J Neurol (2012) 259:611–621
DOI 10.1007/s00415-011-6195-6

REVIEW

The role of advanced magnetic resonance imaging techniques in primary progressive MS

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Received: 31 May 2011 / Revised: 13 July 2011 / Accepted: 14 July 2011 / Published online: 4 August 2011

Abstract Primary progressive multiple sclerosis (PPMS) is characterized by a steady progression of irreversible disability from the onset of the disease. Although magnetic resonance imaging (MRI) is a valuable tool to quantify the disease burden in the brain and spinal cord of patients with MS, measures derived from conventional MRI, including T2-visible lesions, gadolinium-enhancing lesions and atrophy, are correlated only weakly with the clinical manifestations of PPMS. On the contrary, advanced MRI techniques are contributing significantly to the understanding of the mechanisms underlying the irreversible accumulation of disability in PPMS patients. Data from quantitative MRI studies suggest that the extent and topography of "diffuse" damage in different central nervous system (CNS) compartments (i.e. normal-appearing brain white matter and grey matter and the spinal cord) is associated with the severity of disability in PPMS and can predict subsequent medium-term disease evolution. Functional MRI studies have shown that the impairment of the adaptive capacity of the cortex to limit the clinical consequences of structural CNS damage is yet another factor contributing to the manifestations of this condition.

Keywords Primary progressive multiple sclerosis · MRI · MT MRI · DT MRI · ^{1}H-MRS · fMRI

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Introduction

The clinical and magnetic resonance imaging (MRI) characteristics of patients with primary progressive multiple sclerosis (PPMS) are different from those of patients with relapsing-remitting (RR) MS and secondary progressive (SP) MS [48, 74]. Indeed, despite the irreversible accumulation of neurological disability, the majority of PPMS patients show a relatively low lesion activity and burden as detected on T2-weighted, T1-weighted, and gadolinium-enhanced scans of the brain [48, 74].

The application of advanced MR techniques has provided important insights into the pathobiology of MS [5]. These techniques, which include magnetization transfer (MT) MRI, diffusion tensor (DT) MRI, and proton MR spectroscopy (^{1}H-MRS), allow quantitative information on MS-related tissue damage to be obtained with a higher pathological specificity for the most destructive aspects of the disease (i.e. demyelination and neuroaxonal loss) than conventional MRI [5]. In addition, functional MRI (fMRI) is contributing to the definition of the role of cortical reorganization in limiting the clinical consequences of MS tissue damage [29].

After a brief description of neuropathological studies and a concise summary of conventional MRI findings in PPMS, this paper provides an up to date review of the major results of quantitative structural and fMRI studies in these patients and discusses how such MR techniques are contributing to the achievement of a more complete picture of the factors associated with the development of "fixed" disability in this condition. Although only a minority of PPMS patients experience relapses during the course of the disease (progressive-relapsing or transitional progressive MS) [22], this patient subgroup has not yet been characterized using these advanced techniques. As a

consequence, the imaging features in these patients are not discussed.

Pathology

Similar to the relapsing form of the disease, focal inflammatory demyelinating lesions with variable axonal damage are among the main pathological features of patients with progressive MS (PPMS and SPMS). However, in patients with progressive MS most focal white matter (WM) lesions are inactive demyelinated plaques or have a slow expansion at the lesion border, characterized by moderate inflammatory infiltrates and profound microglial activation [11]. Recently, Bramow et al. [12] have demonstrated higher remyelination capacity in the brain of patients with PPMS than in those with SPMS, whereas spinal cord remyelination capacity did not differ between the two groups.

Diffuse abnormalities of the normal-appearing (NA) WM outside lesions have been described in patients with progressive MS. They are characterized by diffuse inflammatory processes and generalized activation of microglia, associated with axonal injury and destruction, followed by secondary demyelination [41]. Importantly, the extent of global injury to the NAWM is not related to the number, size or location of focal lesions in the brain [41] and the spinal cord [28], suggesting that diffuse NAWM axonal injury occurs partially independently from focal plaques.

Extensive cortical demyelination (mainly represented by subpial demyelination), which in extreme cases can affect more than 60% of the cortical area, is another hallmark of the progressive forms of the disease [41].

Conventional MRI

Lesions

In PPMS, the low level of MRI-detectable disease activity and burden in the brain, in terms of T2-visible lesion load and gadolinium-enhancing lesions, is in contrast to the severity of the clinical manifestations and the steady progression of the disease [48, 74]. In the early phase of PPMS (during the first 5 years from onset), MR-detectable inflammation occurs more commonly than later in the course of the disease [34]; however, this has been shown to have only a minimal impact on the accumulation of disability over the subsequent 5 years [39]. Similarly, the number of T2-visible brain lesions at baseline does not seem to influence the rate of clinical progression in the subsequent 15 years in these patients [49].

Differently from the relapsing forms of the disease, where cord lesions are typically multifocal, shorter than two vertebral segments in length and occupy only part of the cord cross-sectional area, PPMS patients relatively often show diffuse mild hyperintensity on T2-weighted images [40, 46]. Disappointingly, these diffuse abnormalities are only weakly associated with clinical disability [46].

Several strategies have been applied to overcome the limitations of conventional MRI in the assessment of MS, including the application of voxel-wise methods for the analysis of the spatial distribution of focal lesions and the use of novel sequences, such as double inversion recovery (DIR), which allow the identification of at least a proportion of the lesions located in the brain grey matter (GM). In 80 PPMS patients, using a voxel-wise approach, one study has shown that the location of T2-visible lesions in the motor and associative WM tracts of the brain is able to predict the progression of disability after 10 years [9]. Another study has shown that the maximum probability for T2- and T1-visible lesions in the WM is higher in PPMS than in RRMS patients [26]. Using DIR sequences, cortical lesions (CL) have been shown in about 80% of patients with PPMS [13]. Notably, the number and extent of CLs have been associated with clinical disability and with its worsening over a 2-year follow up period [13]. A recent study found no difference between PPMS and RRMS patients in the frequency and volume of CLs or in their distribution across brain lobes. Interestingly, the extent of brain lobes affected by the presence of CLs was more widespread in RRMS than in PPMS patients. Conversely, the maximum probability of CL occurrence was twice as high in PPMS than in RRMS patients [14].

Atrophy

Brain and cord atrophy, which is likely to reflect irreversible tissue loss, is detectable on MRI scans from PPMS patients from the earliest clinical stages. A multicentre study of 226 patients demonstrated that both brain and cervical cord atrophy were correlated with the degree of disability measured using the Expanded Disability Status Scale (EDSS) and they were more severe in patients with locomotor disability than in those without [67]. Another multicentre study found that a reduction in brain volume over a 2-year period contributed to the prediction of EDSS progression over 10 years in 101 PPMS patients [38].

Improvements in MRI postprocessing now allow accurate estimates of brain GM and WM atrophy to be obtained separately, and its regional distribution to be defined. Atrophy of both the GM and WM has been shown to occur

in PPMS patients [70]. In particular, GM atrophy was found to worsen significantly over 1 year in these patients; on the contrary, WM atrophy remained stable [70]. Using voxel-based morphometry, several studies have also shown thalamic atrophy in PPMS patients [15, 35, 72]. In one of these studies, at 1 year tissue loss of the basal ganglia and cortical and cerebellar GM was also found [72]. The evaluation of the topography of GM atrophy has undoubtedly improved the correlation with disease clinical manifestations, including cognitive impairment [4, 57]. For instance, Riccitelli et al. [57] showed a significant GM loss in the anterior cingulate cortex and the right superior temporal gyrus in cognitively impaired versus cognitively preserved PPMS patients. Remarkably, the extent of anterior cingulate cortex atrophy was found to be correlated with the cognitive impairment index, a summary measure of neuropsychological deficits. Another study found a correlation between impairment of memory performance and hippocampal atrophy in these patients [4].

Although studies based on conventional MRI with new sequences and postprocessing approaches have undoubtedly contributed to a more complete picture of the extent of CNS involvement in patients with PPMS, the ability of these techniques to define the factors leading to irreversible disability in this condition is still suboptimal. This has led to the increased use of advanced MR techniques which, due to their sensitivity to the most destructive aspects of the disease, have the potential to improve our understanding of PPMS pathobiology.

MT MRI

Basic principles

MT MRI provides an index, called the MT ratio (MTR), whose values reflect the efficiency of the magnetization exchange between protons in tissue water (relatively free) and those bound to the macromolecules. MTR values are decreased when CNS tissue injury occurs. A post-mortem study [78] has provided compelling evidence that marked reductions in MTR values in MS lesions and NAWM are strongly correlated with the percentage of residual axons and the degree of demyelination. Another study performed on human specimens has confirmed the ability of this technique to provide information on tissue integrity, by showing that MTR values of remyelinated lesions are higher than those of demyelinated ones, which in turn are much lower than those of the NAWM [6]. Consistent with this, several in vivo MT MRI studies have shown decreased MTR values in T2-visible lesions, NAWM and GM from MS patients with different clinical phenotypes of the disease.

MT MRI studies of PPMS

Lesions

MTR values of T2-visible lesions are decreased with respect to those of the NAWM in PPMS patients [33, 44], but no difference was found in average MTR values of T2-visible lesions between PPMS and other MS clinical phenotypes [33, 61].

NA brain tissue

Using a region of interest (ROI) analysis, reduced MTR values have been shown in the NAWM of PPMS patients in comparison to the WM of healthy controls [33, 44]. The application of histogram analysis to the study of the NA brain tissue (NABT) and NAWM damage has confirmed and extended previous findings, by showing that such "occult" damage is more pronounced in SPMS and PPMS patients than in patients with other disease phenotypes [30, 75]. On the contrary, no NAWM MTR difference was found between patients with the two progressive forms of the disease [61] (Fig. 1). This may indicate that in both PPMS and SPMS a progressive reduction in cerebral tissue with "truly" normal MTR values accompanies the irreversible accumulation of disability, independent of the concomitant accumulation of MRI-visible lesions. Such a notion is supported by the finding that average brain MTR values are only modestly correlated with T2- and T1-visible lesion load [61]. All of this suggests that NABT/NAWM pathology in PPMS not merely reflects Wallerian degeneration of axons traversing macroscopic lesions, but

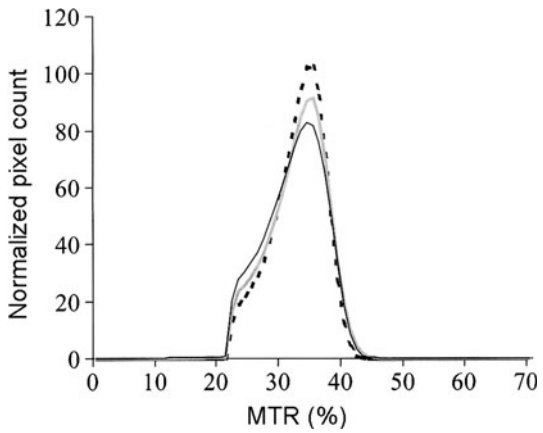

Fig. 1 Average MTR histograms of NABT from healthy controls (*dotted line*), and patients with PPMS (*grey line*) and SPMS (*black line*). The MTR histogram peak heights in both PPMS and SPMS patients are lower than in healthy controls. The MTR histograms are not different between patients with the two progressive forms of the disease (reproduced from reference [61], by permission of Oxford University Press)

might also be related to the occurrence of subtle pathology independent of focal, macroscopic WM lesions.

Grey matter

MT MRI abnormalities have been shown in the GM of PPMS patients [17, 25, 56] and were found to correlate with the severity of clinical disability [17, 25, 56]. More recently, using a voxel-based approach, Khaleeli et al. [35] showed a significant correlation between regional decreases of MTR values in cortical areas of the motor network and the EDSS score, and between MTR values in the cortical areas of the cognitive network and Paced Auditory Serial Attention Test (PASAT) scores.

Longitudinal studies

The results of a few longitudinal studies suggest that MT MRI has the potential to provide surrogate markers of disease progression in PPMS [36, 37]. In patients with early (within 5 years of disease onset) PPMS, lower NAWM MTR values at baseline predict a more severe deterioration of disability over 1 year [36] and 3 years [37], as measured using the EDSS and the MS functional composite scores. More recently, a 5-year follow-up study of this cohort showed that the volume of T2-visible lesion and GM MTR abnormalities at baseline independently predicted disease progression, as measured by the 25-foot timed walk test. A faster progression rate correlated with a steeper increase in the volume of T2-visible lesions and a more rapid decline in GM MTR [76]. In early PPMS, Penny et al. [53] have shown that a low baseline GM MTR predicts a poor performance in neuropsychological tests assessing attention, speed of information processing and executive functions 5 years later.

Cervical cord

MT MRI has been applied to investigate damage to the cervical cord in PPMS patients, using histogram-based analysis [30, 45, 61]. Lycklama a Nijeholt et al. [45] reported that a composite measure taking into account cervical cord MTR and cross-sectional area improves the strength of the correlation between cervical cord MRI findings and the EDSS score. In a study by Rovaris et al. [61], cord MTR histogram metrics were significantly worse in SPMS than in PPMS patients, despite the presence of a similar burden of cervical cord lesions. In the same study, no significant correlation was found between conventional and MT MRI measures of MS pathology in the brain and cord, suggesting that degenerative processes affecting long fibre tracts passing through brain lesions play only a modest role in determining the severity of cervical cord damage in PPMS. By combining cord measures reflecting the severity of atrophy (cross-sectional area at the C2 level) and intrinsic damage to the remaining tissue (MTR histogram peak height) in a composite model, a relatively low ($r = 0.21$) but significant correlation with clinical disability was found.

DT MRI

Basic principles

DT MRI allows quantitative measurements of brain tissue microstructure to be obtained through the exploitation of the properties of water diffusion [42]. Water molecules undergo a random Brownian motion, that can be influenced by the characteristics of the surrounding medium, because of the presence of partially permeable barriers and aligned structures. These characteristics are reflected by the magnitude and directionality of diffusion. Since diffusion in solid tissues is an inherently three-dimensional and anisotropic process, DT MRI has been developed to fully characterize the various aspects of diffusion [7, 54]. From the tensor, it is possible to calculate the magnitude of diffusion, reflected by mean diffusivity (MD), and the degree of anisotropy, which is a measure of tissue organization that can be expressed by several indexes, including a dimensionless one, called fractional anisotropy (FA). The pathological elements of MS have the potential to alter the permeability and geometry of structural barriers to water diffusion in the CNS. Consistent with this, several in vivo DT MRI studies [65] have shown increased MD and decreased FA values in T2-visible lesions, NAWM and GM from MS patients. The main post-mortem correlates of diffusivity changes in MS are demyelination and axonal loss. This is more evident for anisotropy indexes than for MD [50].

DT MRI studies of PPMS

Overall brain damage

In the past decade, several DT MRI studies have been conducted in PPMS patients [17, 19, 20, 27, 31, 62]. Seminal studies [20, 27, 31] with partial brain coverage and based on ROI analysis compared the DT MRI characteristics of MS patients with various clinical phenotypes of the disease and found no significant difference between them.

Using a histogram-based analysis, Cercignani et al. [18] obtained MD and FA histograms from a large portion of the central brain (i.e. including both T2-visible lesions and NABT) from a relatively large sample of MS patients with

different clinical phenotypes, including PPMS. All the histogram-derived quantities were significantly different between PPMS patients and healthy controls, but no difference was found with the other disease phenotypes. In addition, no significant correlation was found between DT MRI findings and disability, contrary to what has been seen for the other MS subgroups [18].

Location of damage

DT MRI has been applied to quantify damage to the NAWM and GM separately in PPMS patients [10, 62]. These studies confirmed that both these brain compartments are involved by the disease. Damage to the NAWM and GM is only partially correlated with the extent of focal lesions and the severity of intrinsic lesion damage [65], suggesting that diffusivity changes in NA tissues are not entirely dependent upon retrograde degeneration of axons transected in T2-visible lesions.

A large-scale study compared DT MRI histogram-derived findings from PPMS patients with those from SPMS patients and healthy subjects [62] (Fig. 2). Average MD of lesions, NAWM and GM were significantly higher in SPMS than in PPMS patients, while FA histogram-derived quantities did not significantly differ between the two groups. The clinical and radiological 15-month follow-up of these patients showed that DT MRI abnormalities of the GM worsen over time [64], and that the severity of diffusion abnormalities in the GM at baseline predicts disability accumulation at 5 years [66]. Recently, Mesaros et al. [47] have investigated whether conventional and DT MRI measures of thalamic damage are predictive of medium-term disability accumulation in patients with PPMS. This study demonstrated that average NAWM MD at baseline and FA thalamic change during the first 15 months of the study were independent predictors of EDSS score deterioration after 5 years.

Topography of damage

Using a voxel-based approach, a study [15] evaluated the distribution of WM and GM damage in PPMS patients, and showed the presence of DT MRI abnormalities in brain areas associated with motor and cognitive functions (Fig. 3). This supports the notion that the assessment of regional damage using DT MRI may be more rewarding than that of "global" brain damage for gaining an insight into the relationship between clinical status and pathological disease burden in MS. Bodini et al. [8] investigated the relationship between damage occurring in the NAWM and GM in patients with early PPMS and found 11 brain regions with an anatomical correspondence between reduced NAWM FA values and GM atrophy, supporting a link between pathological processes occurring in the NAWM and GM of these patients.

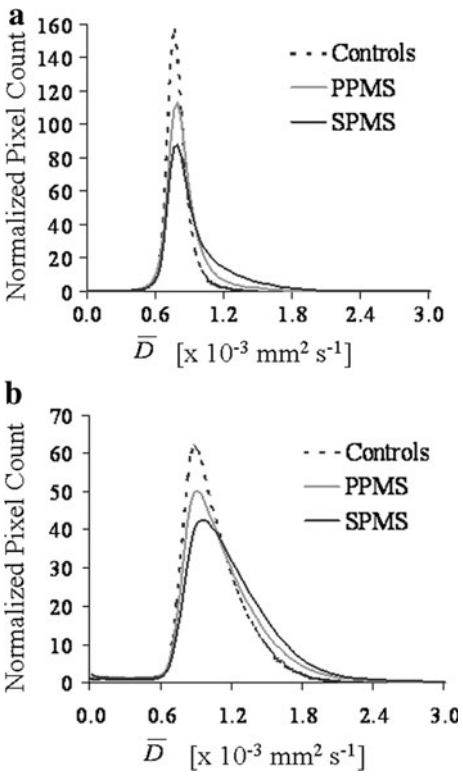

Fig. 2 Average MD histograms of the NAWM (**a**) and GM (**b**) from healthy controls (*dotted line*), and patients with PPMS (*grey line*) and SPMS (*black line*). In comparison with the histogram peak height (which reflects the amount of "truly" normal tissue) in healthy controls, a lower height is seen in both PPMS and SPMS patients, particularly in the latter group of patients (reproduced with permission from reference [62], Copyright 2002, American Medical Association. All rights reserved)

Cervical cord

Diffusion MRI of the spinal cord is technically more challenging than that of the brain, and diffusivity studies of this structure are, therefore, scanty. Nevertheless, the development of novel DT MRI sequences has made it possible to obtain accurate estimates of the extent of damage to this CNS region. Patients with PPMS have abnormal diffusivity and anisotropy of the cervical cord [1]. A 2-year follow-up study of a relatively large cohort of MS patients (including 13 patients with RRMS, 14 with SPMS, and 15 with PPMS) using conventional and DT MRI of the cervical cord [2] showed that the cord area decreased during follow-up at a similar rate in the three patient groups. An increase in average MD and a decrease in average FA of the cord were also observed in these patients. While the increase in MD was independent of clinical phenotype, the decrease in FA was associated with patient age (being higher in younger patients) and clinical

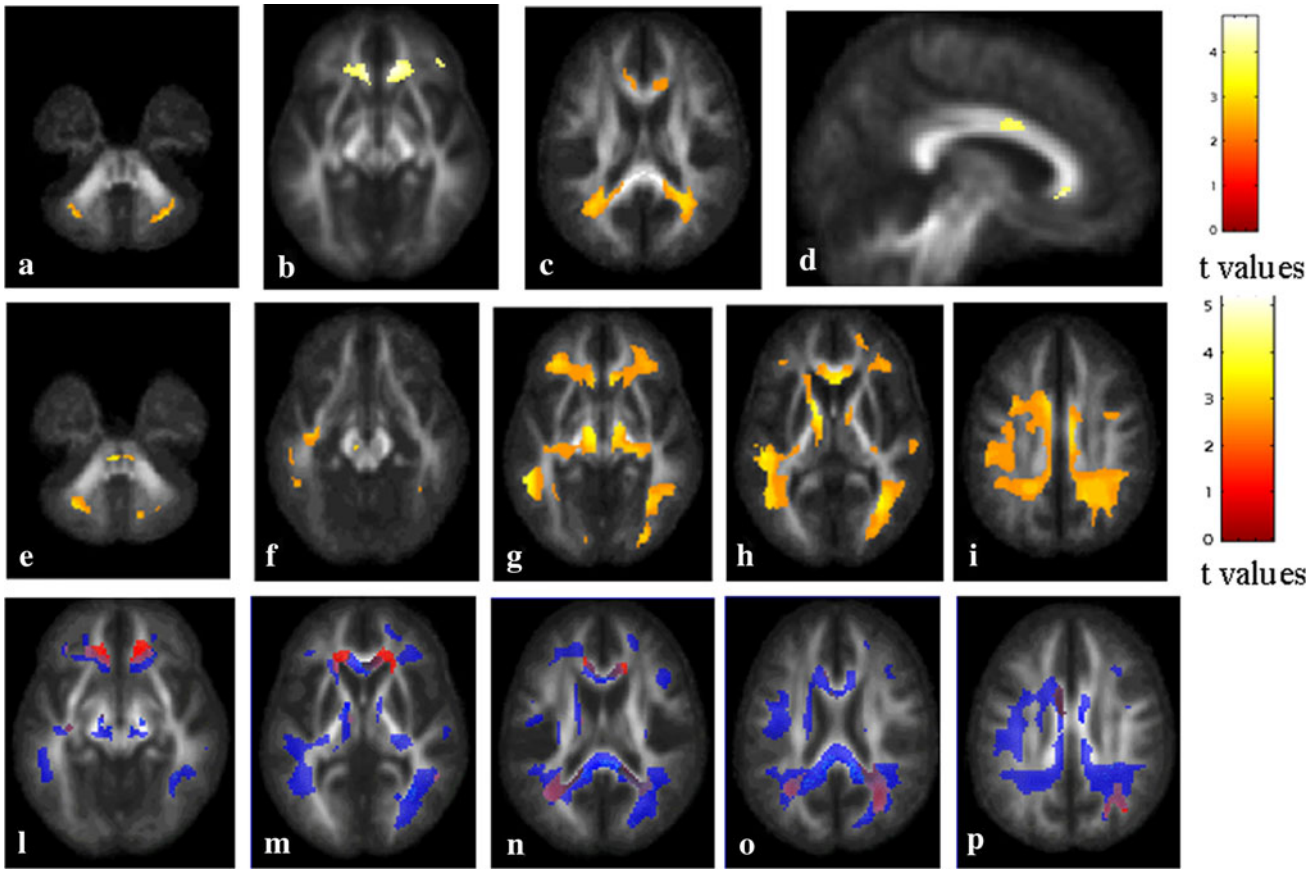

Fig. 3 *Top row* Statistical parametric mapping regions (colour-coded for *t* values) with decreased WM FA values in patients with PPMS compared with controls ($p < 0.001$, false discovery rate-corrected). Several regions of the frontal and temporal lobes, the corpus callosum, cingulum, optic radiations and middle cerebellar peduncle bilaterally, appear to be damaged. *Middle row* Statistical parametric mapping regions (colour-coded for *t* values) with increased WM MD in PPMS patients compared with control subjects ($p < 0.001$, false discovery rate-corrected). Bilateral MD abnormalities are visible in the major short and long intrahemispheric associative pathways, as well as in the corpus callosum and cingulum. *Bottom row* Statistical parametric mapping regions with anatomical correspondence between decreased WM FA (*red*) and increased WM MD (*blue*). An overlap is visible in the corpus callosum, cingulum, left short temporal fibres, right short frontal fibres, optic radiations and middle cerebellar peduncles. Images are in accordance with neurological convention (reproduced from reference [15], with permission)

phenotype (being more marked in PPMS patients than in those of the other two groups).

^{1}H-MRS

Basic principles

Proton MR spectra of human brain tissue at long echo times reveal four major resonances [69]: one from choline-containing phospholipids (Cho), one from creatine and phosphocreatine (Cr), one from *N*-acetyl-aspartate (NAA) and one from the methyl resonance of lactate (Lac). NAA is a marker of neuroaxonal integrity, and Cho and Lac are thought to be the biochemical correlates of inflammation and demyelination. ^{1}H-MRS studies in MS have shown that NAA levels are reduced both in lesions and NAWM [69], and are significantly correlated with patient clinical disability. ^{1}H-MRS data have emphasized the so-called "axonal hypothesis", i.e. the notion that a progressive loss of axons is one of the key factors underlying the irreversible accumulation of disability in MS.

^{1}H-MRS studies of PPMS

Single-voxel and multivoxel studies

The majority of the ^{1}H-MRS studies in PPMS patients [23, 24, 43, 55, 73] have been conducted with single-voxel or multivoxel imaging techniques. Despite differences in patient selection and study design, ^{1}H-MRS data

obtained from PPMS patients show consistently that NAA levels are decreased significantly in the NAWM of these individuals in relation to the WM of healthy controls. Comparisons of ^{1}H-MRS findings between patients with PPMS and those with other disease phenotypes did not show any significant group difference in terms of lesional and NAWM levels of NAA and other metabolites [24, 43, 55, 73, 79], with the exception of a single study [73] that found higher lesional and NAWM Cho/Cr values in PPMS than in RRMS patients. Only a minority of available ^{1}H-MRS studies of PPMS [24, 43, 73] have sought to correlate metabolite values with disability, and no significant clinical/^{1}H-MRS relationship has been reported, with the exception of a study by Suhy et al. [73], who assessed 12 PPMS patients and found a correlation between NAWM NAA/Cr and the EDSS score ($r^2 = 0.67$).

New developments

The development of an unlocalized ^{1}H-MRS sequence for measuring NAA levels in the whole brain has confirmed the presence of marked neuroaxonal pathology in patients with PPMS [63]. No correlation has been found between whole-brain NAA concentration and volume of T2-visible lesions, confirming that T2-visible lesions represent just a small component of overall neuroaxonal injury in this MS phenotype. Metabolite abnormalities, including decreased NAA and glutamate, have been shown in the cortex of patients with early PPMS and have been found to be correlated with the EDSS score [71].

Multicentre studies and treatment trials

In only one multicentre study has ^{1}H-MRS data been used to assess PPMS patients [51]. This study showed comparable cross-sectional ^{1}H-MRS values in healthy controls from different centres, indicating that ^{1}H-MRS is reproducible across sites, when factors such as data acquisition, position and size of the volume of interest, postprocessing, and quantification procedures are standardized. In addition, differences in NAA/Cr ratio between controls and PPMS patients were consistent among centres [51]. A 3-year follow-up study [68] did not detect any significant difference in metabolite ratios in lesions, NAWM and GM between patients treated with glatiramer acetate and those receiving placebo. However, there were also no detectable temporal changes in metabolite ratios in the two groups of patients relative to baseline values during the study period. As a consequence, the sensitivity of ^{1}H-MRS for detecting MS-related changes in clinical trials remains to be established.

Functional MRI

Basic principles

The signal changes seen during fMRI studies depend on the blood oxygenation level-dependent (BOLD) mechanism, which in turn involves modifications of the transverse magnetization relaxation time—either T2* in a gradient echo sequence, or T2 in a spin echo sequence. Such changes are attributable to differences in deoxyhaemoglobin concentration following variations in neuronal activity [52]. The correlation between local deoxyhaemoglobin levels and neuronal activity is thought to result from changes in oxygen extraction, cerebral blood flow, and cerebral blood volume [52]. Activation of a given brain area causes an increase in local synaptic activity, which results in a rise in blood flow and oxygen consumption. The increase in blood flow is greater than oxygen consumption, thus causing an increase in the ratio between oxygenated and deoxygenated haemoglobin, which enhances the MRI signal. Using fMRI with motor, visual and cognitive tasks, several studies have shown that cortical reorganization does occur in MS patients with different clinical phenotypes [29]. The correlation between various measures of structural MS damage and the extent of cortical recruitment consistently found by these studies [29] suggests that adaptive cortical changes limit the clinical consequences of tissue injury in patients with MS.

fMRI studies in PPMS

Movement-associated activations

Only a few studies [16, 21, 32, 58, 59] have assessed the degree of cortical functional reorganization in PPMS patients. Nevertheless, understanding to what extent cortical reorganization occurs in these patients and whether it has an adaptive role might be rewarding in terms of providing a better understanding of the pathophysiology of progressive disability in MS. Since differences in task performance is one of the main factors that might bias the results of fMRI experiments, fMRI studies of the motor system in PPMS patients have typically assessed highly selected groups of patients with a fully normal motor functioning of the limb investigated [16, 32, 58], or analysed the performance of passive motor paradigms [21]. Studies which have assessed the performance of a simple motor task with the dominant right upper limb [16, 32, 58] have shown a significant cortical reorganization of a distributed cortical network considered to function in motor, sensory and multimodal integration processing, which extends well beyond "classical" motor areas involved in different phases of movement planning and execution

(Fig. 4). The absence of a concomitant recruitment of the "classical" motor areas, including the primary and secondary sensorimotor cortices, supplementary motor area and infraparietal sulcus, was interpreted as a loss of the adaptive properties of the cortex in this severely disabling phenotype of the disease. These studies also suggested that sites for multimodal integration, which are not usually activated with a simple motor task, might be recruited to maintain functional capacity in response to tissue damage. Consistent with this hypothesis, significant correlations have been found between relative activations of these areas and the severity of structural damage to the brain and cervical cord [32]. In particular, a recent study [16] that combined DT MRI tractography and functional connectivity analysis of the motor network found that an abnormal functional connectivity between the motor and visual network was correlated with the extent of damage to the inferior longitudinal fasciculus, frontooccipital fasciculus and optic radiations. The notion that high-order cortical areas might play a role in CNS rewiring in PPMS patients is also supported by the results of a study by Ciccarelli et al. [21], who, to avoid biases related to patient clinical impairment in the fMRI results, investigated the performance of an active and a passive motor task. During passive movements, compared to controls, PPMS patients had an increased recruitment of the superior temporal gyrus, rolandic operculum and putamen. The fMRI response to active and passive movements in the ipsilateral inferior frontal gyrus was lower in patients with higher disability and higher load of T2-visible brain lesions.

Cognitive studies

At present, only one study has assessed fMRI correlates of cognitive network function in patients with PPMS during the performance of the two-back task [59]. This study found that the regions engaged during the performance of this cognitive task differ between cognitively preserved and cognitively impaired PPMS patients, with a prominent recruitment of areas located in the frontal lobes in the cognitively preserved patients and in the parietal lobe and cerebellar regions in the cognitively impaired patients. Such fMRI findings were related to T2-visible lesion burden, suggesting that accumulation of T2-visible lesions and the consequent exhaustion of frontal lobe plasticity might contribute to cognitive impairment in PPMS.

fMRI at rest

The exploration of brain activity at rest is a strategy to avoid the influence on fMRI data from between-subject variability in task performance. Using such an approach, Rocca et al. [60] explored abnormalities of the default-mode network (DMN) in patients with SPMS and PPMS. Between-group differences in DMN activity were found in several regions within the anterior portion of this network in both groups of patients. Remarkably, DMN abnormalities correlated with cognitive performance and diffusivity abnormalities in the corpus callosum and cingulum.

Cervical cord

Functional MRI has also been applied to assess functional abnormalities in the spinal cord of MS patients [3, 77]. A study has interrogated neuronal activity in the cervical cord during tactile stimulation of the right upper limb [3], and found that PPMS patients experienced greater average cord fMRI recruitment than controls. Mildly disabled patients had a pattern of fMRI activity distribution similar to that of controls, with a right-sided lateralization, whereas severely disabled patients showed a bilateral pattern of cord recruitment. In PPMS patients, overall cord average fMRI signal change correlated significantly with cord average FA, again suggesting a possible adaptive role of such an abnormal recruitment. More recently, Valsasina et al. [77] compared touch-associated cervical cord fMRI activity between PPMS and SPMS patients and found that, despite similar structural cord damage, cord activity was greater in SPMS than in PPMS patients.

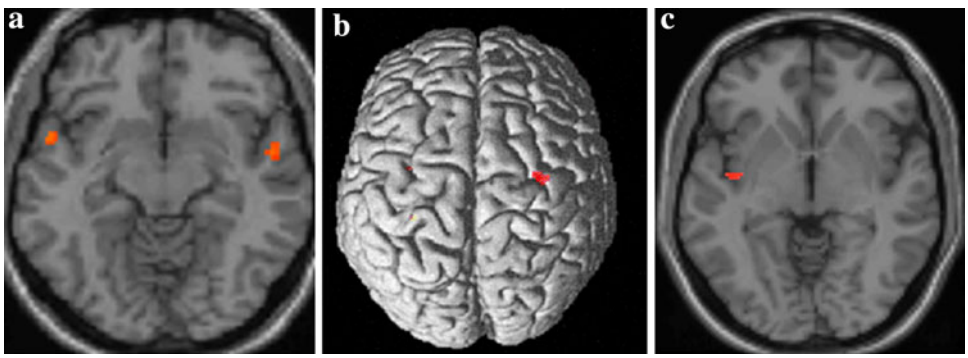

Fig. 4 Relative cortical activations of (**a**) the bilateral superior temporal gyrus, (**b**) the ipsilateral middle frontal gyrus, and (**c**) the contralateral insula/claustrum in right-handed PPMS patients versus healthy controls during the performance of a simple motor task using their clinically unimpaired right hand (reproduced from reference [32], Copyright 2002 with permission from Elsevier)

Conclusion

The application of quantitative MR techniques has contributed significantly to the improvement in our understanding of the mechanisms responsible for the steady irreversible accumulation of clinical disability in patients with PPMS. The results of MT and DT MRI studies of the brain support the notion that tissue damage which goes undetected when using conventional MRI does affect the NAWM and GM of these patients. MT MRI studies of the cervical cord indicate that, whereas MS brain pathology may follow different patterns in PPMS and SPMS, cord damage is important in both phenotypes in determining an irreversible accumulation of disability. ^{1}H-MRS studies have found consistently that neuroaxonal injury is a remarkable feature of brain damage in PPMS patients. fMRI studies have shown that cortical functional changes occur in patients with PPMS, and involve distributed networks. Such abnormalities of function are related to the extent of structural CNS damage, thus supporting the notion that cortical adaptive responses may play a role in compensating for tissue injury in PPMS. As a consequence, the rate of accumulation of disability in PPMS might not only be a function of tissue loss, but also of progressive failure of the adaptive capacity of the cortex. Further studies are needed to investigate the role of MR techniques in characterizing the pattern of damage in patients with less-prevalent phenotypes of PPMS, such as transitional progressive MS.

Conflicts of interest None.

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