrics, which include DTI, PWI and MRS, among others, have been used to assess the microstructural and metabolic changes that occur in newly formed lesions, and have led to a better understanding of the processes that occur in lesion development (Filippi, 1999).

**DTI:** Water molecule self-diffusion, denoting the microscopic random motion in biologic tissues, provides the basis of the modern picture of diffusion weighted imaging (DWI). When water diffusion is measured for a complex medium, the diffusion coefficient of biologic tissue is lesser than that in free liquid, and hence an "ostensible diffusion coefficient" (ADC) is actually measured. In tissues, for example WM, molecular movement is not the same in all directions (so-called anisotropy) due to the structural barrier within the fiber tracts, causing an orientation-dependent diffusion property. DTI is developed with diffusion weighting gradients in at least 6 noncolliner directions that permits the construction of a tensor (Gharib Salehi, 2016). The tensor can be used to produce images of both mean diffusivity (MD) and fractional anisotropy (FA), which demonstrate voxel-by-voxel differences in the magnitude and directionality of water diffusion, respectively(Fatehi, 2016). Therefore, DTI may provide information about tissue microstructure and architecture including size, shape, and organization and in turn constitutes a proved and effective quantitative method for evaluating tissue integrity at a microscopic molecular level. In addition, the info provided by FA can also serve as the foundation for fiber tractography, a method to control the pathways of anatomic WM connectivity. Promote DTI as anperfect tool for the clinical routine in addition to for longitudinal studies on neurodegeneration and neuroprotection. The objective of the present study was to exploit this new imaging method to examine the source of aache episode in MS patient considered as central pain and to test the theory whether the origin is associated with WM/GM plaques. On the other hand, DTI providesin vivo info about brain tissue microstructure andarchitecture. It also provides quantitative parameters like FA and MD, correlatedwith tissue damage that is not detectable in T2 and FLAIRimaging. The most frequent neurological complaint in young white adults is characterized pathologically by areas of swelling, demyelination, axonal loss, and gliosis scattered throughout the brain and spinal cord. MS has been classically considered a WM disease, but recent pathology and imaging studies have secure the notion that the grey matter is also affected by these pathological changes (Roosendaal, 2009).

**PWI:** Since it has long been noted that vascular swelling in the brain is the critical event in the pathogenesis of MS, there has been a cumulative attention in studying the microvascular abnormalities in MS by using advanced MRI. The assessment of brain hemodynamics, besides cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) is now possible by applying dynamic susceptibility contrast MRI (DSC-MRI), a method that is being used more extensively in clinical practice for measuring blood perfusion. Studies by using DSC-MRI prove a suggestively reduced CBF and prolonged MTT in periventricular areas of NAWM in MS patients compared with controls. The diminished perfusion in NAWM is supported by the histopathologic evidence and may indicate that MS has a primary vascular pathogenesis. The frequent edematous onion skin changes on the vein wall and vascular occlusion have been documented in the early pathologic studies. Recent work based on modern histopathologic techniques also demonstrates the hypoxia-like tissue injury or thrombosis of small veins. Studies of MS lesions by using perfusion MRI have also shown evidence of hemodynamic abnormalities including the increased CBV in acute lesions, which suggests that microcirculation may be modulated by inflammation or acute hypoxia. By detecting various lesion types, Ge, create not only enhancing lesions, but also some chronic nonenhancing lesions showing improved perfusion, which may specify lesion reactivity or renewed inflammatory changes, which are also before BBB breakdown and not visible on cMRI. These findings are significant in that hemodynamic abnormality is a key factor in the pathophysiology of MS lesions. Perfusion imaging might have a predictive role of lesion reactivity and/or new lesion creation and, consequently, has the potential to predict disease activity, and monitor disease progression or the effects of therapy (Holdsworth, 2008).

**MRS:** MRS allows noninvasive characterization of metabolic abnormalities in the central nervous system. MRS provides significant insights into the chemical–pathological fluctuations that happen in patients with MS, not only within focal lesions visible on cMRI, but also within the normal appearing brain tissue, thereby increasing our knowledge about the pathological processes occurring in this disease. This method is particularly

valuable for assessing the neurodegenerative component of MS, which is known to start in the early phases, through quantitative valuationof the amino acid N-acetyl aspartate (NAA), reflected a marker of neuronal/axonal function and density. Other metabolites, for examplecholine (Cho), myo-inositol (mIns), creatine (Cr), glutamate (Glu), lipids, and lactate (Lac) which play an significant role in the pathophysiology of the inflammatory factor and repair mechanisms of MS, can also be detected with MRS. The aim of the first MRS studies was to characterize MS lesions in their different stages of evolution. Acute gadolinium-enhanced MS lesions normally display surges in Cho and Lac resonances throughout the first 6–10 weeks following their appearance on cMRI. Enlarged Cho concentration can be inferred as a measure of membrane phospholipids released throughout active myelin failure and of increased cell density due to the presence of inflammatory cells. Lac increases mainly reflect the metabolism of inflammatory cells or neuronal mitochondrial dysfunction. The NAA pattern in the acute phase of lesion development is highly adaptable, ranging from almost no change with respect to normal brain tissue to significant decreases. Since NAA is spotted almost fully in neurons in the healthy adult brain, decreases in this metabolite are interpreted as a measure of neuronal/axonal dysfunction or loss. This initial NAA reductionmay continue, indicating lasting neuroaxonaldamage, or show partial recovery starting a few weeks after the onset of lesion growth and continuing for numerous months. Few MRS studies have concentrated on the changes that take place in other metabolites, and the results are sometimes contradictory. Of specific significance in MS plaques is the behavior of Cr, a metabolite present in both neurons and glial cells, with higher doses in glia than in neurons Cr, which commonly remains stable, can show significant increases or decreases. These changes may be related to varying amounts of neuroaxonal and oligodendroglial loss, and astrocytic proliferation. Short echo time spectra provide indication of transient rises in visible lipids in some lesions, maybe released during myelin breakdown. These lipid peaks have been identified in prelesional areas; areas of NAWM that subsequently developed an MRI visible plaque. A localized increase in Cho has also been defined in areas of NAWM months before subsequent development of an MRI-visible plaque, which is consistent with focal prelesional myelin membrane disease. These remarks suggest that demyelination can occur months before acute inflammatory changes become evident. Other nonconventional MRI techniques, such as MTI, DWI, and dynamic susceptibility-weighted sequences have also shown abnormalities in this prelesional stage, further supporting the presence of subtle progressive changes in tissue integrity before focal leakage of the blood–brain barrier as part of plaque development in MS (Poser, 1983).

**Monitoring Treatment Efficacy:** MRI quantities are applied as surrogate outcome measures in treatment trials of MS because they are noninvasive, have high sensitivity toward disease activity, and are very reliable. Despite the fact that lesion activity and burden on post-contrast T1-weighted and dual-echo scans are the most commonly used measures to monitor treatment efficacy in MS trials, a recent pivotal study found a significant effect of pioglitazone in slowing GM atrophy accumulation during 1 year in patients with relapsing-remitting multiple sclerosis (RRMS). New MRI sequences such as double inversion recovery (DIR) that is a MRI pulse sequence which destroys signal from the CSF besides from the white matter and hence enhances any inflammatory lesion; have not yet been tested in the setting of clinical trials of MS, perhaps because they still need to be validated and standardized across different centers. On the other hand, several MS trials have incorporated MTI quantities as additional outcome measures. Two multicenter studies used MTI to determine GM damage in CIS and in patients with primary progressive multiple sclerosis (PPMS) (Fatehi, 2016). After correcting for the acquisition center, the researchers found pooled GM average MTI values to be different between patient groups and controls. One study used MRS to assess the efficacy of glatiramer acetate in patients with PPMS. At 3-year follow-up, no significant difference in metabolite ratios between treated and placebo patients was found in lesions, NAWM, and GM. Only recently has the potential of fMRI in prospective multicenter studies been considered in an international collaborative effort. Compared with controls, patients with MS had more important activations bilaterally in several regions of the sensorimotor network and abnormalities of effective connectivity during the performance of a simple motor task (Rahmani Tanha, 2016; Poser, 1983; Rasolabadi, 2015)

**What selection best method for diagnostic and following:** Hesseltine, shows that DTI (in combination with other MRI techniques such as MRS and PWI) may offer understanding into whether the pathophysiology of MS within the spinal cord is related to Wallerian degeneration or a primary ischemic phenomenon. In the diagnosis of RRMS by using DTI metrics, we have found that models using spatial DTI metrics are significantly more precise than models using the mean of metrics or central cord interrogation alone; we also found that models that used FA were superior to those that used MD (Fatehi, 2016). These findings help to explain the position of 3-Dinfo in DTI evaluation of the spinal cord. DTI measures free diffusion of water molecules, with directional information obtained by applying diffusion gradients along 6 or more noncollinear directions. In that the free diffusion of water molecules is hindered by factors counting cell membranes and myelin, DTI has shown theoretic capacity in detecting and evaluating the integrity of WM tracts; in animal models, DTI metrics in the various spinal cord tracts have been uncovered to correlate with specific histologic measures counting axon counts, extracellular and myelin volume, and axon diameter and spacing. Bot, have investigated the spinal cords of patients with MS postmortem using high-field

MRI with histopathologic association. These parameters were unresponsive to changes in axonal attenuation. The researchers also suggested that the decrease in spinal cord area seen in MS may relate to demyelination in addition to axonal attenuation, potentially limiting the utility of this nonconventional technique in the assessment of axonal damage. Given these postmortem findings as well as the histopathologic correlation in animal models, it is plausible that the measurement of DTI metrics may prove superior to other nonconventional techniques in the quantification of axonal pathology. Furthermore, DTI could be better than measurement of spinal cord area in measuring axonal damage, though the latter method of atrophic measure has been shown to correlate considerably with patient incapacity. In formulating quantitative diagnostic criteria for MS by using DTI metrics may be more useful than interrogation of regions of signal intensity irregularity. Changes in DTI metrics have been demonstrated within focal spinal cord plaques. Though, these findings are nonspecific; similar changes in DTI metrics have also been demonstrated in regions of signal intensity abnormality in patients with myelomalacia secondary to chronic spondylotic spinal cord compression. Furthermore, changes seen in the regions of spinal cord plaques, which probably reflect only the local effects of MS, may not relate to patient sickness which are probable reflect both the local effects of MS and secondary effects associated to brain lesions. Clinical DWI and DTI of the cervical spinal cord remain technically difficult. The small size of the spinal cord necessitates the employment of small voxel sizes for spatial resolution at the expense of signal intensity–to-noise ratio. Images may be degraded due to macroscopic motion associated to CSF pulsation, patient breathing, or gross patient motion. Local field inhomogeneity similarly add to image degradation. Echo-planar DTI can be done in a realistic amount of time for clinical use, and single-shot technique may limit the adverse effect of in-plane bulk motion to some extent. In the future, new techniques using parallel imaging, as well as pulse-triggering or cardiac gating, should further minimize image degradation. Another distinguished benefit of using high-field strength is that the susceptibility (T2*) effects are boosted, which improves the examination of microscopic venous structures, brain iron, and micro bleeds in the CNS diseases. The enhanced visualization of micro vascularity in brain tumors has been shown at higher strength. In MS, the distribution of lesions usually follows a peri-venous origin2; therefore, the relationship between microvascular abnormalities and lesions will be more appreciated at higher field. The enhanced T2* effects are also beneficial for dynamic contrast-enhanced perfusion MRI and functional MRI due to the increased resolution and conspicuity of paramagnetic contrast agents and deoxyhemoglobin. However, the susceptibility-induced signal intensity loss and distortion near the skull base and air sinuses are alsonoticeable at higher field strengths and should be carefully considered in clinical applications. In addition, with the improved sequence and design of the RF coil, the advantages of performing MRS at higher field strengths should also achieve increased SNR for more detailed compounds that are obscured at 1.5T. Thus, with the appropriate optimizations, high-field MRI will further strengthen the role of MRI in the study of MS (McDonald, 2001; Poser, 1983; Lee, 1991; Paty, 1988)

## 2. CONCLUSIONS

The application of nonconventional MRI based techniques has shown consistently that GM is not spared by MS and that GM damage, albeit with different patterns of regional distribution, is present in all MS phenotypes since the earliest clinical stages of the disease, affects various GM compartments, and is associated with the main clinical manifestations of MS. Several factors likely contribute to the GM damage of MS, including focal macroscopic lesions, intrinsic “diffuse” changes, and irreversible tissue loss. All of these abnormalities increase with time and are only partially associated with the extent of WM pathology. More recently, variable degrees of cortical plasticity with the potential to limit the functional consequences of tissue damage have been shown in patients with MS, suggesting that their disability is likely to result from the balance between structural damage and cortical reorganization, rather than being a mere reflection of tissue disruption. Measuring GM MRI variables might, therefore, bearewarding exercise for improving our understanding of MS pathobiology, which might result, in the future, in the identification of additional markers to monitor disease evolution, either natural or adapted by treatment. The extensive application of orthodox and modern MR-based methods to the study of MS has undoubtedly improved our aptitude to diagnose and monitor the disease, as well as our understanding of disease pathophysiology. Nevertheless, there are many remaining challenges. New acquisition schemes and analysis procedures require standardization and optimization so that they can be used in multisite settings, both in natural history studies and treatment trials. From the data available, it is clear that combining different MRI modalities, which are sensitive to different aspects of MS pathology, is a promising way to further increase our indulgent of the mechanisms accounting for the accumulation of permanent incapacity in this disease. Such an approach should include not only the assessment of brain damage, but also that of the spinal cord. Finally, the precision and correctness of quantitative MRI scans in spotting longitudinal, MS-related changes also need to be defined and individual extensive, prospective studies are necessary. This is a central issue for a future application of quantitative MRI to the monitoring of MS evolution in clinical trials.

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