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REVIEW

The Role of Advanced Magnetic Resonance Imaging Techniques in Multiple Sclerosis Clinical Trials

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Abstract Magnetic resonance imaging has been crucial in the development of anti-inflammatory disease-modifying treatments. The current landscape of multiple sclerosis clinical trials is currently expanding to include testing not only of anti-inflammatory agents, but also neuroprotective, remyelinating, neuromodulating, and restorative therapies. This is especially true of therapies targeting progressive forms of the disease where neurodegeneration is a prominent feature. Imaging techniques of the brain and spinal cord have rapidly evolved in the last decade to permit *in vivo* characterization of tissue microstructural changes, connectivity, metabolic changes, neuronal loss, glial activity, and demyelination. Advanced magnetic resonance imaging techniques hold significant promise for accelerating the development of different treatment modalities targeting a variety of pathways in MS.

Keywords Advanced imaging · Clinical trials · Multiple sclerosis · Magnetic resonance imaging · MRI

Conventional Imaging

In clinical trials, conventional magnetic resonance imaging (MRI) has been used to confirm the diagnosis and determine efficacy of disease-modifying treatments (DMTs) through measurement of new lesion counts and volumes. A very strong correlation between the effect on new lesion formation and the effect on relapses has been found with DMTs and allowed for screening of novel therapeutics in phase II trials [1]. The term "no evidence of disease activity", referring to a composite of a lack of 1) clinical relapses; 2) Expanded Disability Status Scale (EDSS) progression; and 3) MRI activity [new/enlarging T2 or gadolinium-enhancing (GdE) lesions and possibly brain atrophy] was based on outcomes routinely collected in contemporary clinical trials, but may be applied in clinical practice [2]. Furthermore, the presence of T1 hypointensities ("black holes"), has been characterized as the hypointensities indicate more significant axonal loss [3] and correlate with increased disability [4]. More diffuse measures of tissue injury, including measurement of whole-brain or gray-matter volumes, have been used extensively in clinical trials as secondary outcomes. There are ongoing improvements in acquisition methods [5], increased field strengths for superior signal or contrast to noise ratio [6], and contrast agents [7] to improve lesion identification.

There are noteworthy limitations with conventional imaging that contribute to the so-called clinicoradiological paradox. "Normal-appearing" white and gray matter (NAWM and NAGM, respectively) by conventional standards retain significant abnormalities detectable only by more advanced techniques. Even the canon that white matter (WM) T2/fluid-attenuation inversion recovery (FLAIR) lesions depict demyelination has been challenged with findings of normal myelin content in up to 30% of T2 hyperintense/T1 hypointense/low magnetization transfer ratio (T2/T1/MTR) lesions [8]. Developments in imaging methodology with histopathologic and clinical correlations will greatly improve our ability to test specific pathogenic mechanisms and therapeutic targets.

Whole-brain atrophy (WBA) in multiple sclerosis (MS) occurs at a rate approximately 3 times faster than healthy

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controls [9] early in the course [10], can limit brain grown in pediatric-onset MS [11], correlates with disability progression [12], and is associated with cerebrospinal fluid (CSF) levels of neurofilament light chain and tau [13]. Evaluating brain volume as a secondary outcome in trials is feasible and has demonstrated effects for nearly all approved MS DMTs and has been used as a primary outcome in secondary progressive MS [14]. WBA, however, has been criticized as it changes slowly, and there is considerable variability within subjects and across different atrophy software algorithms.

Advanced Imaging

Techniques discussed here strive to provide greater *in vivo* insight into the neurodegenerative and inflammatory aspects of MS otherwise unrecognized using conventional imaging. These methods may provide improved sensitivity as biomarkers of disease activity and progression, and may even be used as surrogate outcome measures of efficacy in therapeutic clinical trials.

Cortical Lesions

Lesion detection is paramount for monitoring disease activity and efficacy of DMTs [15, 16]. Cortical lesions (CLs), more common in secondary progressive MS (SPMS) than in clinically isolated syndrome (CIS) or relapsing remitting MS (RRMS) [17], are nearly invisible by conventional techniques but can be more readily identified using advanced methods. Cortical and deep gray matter (GM) pathology surpasses WM lesions in association with disability, progression [18], and cognitive impairment [19, 20]. Use of ultra-high field 7 Tesla (T) MRI nearly doubles CL detection *versus* 3 T and is able to detect 100% leukocortical, 11% intracortical, 32% subpial, and 68% subpial extending entire width of the cortex (types 1–4, respectively), with postmortem validation [21]. Three-dimensional (3D) double inversion recovery (DIR) allows for suppression of the CSF and WM in FLAIR, detects 18% of CLs *versus* postmortem verification, and is 1.6-fold superior to 3D-FLAIR [22]. Phase-sensitive inversion recovery may be useful concomitantly with DIR to further improve CL contrast [23]. GM juxtacortical lesions have been identified with phase difference-enhanced imaging [24], and 3D magnetization-prepared rapid acquisition with gradient echo can also help classify CL type [25].

CL volume may be an additional outcome measure to WM lesion burden in clinical trials given its potential for correlating with EDSS. Trials that employ neuroprotective measures or target cognition may specifically benefit from CL measurement. Furthermore, distinguishing specific CL types, such as leukocortical lesions, may improve correlations with cognitive impairment [26].

Regional Atrophy

Regional measures in atrophy may provide improved specificity for different pathogenic processes in MS and may be used as candidate measures for clinical trials. Regional and deep GM atrophy is noted early in MS and correlates with disability progression more than WBA or T2 lesion volume (T2LV) [27]. Evaluating GM fraction independently has unmasked its potential for predicting disability and risk of secondary progression [28]. Thalamic atrophy, in particular, is present even in CIS [29]; is associated with the risk of clinically definite MS; and can be useful in discriminating MS from neuromyelitis optic spectrum disorders (NMOSD) [30]. Thalamic volume is overwhelmingly associated with cognitive impairment in MS [31], and is a reflection of extrathalamic injury more significantly than thalamic lesions [32].

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an imaging technique that reflects microstructual changes in tissue by investigating the Gaussian diffusivity of water. Each voxel represents a measurement of multiple diffusion-weighted acquisitions that is modeled mathematically as a diffusion tensor—a 3 × 3 matrix comprised of 3 perpendicular eigenvectors with corresponding eigenvalues. Diffusion in WM is anisotropic (not equally restricted in all directions) and follows the direction of the axon. DTI measures include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) (sometimes referred to as longitudinal diffusivity), and radial diffusivity (RD) (sometimes referred to as transverse diffusivity).

RD is calculated as the mean of the 2 eigenvectors perpendicular to the long axis of the diffusion ellipsoid and inversely correlates with myelin content [33]. AD is the eigenvector parallel to the direction of the ellipsoid and has been loosely correlated with axonal content [34]. MD is calculated as the mean of all 3 eigenvectors and increases with architectural injury from increased isotropic water diffusion [35]. FA is an index of the asymmetry or directional preference of diffusion in a voxel and correlates with axonal counts and myelin content in MS [36]. While the degree of decrease in FA correlates to decreased axons and myelin [37], an increase in GM (cortex and thalamus) is thought to be due to decreased dendritic arborization [38]. These metrics are able to identify subtle changes in prelesional NAWM and NAGM, and lesional tissue that is otherwise unapparent or indistinguishable by conventional imaging.

In acute MS lesions, a reproducible pattern of decreased FA, increased MD, and increased RD is generally seen. Changes in NAWM, such as decreased FA and increased MD and RD, can be detected at baseline in CIS and progress over time. [39]. Comparing progressive courses, the average lesional, NAWM, and NAGM MD is higher in SPMS *versus*

primary progressive MS (PPMS) [40]. DTI is also able to detect changes in normal-appearing cortical and deep GM. MD increases in NAGM of untreated patients with RRMS over time independent of brain atrophy [41]. DTI measurements in the thalamus also change in patients with MS *versus* controls [42]. Increases in thalamic MD are relevant as they correlate with global EDSS, as well as T1 and T2LV [43]. While reduction in thalamic FA correlates with thalamic atrophy, thalamic or WM lesions do not [44].

DTI changes are apparent in even in prelesional NAWM. Increase in NAWM MD, suggestive of tissue injury, precedes GdE by 6 weeks [45]. RD and MD increases also have been noted 10 months prior to GdE, suggesting tissue injury prior to breakdown of the blood–brain barrier [46].

DTI has the potential to discriminate evolution of lesions, as well as mechanistic differences. FA has been shown to decrease in major WM tracts following GdE, even in locations distinct from the lesion location when tracked longitudinally [47]. The majority of chronic T2 lesions have a T1 hypointensity ("black hole") at their core characterized by axonal loss [3] with higher AD and RD [48]. Active lesions with increased RD in 1 study suggested more severe demyelination and predicted the development of T1 hypointensities [49]. Another study found increased AD in active lesions, and the authors speculated glial recruitment may have been responsible [50]. Interestingly, the T2 rim in the periphery of a lesion has significantly higher RD compared with AD, suggesting relative axonal preservation [48].

Other methods to characterize myelin injury or clinical disability corroborate DTI measurements. Changes in DTI metrics along WM tracts correlate with quantitative T2*, a marker of iron deposition due to myelin injury, in associated and unrelated cortical projections. Associations between DTI metrics (e.g., AD and RD) also correlate with clinical measures such as the pyramidal EDSS subscore and Symbol Digit Modalities Test (SDMT) [51].

DTI has been used to identify the association between specific cognitive domain impairment and functional networks. FA was found to be decreased in the limbic pathway, particularly the cingulum, fornix, and uncinate WM tracts, in relapsing MS *versus* control [52]. Decreased FA and increased RD correlated with SDMT measures in tracts associated with cognition [53]. A decrease in hippocampal FA was present in patients with CIS more than controls and an increased hippocampal MD was able to discriminate patients with CIS and poor delayed recall [54].

DTI has been used to evaluate therapeutic effects in small studies and clinical trials. A study evaluating walking performance with patients with MS found correlations between MD, AD, and RD with clinical outcomes [55]. A longitudinal study of patients with MS who underwent balance training with a video game balance board (Nintendo Wii®), had transiently increased FA and RD in the superior cerebellar peduncles paralleling clinical balance improvement with static posturography after 12 weeks [56].

There have been some promising findings in pilot studies using DTI to investigate DMTs. A longitudinal study of 23 patients with various MS courses on dalfampridine for 2 weeks found 12 clinical responders who were also noted to have reductions of MD and RD involving the corticospinal tract and optic radiations among other tracts. [57]. The authors speculated the changes were due to a sensitive pool of potassium channels that changed the osmotic balance along the axon upon closure. A short observational study of 4 patients followed on fingolimod for 4 months with DTI noted widespread increase in MD in NAWM and FLAIR lesions without any clinical manifestations [58]. A 1-year longitudinal study noted the differential effect on FA when comparing natalizumab, interferon (IFN)-β, and glatiramer acetate [59]. These findings supported decreased severity of damage with natalizumab, which correlated with cognitive performance [59]. In an open-label phase IIA study of patients with progressive MS with oral methylprednisolone 1.5 g monthly, decreases in MD in NAWM and NAGM were found after 15 months [60]. The SPRINT-MS trial will be using DTI as an outcome measure for neuroprotection in a study of ibudilast in progressive MS [61].

Some limitations exist with DTI measures. The complexity of MS pathology, including infiltrating cells and crossing fibers, may interfere with DTI measurements. Equating AD with axonal integrity may be an oversimplification of a complex process. Increased RD appears to be a sensitive measure of active lesions, but its utility in NAWM is less clear. Efforts have been made to overcome some of these limitations. The development of diffusion basis spectrum imaging, a novel computational method to separate cellular edema (isotropic) from axonal/myelin integrity (anisotropic), can potentially be applied to progressive MS to follow neurodegeneration more effectively [62]. Other advanced diffusion modeling methods, such as neurite orientation dispersion and density imaging, improve on DTI parameters to provide greater microstructual specificity [63].

Despite these limitations, DTI can be a valuable metric to evaluate microstructual changes in tissue and integrity of tracts. These metrics could particularly serve as useful outcome measures in clinical trials seeking to evaluate the extent of neurodegeneration and evaluate the efficacy of neuroprotective strategies.

Functional MRI and Connectivity

Functional MRI (fMRI) exploits the diamagnetic and paramagnetic properties of oxyhemoglobin and deoxyhemoglobin, respectively, as a noninvasive blood oxygen level-dependent endogenous contrast in a gradient-echo (GRE) sequence [64]. The oxy/deoxyhemoglobin ratio in GM

provides insight into activated areas in resting-state (rs-fMRI), default mode network, and task-related recruitment fMRI. These techniques provide a window into correlating clinical metrics with reorganization, plasticity, and functional reserve in MS phenotypes.

fMRI is a unique MRI modality as it allows detection of functional changes in addition to anatomical and pathological changes. Several early studies support the hypothesis that subjects with MS have an increase in activation and functional connectivity in several brain regions as a likely adaptive mechanism [65]. In multiple regions in CIS, rs-fMRI synchronization increases initially but later declines in advanced stages of MS, suggesting early adaptive increased connectivity with subsequent reduced reorganization later in the course owing to tissue injury [66]. Another method used to study rs-fMRI in CIS found an initial decrease in activity in several brain regions [67]. The precise timing and biology of these compensatory changes is unclear. In radiologically isolated syndrome (RIS), no differences between rs-fMRI and healthy controls are found, despite the presence of brain and spinal cord lesions, CSF oligoclonal bands, dissemination in time, and atrophy [68]. During the more manifest stages of RRMS most studies have shown increased connectivity and activation. In the later stages of disease, it appears that connectivity tends to decrease and these changes are associated with cognitive manifestations [69]. Functional connectivity decreases with disease progression [70] and disruption in thalamocortical connectivity occurs independently of T2LV and thalamic volume [71].

Compared with healthy controls, task-related activation fMRI in CIS exhibits increased recruitment in cortical and thalamic regions [72]. Task-related fMRI can discriminate between CIS, relapsing MS without disability or with mild disability, and SPMS [69]. Increased recruitment may also explain favorable clinical outcomes, as a more "benign" phenotype [73]. Patients with PPMS have increased nonmotor activation, suggesting an adaptive response [74]. Hyperactivation is also noted in the cervical cord in PPMS following tactile stimulation and correlates with disability [75].

Cognitive impairment has been evaluated along with several fMRI methods. The Paced Auditory Serial Addition Task (PASAT), a component of the MS Functional Composite, is a validated tool to screen for cognitive impairment in MS and correlates with rs-fMRI functional connectivity and task-related activation differences in MS [76]. Other neuropsychological assessments evaluating processing speed and executive function correlate with rs-fMRI [77] and activation [78] in cortical and deep GM regions. Task-related activation is able to identify patients with working memory impairment [79]. Default mode network, a state that is active at rest and deactivated with goal-directed tasks, is aberrant in cognitive impairment in MS [80]. Changes in functional connectivity patterns are also present in MS using MRI with resting-state magnetoencephalography [81].

Fatigue is prevalent in MS and is associated with unique hyperactivation of certain motor-attention networks during the performance of a simple task [82]. Cognitive fatigue, or impaired ability to sustain mental effort, is associated with cortical and subcortical hyperconnectivity following PASAT administration using rs-fMRI [83] and with a modified SDMT during task-activated fMRI [84].

Early recognition of functional connectivity changes in MS with fMRI provides a window for intervention before significant cognitive impairment takes hold and adaptations are no longer adequate. Many multicenter studies have been performed by the MRI in MS group, demonstrating their feasibility [85]. A few small trials have investigated connectivity changes with task-related fMRI for cognitive rehabilitation with transcranial magnetic stimulation [86], with rs-fMRI for Nintendo® [87], and memory retraining (modified Story Memory Technique) [88]. Given these findings and small studies suggesting the between-scanner and between-subject reproducibility of rs-fMRI [89, 90] and task-related fMRI [91] measures, there exists a significant potential for their use as key secondary outcomes in cognitive rehabilitation trials.

Magnetization Transfer

Magnetization transfer (MT) is a method to observe exchange between unbound protons in a free water pool with protons bound to macromolecules (myelin and cells) [92]. A MT radio-frequency pulse transfers energy to the bound pool and then to the unbound pool by dipole interactions. The MTR is the difference in the signal before and after the MT pulse divided by the signal before the pulse. Histopathologic studies have confirmed MTR correlates with myelin content and axonal density [93]. MTR can also distinguish remyelinated lesions from NAWM and demyelinated lesions [94].

MTR decreases 3 to 18 months prior to the appearance of a new T2 or GdE lesion [95], possibly as a result of edema, perivascular inflammation, demyelination, or activation of astrocytes/microglia, and predicts the likelihood of recovery. In patients with CIS, MTR is noted to be decreased in NAWM and NAGM [96]; the decrease is less prominent than in relapsing MS but can predict progression to clinically definite MS [97], and correlates with future disability [98]. MTR decreases in NAWM in MS correlate with disease duration [99] and also predicts disability [100]. MTR decreases in GM occur early and are associated with disability and cognitive impairment in MS. With ultra-high-field MRI, CLs have been detected using MTR [101]. Global [102] and cortical [103] MTR decreases correlate with cognitive impairment even more than T2LV.

MTR has been proposed as a measure of remyelination for therapeutic trials. MTR exhibits temporal changes with decrease in prelesional tissue and GdE lesions and recovery to

baseline in subsequent months [104]. Improvement in MTR was observed with IFN-β1α in RRMS [105] but not SPMS [106]. Increase in MTR in acute and chronic black holes with glatiramer acetate are also observed [107]. Variable results are noted in trials involving dimethyl fumarate, either reaching [108] or not reaching [109] statistical significance for increase in MTR. Natalizumab shows increases in both NAWM and cortical GM [110] and more robustly so than IFN-β1α [111]. Alemtuzumab treatments have been shown to stabilize MTR in NAGM [112]. Ongoing phase II clinical trials have also used MTR to evaluate for possible recovery or neuroprotective effects, including GSK239512, a histamine H3 receptor antagonist [113], and ibudilast in progressive MS (SPRINT-MS) [61]. These findings are promising for its use in future clinical trials striving to detect improvement of microstructual injury with protective strategies.

Proton magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) provides 3D quantitative information based on the properties of different nuclei (e.g., ^{1}H, ^{31}P, ^{13}C, ^{23}Na) and their respective relaxation times. Proton (^{1}H) MRS, in particular, has been utilized for characterizing MS pathology since the early 1990s and can typically be acquired in < 20 min [114]. Using characteristic ^{1}H shifts, metabolites can be identified with a resonance signal intensity proportional to its relative concentration. Novel methods overlying spectrographic maps on anatomic sequences (T1 and FLAIR) have also improved resolution [115] and allowed for global and local measurements [116]. Tracking metabolic changes in lesional and normal-appearing tissue allows indirect detection of neuronal, axonal, and glial differences.

Pathologic confirmations of MRS changes in human demyelinating lesions demonstrate significant correlations between *N*-acetylaspartate (NAA) and decreases in myelin and axonal density. Increases in choline (Cho) and myo-inositol (mIns) are associated with glial proliferation [117]. Animal models, including a longitudinal model of demyelination using cuprizone, have also detected decreases in NAA and glutamate with demyelination and a return to normal following near-complete remyelination [118].

NAA is synthesized in neuronal mitochondria and has been extensively used as a surrogate for neuronal/axonal loss and correlates with disability [119]. Correlations have been found also in those with moderate disability (EDSS < 5) [120], shorter disease duration [120], and in the cortex [121]. Although whole-brain NAA does not correlate with disability or lesion load [122], reductions of NAA in patients with mild symptoms suggests their lack of significant disability may be due to fortuitous avoidance of eloquent cortex or compensatory changes from plasticity. Decrease in NAWM NAA appears to occur independently to changes in NAGM [123]. Changes in NAA and other metabolites have been useful to discriminate from healthy controls [124] or patients with NMOSD [125]. Parallel reduction of NAA with retinal nerve fiber layer thinning over 1 year without EDSS changes [126] further validates its utility for detecting subtle changes.

Other metabolites such as creatinine, Cho, mIns, γ-aminobutyric acid, glutamate/glutamine, and glutathione have been used to study non-neuronal changes, such as gliosis, demyelination, inflammation in particular disease courses, spatial tracts, degrees of disability, and symptoms such as pain [127]. Table 1 summarizes metabolite patterns and their hypothesized significance in lesional and normal-appearing tissue.

^{1}H-MRS may be a useful outcome in MS clinical trials [137], and guidelines have been proposed for its use [138]. MRS has been studied with IFN-β, glatiramer acetate, biotin, and natalizumab. With IFN-β, results have been mixed, with NAA shown to increase [139] or decrease [140] while on treatment,and with either an increase or no change in Cho [141, 142]. In a cross-sectional study, an increase in NAA was noted after 4 years of treatment with glatiramer acetate, which correlated with EDSS [143]. No differences in NAA and Cho were seen comparing glatiramer acetate with placebo in patients with a primary progressive course [144]. Despite treatment with natalizumab, increased creatinine and Cho (measures of membrane phospholipid turnover) correlating with increased levels with CSF inflammatory markers IL-1β and CXCL8 may indicate persistent gliosis and inflammation [145]. However, lesional levels of NAA, Cr, and phosphocreatine increase with natalizumab *versus* IFN-β or glatiramer acetate, suggesting improved axonal metabolism [146]. Neuroprotective effects in pilot studies with high doses of biotin show some normalization of Cho in NAWM [147]. Similarly, an increase in NAA after 2 weeks of fluoxetine has been described [148].

Several challenges to the use of spectroscopy in MS remain. Changes in metabolite levels in MS are expressed as a ratio rather than an absolute measure. Use of an external standard (phantom) with a defined amount of metabolite can be used for quantification. Other limitations of MRS include partial volume effects with small lesions and inability to perform whole-brain acquisitions on clinical scanners. Although the technique is becoming more refined, low reproducibility of ^{1}H-MRS across centers may present a challenge for implementation in a multicenter study [128].

Sodium MRS

Sodium (^{23}Na) MRS has been used in MS and is attractive as an outcome measure as it may reflect several underlying pathological pathways. Elevated sodium concentrations in tissue may reflect demyelinated axons that redistribute sodium (Na^{+}) channels from nodes of Ranvier to along the axon and Na^{+} channel upregulation in astrocytes and microglia/

Table 1 Characteristics of ^{1}H-magnetic resonance spectroscopy metabolites in multiple sclerosis

ppm	Metabolite	Pathologic correlate	NAWM/ prelesional	CGM/ NAGM	Acute or GdE lesion	Chronic lesion
0.9–1.4	Lipids	Tissue destruction	↑ [128]	↑ [128]	↑ [128]	–↓[128]
1.33	Lactate	Anaerobic glycolysis Inflammatory cell metabolism, neuronal mitochondrial dysfunction, ischemia			↑[129]	–[128]
2.02	NAA*	Present in neuronal/axons	↓ [130, 131]	↓ [128]	↓ [132]	↓ [133]
2.0–2.4	Glutamate, GABA	Neuroexcitotoxicity	↑ [133]	↓ [128]	↑	–[133]
?	Glutathione		–[134]	↓ [134]		
3.03	Creatine, phosphocreatine	Energy metabolism in neurons and glia	↑ [135]	↑ ↓ [128]	↓	↑
3.22	Choline compounds*,†	De-/remyelination, inflammation Release of membrane phospholipids	↑ [136]	↓ [128]	↑[129]	↓ [132], ↑ [128]
3.56	Myoinositol	Glial marker, osmolyte	↑ [128]	↑ ↓ [128]	↑ [129]	↑

(–) = unchanged; ↑ = increased; ↓ = decreased; NAWM = normal-appearing white matter; CGM = cortical gray matter; NAGM = normal-appearing gray matter; GdE = gadolinium-enhancing; NAA = *N*-acetylaspartate; GABA = γ-aminobutyric acid

*Typically normalized to creatine in voxel

† Includes free choline, phosphorylcholine, glyceryl-phosphoryl-choline; possibly taurine and betaine

macrophages [149]. Additionally, mitochondrial dysfunction in MS likely limits compensatory mechanisms, such as the sodium/potassium pump and sodium/calcium exchanger in injured tissue [150], causing accumulation of intracellular sodium [149] and serving as a potential biomarker. Despite the 1/5000th signal intensity compared with ^{1}H-MRS [151], causing poorer signal-to-noise ratio, advances have permitted ^{23}Na-MRS to detect total (TSC), intracellular (ISC), and indirect extracellular sodium concentrations in tissue.

TSC is increased in the NAWM, NAGM, GdE lesions, and T1 hypointense lesions in RRMS *versus* healthy controls [152, 153]. TSC increases in NAWM with disease duration and TSC levels in NAGM correlate with EDSS and T2LV [154]. In both SPMS and PPMS, TSC is increased in NAGM and T2 lesions *versus* healthy controls [155], and patients with SPMS have elevated TSC in NAWM, cortical GM, and deep GM *versus* those with RRMS [156]. TSC distribution is more restricted to motor regions in PPMS than in SPMS [155] and associated with disability in particular motor regions. Irrespective of the course, TSC in deep GM and T1 hypointense lesions correlate modestly with disability measures [156].

More recent adaptations can discriminate ISC from TSC. With fluid-attenuated ^{23}Na-MRS, ISC is increased in GdE lesions *versus* chronic lesions in RRMS, and levels decrease following intravenous methylprednisolone [157]. ISC is also elevated in cortical, subcortical, and NAWM in patients with RRMS *versus* healthy controls using triple-quantum-filtered ^{23}Na-MRS at 7 T and indirect extracellular sodium concentration measures and TSC correlate with T2LV, T1LV, and EDSS [158].

^{23}Na-MRS may prove useful in future clinical trials with therapeutics targeting neuroprotection and mitochondrial dysfunction. However, multicenter application of this technology may pose challenges and remains to be tested. Preclinical evidence in animal models of MS show promise and phenytoin has shown protective effects in the optic nerve [159], whereas lamotrigine did not seem to have an effect on atrophy measurements [160]. Oxcarbazepine is currently being investigated in a clinical trial incorporating TSC as an outcome (NCT02104661).

Positron Emission Tomography

Positron emission tomography (PET) has been used since the 1950s to localize brain tumors and has been used in MS since the 1990s. Specific isotope-labeled tracers have been developed that target receptors, β-amyloid, and metabolites. These targets putatively provide *in vivo* functional information about axonal degeneration, demyelination/remyelination, microglial activation, and astrogliosis. Differences have been observed in CIS, early MS, and between relapsing and progressive MS. Correlation of PET ligand uptake with other modalities such as T2LV, T1 black holes, atrophy, and disability measures will be reviewed below. PET ligands are also summarized in Table 2.

^{11}C-Flumazenil binds to the benzodiazepine site of the γ-aminobutyric acid A receptor expressed on cortical and deep GM neurons and reduction in its uptake correlates with neuronal loss [186]. Correlation of its uptake with cognitive impairment [186] is consistent with the loss of hippocampal

Table 2 Summary of positron emission tomography ligands used in clinical multiple sclerosis (MS) studies

Isotope	Clinical study findings
TPSO	Glial activation
Microglial activation	22 MS, 7 HC [161]
^{11}C-PK11195	– ↑GdE *vs* NAWM
First-generation	– ↓ in T2 lesions overall, but ↑ in T2 lesions during relapse
	– ↑ in NAWM during progression
	22 MS, 8 HC [162]
	– ↑ in NAWM correlated with atrophy
	– ↓ in T2 lesions correlated with atrophy
	18 MS (10 RR, 8 SP), 8 HC [163]
	– ↑ in cortex (MS *vs* HC) correlated with EDSS (SP > RR)
	– SP > RR ↑ specific cortical regions
	10 SP, 8 HC [164]
	– ↑ in periventricular WM, NAWM, and thalamus (SP *vs* HC)
	- ↑ in 57% chronic T1 black holes
	10 RR, 9 SP/PP [165]
	– ↑in 947/1242 (76%) T1 black holes in all cases
	– ↑ in 437/1242 (35%) SP/PP T1 black holes; correlated with EDSS
	18 CIS, 8 HC [166]
	– ↑ in NAWM in CIS *vs* HC correlating with EDSS and risk for MS at 2 years – ↑ in deep gray matter in CIS *vs* HC
	9 RR [167] – ↓ globally by 3.2% and also in cortical GM and cerebral WM after treatment with glatiramer acetate for 1 year
Second-generation	1. 9 RR with GdE, 5 HC [168]
Higher affinity and greater specificity	– no difference
1. ^{18}F-FEDAA1106	2. 11 MS, 7 HC [169]
2. ^{11}C-PBR28	– ↑ in GdE *vs* NAWM
3. ^{11}C-vinpocetine	– ↑in prelesional areas
4. *^{18}F-DPA-714*	– global levels correlated with disease duration
5. *^{18}F-PBR06*	RR stable, 1 RR active [170]
6. *^{11}C-PK-1195*	– reproducible and ↑ in GdE
	15 SP, 12 RR, 14 HC [171]
	– ↑ in cortex and cortical lesions (7T T2*)
	– ↑ SP > RR
	– uptake in cortex, deep GM, and NAWM correlated with disability and cognitive impairment
	– cortical thinning correlated with ↑ in thalamus
	3. 4 MS [172]
	– ^{11}C-vinpocetine parallels ^{11}C-PK11195 but has higher signal
	4. NCT02305264: ongoing trial recruiting patients with relapsing and progressive MS
	5. NCT02649985: ongoing trial recruiting patients with relapsing and SPMS in comparison with HC and Alzheimer's disease
	6. NCT02207075: ongoing trial recruiting patients with SPMS
A2A adenosine receptor	8 SPMS, 7 HC [173]
Upregulated in activated microglia	– ↑ NAWM and correlated with disability
^{11}C-TMSX	
Astrocyte marker	6 RRMS, 6 HC [174]
^{11}C-acetate	– ↑ WM and GM in MS
	– correlates with T2 lesions and T1 black holes
High affinity for CNS myelin	1. 2 MS [175]
	– correlates with myelin
Amyloid tracers	20 RR, 8 HC [176]
1. ^{11}C-PiB	– ↓ in MS lesions
2. ^{18}F-florbetaben	– longitudinal variability suggested remyelination and inversely correlated with disability
	2. 12 MS (5 RR, 2 SP, 2 PP), 3 HC [177]
	– ↓ in T2 lesions and correlated with EDSS
	– ↓ in progressive *vs* relapsing patients
Glucose metabolism	8 MS, 8 HC [178]
^{18}F-FDG	– ↓in thoracic and lumbar spinal cord after walking
	1 MS [179]
	–↑ in 2 T2 lesions in acute presentation of tumefactive MS
	2 MS [180]
	– no uptake in lesions resembling tumefactive MS or Balo's concentric MS
	17 RR, 18 HC [181]
	– ↓ uptake in cortical and deep GM structures with variable correlation to lesions
	10 MS [182]
	– ↓ in cortex over 2 years
	23 MS, 9 HC [183]
	– ↓ uptake in cortical and regional (dorsolateral prefrontal, orbitofrontal, caudate, putamen, thalamus, and hippocampus)
	– ↓ cortical correlated with T2LV
	– ↑ in right thalamus correlated with improved cognitive performance
	16 RR, 12 SP, 10 HC [184]
	–↓ in thalamus and other deep grey matter structures (e.g., hippocampus and cingulate gyrus)
	47 MS, 16 HC [185]
	– ↓ in prefrontal areas and ↓ right prefrontal cortex negatively correlated with fatigue severity
	NCT02305264: ongoing trial recruiting patients with relapsing and progressive MS; characterizing ^{18}F-FDG in WM inflammatory cells
Neuronal and axonal degeneration	18 MS (9 SP/PP, 9 RR) [186]
$GABA_A$-R	– ↓ in cortical and deep GM in both relapsing and progressive
^{18}C- and ^{18}F-flumazenil	– ↓correlated with T2LV and cognitive performance
	NCT01651520: ongoing trial recruiting patients with early MS to quantify cortical and deep GM neuronal loss.

↓↑ = decreased or increased uptake, respectively; TPSO = translocator protein; HC = healthy controls; GdE = gadolinium-enhancing lesions; NAWM = normal-appearing white matter; RR = relapsing remitting; SP = secondary progressive; EDSS = Expanded Disability Status Scale; WM = white matter; PP = primary progressive; CIS = clinically isolated syndrome; GM = gray matter; SPMS = secondary progressive MS; CNS = central nervous system; ^{18}F-FDG = fludeoxyglucose; T2LV = T2 lesion volume; $GABA_A$-R = γ- aminobutyric acid A receptor

cholinergic neurons previously described in patients with MS [187].

Amyloid tracers (^{11}C-PiB and ^{18}F-florbetaben) studied in dementia also correlate with T2 lesions in patients with MS and may correlate with demyelination [175, 177]. Whether their uptake in WM is nonspecific or reflects β-amyloid pathology in MS is yet unknown. The ^{11}C-MeDAS tracer has been studied in animal models of demyelination [lysolecithin

[188], experimental autoimmune encephalomyelitis (EAE) [189], and cuprizone [190] and shows promise in improving detection of myelin.

Microglial activation has been characterized by uptake of ligands targeting the translocator protein, also known as the peripheral benzodiazepine receptor, and the ^{11}C-TMSX ligand, which selectively binds to the A2A adenosine receptor. TSPO is expressed in activated microglia and reactive astrocytes [191], whereas ^{11}C-TMSX is expressed throughout the central nervous system [192] and is upregulated in activated microglia *in vitro* [193]. In patients with CIS, the translocator protein tracer ^{11}C-PK11195 is increased in T2 lesions, NAWM, and deep GM *versus* controls, and correlates with disability and risk of MS in 2 years [166]. TSPO uptake is increased in GdE lesions [170] and NAWM in patients with MS. TSPO levels also parallel progression [163] and atrophy [162]. Treatment with glatiramer acetate decreases its uptake globally in both GM and WM [167]. The ^{11}C-TMSX ligand is also higher in NAWM and correlates with EDSS scores [173]. Chronic lesions with T1 hypointensity in patients with SPMS also show perilesional TSPO uptake which parallels microglial/macrophage (CD68) immunohistochemistry on chronic MS tissue [194] and in EAE [195]. TSPO uptake parallels neuronal loss (NAA with MRS), GM atrophy, and disability [171, 196]. Many other novel TSPO ligands in development for MS are currently being studied (Table 2).

Benzyl ^{11}C-acetate [197] and its ^{18}F derivative [198] have been proposed to label astrocytes as acetate accumulates in astrocytes in MS lesions [174]. With greater recognition of the role of astrocytes in MS, development of similar *in vivo* ligands will prove useful in determining efficacy of targeted therapeutics.

Glucose metabolism with fludeoxyglucose has been studied to determine whether metabolic dysfunction precedes demyelination. Metabolic activity is also hypothesized to predict symptoms such as cognitive impairment or fatigue. In animal models of MS, no differences with EAE [199] or with lysolecithin [188] in the brain have been noted, but fludeoxyglucose is increased in spinal cord lesions from EAE [200]. Cognitive impairment is associated with glucose hypometabolism in cortical regions [183], as well as the thalamus and other deep GM structures [183, 184]. Fatigue severity is associated with glucose hypometabolism in the prefrontal cortex [185] and thalamus [201].

Multiple ligands with novel targets have been developed, tested *in vitro*, or tested *in vivo* in animal models of demyelination (cuprizone [190], lysolecithin [202], EAE [203]). The high costs associated with producing radiopharmaceutical agents and the availability of cyclotrons present an obvious limitation but will likely diminish with its further use. As with other advanced imaging techniques, PET imaging hopes to increase the specificity of identifying MS lesions and understanding the underlying biology.

Myelin Measures

Water constitutes approximately 40% of myelin, is thought to be present between its layers, and can be imaged from short T2 relaxation components in < 50 ms [204]. Myelin water fraction (MWF), a ratio of myelin water to total water [205], correlates with myelin density histologically (Luxol fast blue) [206]. Regions with intermediate T2 signal between NAWM and T2 lesions, termed "dirty-appearing white matter", were also found to have decreased MWF corresponding to decreased myelin (Luxol fast blue) and axonal density (Bielschowsky stain) [207].

While initially time consuming, MWF can now be acquired in feasible acquisition times [208] and whole-brain coverage using fast acquisition with spiral trajectory and T2prep, or multicomponent-driven equilibrium single pulse observation of T1 and T2 can be attained in 4 [209] or 14 min [210], respectively. Another approach to improve MWF resolution, direct visualization of short transverse relaxation time component, suppresses long T1 signal leaving a short T2* signal in the myelin water range and can be acquired in a very short time (3 min) [211].

MWF in MS lesions and NAWM correlates with disability measures, discriminates MS types, and can be used to track longitudinally evolution of lesions. Lesions contain 6% more water but 52% less MWF, on average, *versus* control WM. MS NAWM contains 2% more water and 16% less MWF *versus* control WM [212]. NAWM MWF in PPMS is decreased by 6% *versus* controls and correlates with EDSS [210] and 9-hole peg test [213]. Lesional MWF varies between GdE and T2 lesions, and T1 black holes [208] and differences are hypothesized to be due to pathologic variations of the lesion types. MWF may be useful as an outcome measure for therapeutics that promote repair as it is sensitive to recovery following GdE [214].

Myelin imaging can be supplemented by measurement of axonal content, estimated with MRI diffusion measures. The myelin G-ratio (axon diameter/axon + myelin diameter) can be directly measured with electron microscopy and an *in vivo* surrogate can be obtained with MRI by calculating the myelin and axonal volume fractions [215, 216].

Spinal Cord Imaging

Spinal cord MRI can aid in the diagnosis of MS [217], assist in risk stratification in RIS [218] or CIS [219], and monitor for disease activity on treatment. Inherent difficulties of MR spinal cord imaging include small cross-sectional size, physiological motion, and the local environment of the cord with surrounding bone structure [220]. These conditions have made implementation of spinal cord imaging difficult in clinical trials. The MAGNISMS group has made recommendations for spinal cord clinical acquisition parameters to include both sagittal and axial

planes with 1) T2; 2) short T1 inversion recovery or DIR [221]; and 3) postcontrast T1 [217]. Other methods, such as T1 3D magnetization-prepared rapid acquisition with gradient echo [222] and proton density fast spin echo [223], may add value in lesion detection. Spinal cord lesions may be missed without axial views [224] or including T2 with either short T1 inversion recovery or DIR [221, 225]. Novel methods strive to image the entire cord efficiently [226] as the thoracic region, often ignored, includes 40% of spinal cord lesion burden [227]. For clinical trials, imaging of the cervical spine is probably the best candidate for a multicenter outcome measure.

Spinal cord atrophy measures, such as cross-sectional area, have been studied extensively in almost all forms of MS and are good candidates for clinical trials. Cervical cord atrophy in CIS [228] is independently associated with accrual of disability [229] and suggests axonal loss and demyelination [230] occur early in the disease course. The cervical cord is extensively imaged in MS and is an attractive outcome measure as its atrophy correlates with disability, particularly in progressive MS [231, 232]. Reproducible medulla oblongata volumes [233] or cross-sectional area at C2 [234] seem to follow this trend and could be a surrogate for cervical cord involvement in clinical trials. GM lesions may be more readily detectible in the cord than in the cortex [235]. GM loss occurs in both cervical [236] and thoracic [237] segments, is more pronounced in progressive courses [238], correlates with disability, and is independent of WM atrophy in relapsing MS [236]. Accrual of cervical cord lesions increases the odds of thoracic cord lesions [239] and overall cord lesion burden are associated with certain *HLA-DRB1* alleles [240] and risk loci [241]. Measuring loss of cord volume to monitor efficacy of neuroprotective therapeutics [242], such as IFN-β1α [243], IFN-β1b [244], and glatiramer acetate [245] have been attempted in small trials.

Multiple advanced imaging techniques have been applied to the spinal cord in preliminary studies [246], and hold promise for future clinical trials. Advanced measures have been useful in distinguishing differences in clinical phenotypes [247] and correlating with disability measures. DTI has been extensively applied to the spinal cord in normal-appearing and lesional regions, correlates with demyelination histologically [248], and can be used to track recovery longitudinally [249]. These changes reflect global changes in the disease as they also correlate with retinal nerve fiber layer thickness [250]. Decrease in normal-appearing cervical cord FA is specific and sensitive in distinguishing MS from controls [251], and is more markedly decreased in progressive than in relapsing courses [252]. Spinal cord GM is increasingly involved in comparing CIS, RRMS, and SPMS with respect to FA (decreased suggesting demyelination), RD (increased suggesting demyelination), and MD (increased with injury) [253].

Other methods include MWF, MRS, MT, and fMRI. MWF, an estimate of myelination [254, 255], is reduced in the cervical cord of patients with progressive MS [213], and does not appear to change with glatiramer acetate after 2 years [256]. MRS is susceptible to artifact, low signal-to-noise ratio, and mostly limited to the cervical cord [257]. Some changes in mIns, NAA, and Cho have been found in patients with MS, albeit in small studies with variable results [258], and some association with disability [259]. MT in the spinal cord is associated with myelin and axonal density and can be acquired quantitatively the spinal cord with reasonable acquisition times [260]. Decrease in spinal cord MT is observed early in MS, involves both WM [261] and GM [262], correlates with disability [263], and appears to be more affected in the outer pial/subpial region in CIS, relapsing, and progressive MS *versus* controls [264]. MT reduction in the dorsal and lateral columns correlates with impaired vibratory sense and muscle power, respectively [261]. Lastly, fMRI has been used to characterize disability and typically shows diffuse cord recruitment with fatigue [265] and overactivation with tactile stimuli in relapsing [266], as well as progressive [75], courses.

Leptomeningeal Enhancement

Persistent enhancement of the leptomeninges may reflect populations of immunologic cells that may contribute to ongoing neurodegeneration, cortical demyelination, and cortical atrophy seen in MS [267]. Leptomeningeal enhancement (LME) has only recently been described in MS and T2 FLAIR postcontrast is more sensitive than T1 in detecting enhancement due to improved CSF contrast. LME is more prevalent in progressive MS and correlates with global and cortical atrophy [268]. The association between LME and cortical subpial demyelination and perivascular macrophages and T and B lymphocytes has been demonstrated in a small postmortem study [269].

Although LME occurs in 25% [269, 270] of patients with MS, it is not specific. A similar pattern of proximity to vessels, nodular or linear shape, and supratentorial more than infratentorial location, is seen with other inflammatory/infectious (human T-lymphotropic virus, HIV, Behçet's disease, Susac syndrome [270, 271]) and noninflammatory/noninfectious conditions. Also, 4 of 65 female asymptomatic first-degree relatives of patients with MS have persistent LME [272]. There has been speculation, owing to the increased frequency of these lesions in PMS and their location, that these lesions may represent meningeal follicles and contribute to ongoing progression. It is possible this could be targeted and used as an outcome measure in trials, but validation is still required.

Iron Imaging

Iron is the most abundant trace metal in brain and is stored predominantly in oligodendrocytes and myelin [273], making it an attractive imaging contrast in MS. In active MS lesions, dying oligodendrocytes release iron, which accumulates in

astrocytes, microglia/macrophages, and axons [274]. This process contributes to oxidative injury and mitochondrial dysfunction of axons, neurons, and glia in the lesional milieu [275]. Nonphagocytosing proinflammatory M1 macrophages/microglia accumulate iron at the edge of chronic active WM and cortical demyelinated lesions [276]. Iron contrast can be assessed on MRI with spin echo T1 or GRE and in tissue confirmed with immunohistochemistry (Perls' stain for iron and CD68 for microglia). Remarkably, chronically active lesions with rims are more likely to continue expanding, whereas chronically inactive lesions do not [277]. Rims are not only more common in active relapsing MS, but also present in SPMS [276, 278], and their persistence correlates with more tissue injury (T1 hypointensity) [279].

In addition to accumulation of iron in WM lesions [274, 276], in both CIS [280] and RRMS [281] iron accumulation is also found in deep GM. Deep GM iron content correlates with disability [282], WM tract injury by DTI metrics [283], and cognitive impairment [284, 285]. Over time, iron in NAWM decreases in MS, possibly because of glial uptake [274, 286].

There is a plethora of MRI techniques, each with their advantages and disadvantages, used to evaluate iron accumulation *in vivo* at 7 T [287]: T2 hypointensity [288], phase [289], transverse relaxivity (R2*) [290], T2*GRE [291], susceptibility-weighted imaging [292], T2* coupled with phase-dynamic contrast-enhanced T1 [293], magnetic field correlation [294], FLAIR* [295], 3D-T2*-angiography (3D-ESWAN) [296], quantitative susceptibility mapping (QSM), and inversion recovery-ultrashort echo time (concomitantly images myelin and iron [297]). Also, an exogenous method to evaluate iron uptake exists with ultra small (nano) super paramagnetic particles of iron oxide that are phagocytosed by active monocytes/microglia. These particles show promise in detecting more active lesions than gadolinium in pilot studies [298] and correlate with tissue injury in CIS [299, 300].

Of particular interest, QSM, has fewer artifacts than conventional imaging [301], advantages to phase imaging [289], correlates well with iron in microglia/macrophages [301], and can be used to longitudinally follow active lesions. QSM shows 90% sensitivity and specificity with GdE [302], starts to increase following a GdE lesion, and falls to baseline after 4 years [303]. Iron accumulation in the deep GM by QSM correlates with cognitive impairment [304] and impaired ability to suppress task-irrelevant information (inhibitory control) [305].

Because inflammation precedes and continues following GdE, QSM may prove to be an invaluable complementary tool to monitor inflammation. Detection of rimmed lesions carries the potential to supplement established measures of "activity" (new/enlarging T2 or GdE lesions) without the need for exogenous contrast agents. Furthermore, it may be possible to discriminate MS from microvascular disease [295] or NMOSD by the appearance of central veins, hypointense rims [306], and deep GM iron accumulation [296].

Overlap in the appearance of MS lesions with mimics, such as cerebral small vessel disease or migraine, present a challenge in clinical trials. The T2 lesion volume attributable to MS can potentially be misrepresented by comorbidities, particularly early in the MS disease course. The North American Imaging in Multiple Sclerosis Cooperative noted improved visualization of central vessels, a feature associated with demyelinating lesions to help discriminate MS lesions, by incorporating T2* and FLAIR (FLAIR*) [307, 308].

Iron imaging may represent a suitable clinical trial outcome measure especially for therapies that target iron metabolism or microglia. Future trials which use medications that target iron or microglia may use iron MRI measures as intermediate outcomes.

Magnetic Resonance Fingerprinting

Magnetic resonance fingerprinting (MRF) can collect whole-brain quantitative T1, T2, and spin density images in under 5 min by pseudo-random acquisition of flip angle and repetition, echo, and inversion times [309]. This novel technique is able to discriminate healthy controls from patients with MS and note differences between patients with SPMS and RRMS with respect to T1 and NAWM [310]. Furthermore, T1 and T2 values in particular regions correlate with disability measures including MS Functional Composite and Expanded Disability Status Scale scores [310]. The quantitative nature of this method makes it of particular interest in multicenter clinical trials using different MRI scanners. Ongoing studies are looking to characterize MRF measures in the thalamus, acquire MRF at 7 T, and include chemical exchange characteristics with sensitivity to myelin content (unpublished work and [311]).

Conclusions

Advanced MRI imaging techniques in MS are rapidly evolving and will only continue to increase in their value as a surrogate *in vivo* biomarker for inflammation and neurodegeneration. Although many of these tools still require validation and development for multicenter application given they may have been restricted to smaller studies, their usefulness in clinical trials and practice will be of great value. The development of therapeutics that target specific pathogenic mechanisms will require these techniques to evaluate their efficacy as outcome measures.

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