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# An update on the role of magnetic resonance imaging in predicting and monitoring multiple sclerosis progression

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## ABSTRACT

**Introduction:** While magnetic resonance imaging (MRI) is established in diagnosing and monitoring disease activity in multiple sclerosis (MS), its utility in predicting and monitoring disease progression is less clear.

**Areas covered:** The authors consider changing concepts in the phenotypic classification of MS, including progression independent of relapses; pathological processes underpinning progression; advances in MRI measures to assess them; how well MRI features explain and predict clinical outcomes, including models that assess disease effects on neural networks, and the potential role for machine learning.

**Expert opinion:** Relapsing-remitting and progressive MS have evolved from being viewed as mutually exclusive to having considerable overlap. Progression is likely the consequence of several pathological elements, each important in building more holistic prognostic models beyond conventional phenotypes. MRI is well placed to assess pathogenic processes underpinning progression, but we need to bridge the gap between MRI measures and clinical outcomes. Mapping pathological effects on specific neural networks may help and machine learning methods may be able to optimize predictive markers while identifying new, or previously overlooked, clinically relevant features. The ever-increasing ability to measure features on MRI raises the dilemma of what to measure and when, and the challenge of translating research methods into clinically useable tools.

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## KEYWORDS

Multiple sclerosis; progression independent of relapse; PIRA; disability progression; compartmentalized inflammation; chronic inflammation; brain atrophy; neurodegeneration

## 1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating neurodegenerative disease of the central nervous system (CNS) [1]. It affects over 130,000 people in the UK and is the commonest cause of non-traumatic disability among young adults [2–4]. Approximately 85% present with an episode of neurological deficit (termed a clinically isolated syndrome; CIS) [5] and then initially run a relapsing-remitting (RRMS) course characterized by episodes of neurological deficits (relapses) with at least partial recovery of function [1]. Current evidence suggests that half or more of people with RRMS will transition to secondary progressive (SP) MS, typically around 15–20 years after first symptom onset, characterized by progressive neurological impairments with few or no relapses [6–8]. A minority of people with MS (~15%) have a primary progressive (PP) form, in which progressive neurological disability accrues from disease onset without any clearly discernible relapses [1]. The transition between RRMS and SPMS can be challenging to establish clinically [9] and can take years to determine. Pathologically, there are no distinct new processes which occur among those developing progressive compared with RR MS, but instead there appear to be differences in the extent and degree of pathogenic mechanisms, which may be seen in all clinical

forms of MS. Recently, the division between RRMS and SPMS has been further challenged by the recognition that even in people with RRMS clinically significant progression independent of relapses (PIRA) commonly occurs [10], which we consider in more detail below.

Magnetic resonance imaging (MRI) has an established role in the diagnosis and prognostication of MS [11], but this is mainly based on the detection of white matter (WM) lesions and their association with relapses. The role of MRI in the assessment of MS progression is less clear-cut in clinical practice, although it is typically used in early phase treatment trials and has provided useful insights into the *in vivo* evolution of pathology and pathogenesis of disability in progressive MS. Members of our group reviewed this in secondary progressive (SP) disease in this journal in 2016 [12]. In this review, we build on this earlier review, and discuss the potential role of MRI as a predictor of clinical outcomes and as a measure of progression viewed from the perspective of pathogenic mechanisms that may underlie disease progression. We focus on significant developments since the 2016 SPMS review article, and so do not aim to replicate it here. In addition, while spinal cord pathology has a clear and significant role in progressive MS, this has been recently reviewed in detail [13] and so will not be reprised here.

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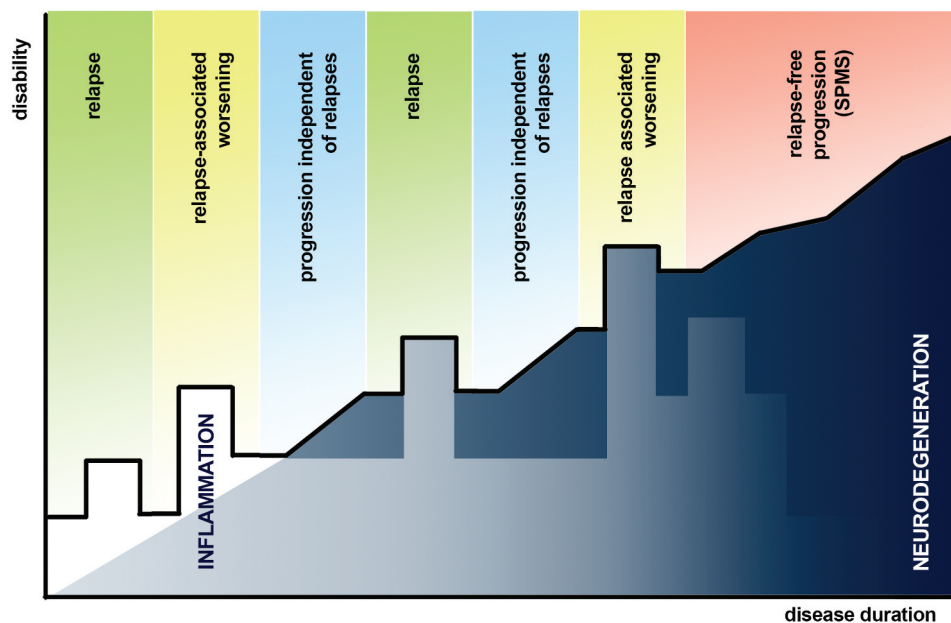
### Article highlights

- Multiple sclerosis (MS) is a chronic, inflammatory demyelinating neurodegenerative disease of the central nervous system (CNS) affecting over 130,000 people in the UK.
- Rather than relapsing–remitting and progressive MS being considered distinct phenotypes, there is a growing recognition that there is considerable overlap between them, and that substantial progression independent of relapses can occur in relapsing–remitting MS.
- There is increasing interest in MRI measures that assess specific pathological processes that may underpin disease progression, for example, compartmentalized inflammation.
- Mapping the effects pathology has on neural networks may help bridge the gap between MRI measures and clinical outcomes, but to date studies have mainly considered effects on white matter and gray matter separately rather than together.
- There is an emerging role for machine learning in optimizing prognostic models and identifying new or previously overlooked clinically relevant predictive markers of disease progression.

## 2. Clinical characteristics of progression

It is increasingly suggested that traditional clinical MS phenotypes (RRMS, PPMS, and SPMS) [7,14,15] do not adequately capture the disease's full clinical spectrum, and that clinical differences reflect the predominant pathological mechanisms at a given time rather than absolute differences in pathology [7]. This is reflected in the recently proposed redefinition of disease course [16] which frames disease activity in terms of relapses and progression in MS, but not does not expect these to be mutually exclusive features. While conventional phenotypes separate PPMS from SPMS, PPMS shows similarity with SPMS in terms of the age at onset, the rate of disability progression and frequency of (albeit sparse) clinical relapses [7]. Although PPMS was previously considered less inflammatory than SPMS [6], more recently, inflammation elsewhere

(for example meningeal, perivascular and extra-lesional brain tissues) has been implicated in progression in both PP and SPMS [7,15,16]. Reflecting the phenotypic overlap between RR and progressive MS, the concept of PIRA has emerged as a way of capturing and quantifying non-relapse associated disability progression in RRMS (Figure 1). PIRA has been defined as an increase in expanded disability status scale (EDSS) scores of  $\geq 1.5$  points from baseline EDSS 0, an increase of  $\geq 1.0$  points from baseline EDSS 1–5, or an increase of  $\geq 0.5$  points from baseline EDSS  $\geq 5.5$ , confirmed by a second assessment after at least 3 months (in order to confirm true worsening disability) and with either no prior relapse or an onset of more than 90 days from the start of the last reported relapse [17]. Despite clinical relapses being traditionally thought to be the main cause of disability accrual in RRMS, PIRA may actually account for at least half or more (53.6–70.9%) of all confirmed EDSS-worsening events in those with RRMS [17]. It is also worth recalling here the well-recognized limitations of the EDSS scale; in particular, its limited sensitivity to clinical changes and the dominance of motor disability components (e.g. walking) throughout much of the scale [18] and that the inclusion of additional clinical measures may improve sensitivity to change (e.g. 9-hole peg test and timed 25-ft walk) [19]. Kappos and colleagues [20] found that in RRMS patients, approximately 78–89% of composite confirmed disability accumulation was likely due to PIRA rather than relapse-associated worsening, although this was with the caveat that they had used less stringent EDSS thresholds for confirmed disability worsening and did not require PIRA events to be sustained. A recent longitudinal study [10] demonstrated that 25% of MS patients experienced PIRA events within 12 years from first symptom onset (while  $\sim 10\%$  of patients had PIRA events within 5 years) significantly increasing the risk of developing later severe



**Figure 1.** Graphical representation of disability progression in MS with clinical descriptors of events associated with disability accumulation highlighted above the line in bold (reflecting disability at that timepoint). Underneath the line, the interplay and evolution of underlying inflammatory and neurodegenerative processes are depicted. Whilst neurodegeneration is thought to ultimately drive irreversible disability progression in MS, it is important not to assume that the same processes underlie PIRA and SPMS, although they may.

disability. Taken together, these studies suggest that PIRA affects a significant proportion of people with RRMS, in whom PIRA events are a substantial contributor to disability. They also reinforce the view that the division between RRMS and progressive MS is not absolute and may to a degree be based on observation bias, and that the processes underlying progressive MS, and their assessment, may be of significant clinical relevance even before the onset of SPMS.

It is also worth recalling that a substantial proportion of people with RRMS show no signs of developing SPMS over two or more decades [21]. For instance, in one longitudinal study spanning 30 years [22], it was reported that up to a third of people with RRMS did not ultimately progress to progressive stages following first symptom onset. When looked at in retrospect, these people show no clear signs of progression earlier in the clinical course, and this seems to be reflected in a slower rate of brain atrophy and lower accrual of gray matter (GM) brain lesions when compared with people who do develop SPMS [23]. It is also worth noting that progression in SPMS does not appear to be strongly influenced by preceding clinical course or prior relapse frequency [24], although the time to a diagnosis of SPMS does appear to be shorter in people with more frequent relapses [7,8,25].

### 3. Effects of disease modifying therapies on progression

The role of MRI in monitoring disease modifying therapy (DMT) efficacy and risk has been reviewed in detail elsewhere [26], but in current clinical practice MRI is used to monitor disease activity and DMT efficacy by assessing new or enlarging, or contrast-enhancing, WM lesions. MRI also has an important role in surveillance for progressive multifocal leukoencephalopathy, primarily in patients treated with Natalizumab.

There is growing evidence that the early use of DMTs slows the accrual of relapse associated disability, delays conversion to SPMS [27,28], and reduces long-term disability [29,30], which has led to increasing support for early treatment with high-efficacy DMTs over escalation-based paradigms [31]. The effects of current DMTs appear to be greatest in early RRMS, where inflammatory activity (clinical relapses and new WM lesion formation) is the predominant pathology: there remains a paucity of treatment options available for established progressive MS, and to date none that are mechanistically clearly different from those used in RRMS. It is also worth considering here how earlier treatments may have significant persistent effects that need to be taken account of in clinical practice and trials. For example, alemtuzumab and cladribine are given as time-limited courses over days but have effects that persist for years, and while they do not necessarily prevent progression entirely, they may significantly modify pathological processes underlying it. Other DMTs may have similarly long-term effects that need to be accounted for.

### 4. Pathological processes underlying progressive clinical disability

The main driver of functional neurological decline in progressive MS is thought to be neurodegeneration, and, while not

necessarily clinically apparent, it begins early in the clinical course of the disease [1,32]. However, the main cause of neurodegeneration in MS is unknown, and multiple processes may lead to it, both in GM and WM. In acute WM lesions, axonal transection occurs in parallel with inflammation and demyelination [33], and in lesions that do not fully remyelinate there is chronic axonal loss [34]. Further, a significant proportion of WM lesions are thought to remain chronically active (~30% from histopathological studies) [35,36], which is associated with on-going axonal loss [35,37]. These processes may unfold over years, and the true effects of WM lesions may not be apparent for a decade or more after they first form [38]. GM lesions, in particular ribbon-like subpial lesions, appear to be relatively specific for MS and are rarely seen in other neurological diseases [39] or healthy controls [40,41]. GM lesions also appear to be overall more extensive than WM lesions (26.5% of total GM involvement versus 6.5% in the WM) [42]. Features of neuroaxonal loss are also seen in both GM lesions and the surrounding normally-appearing gray matter (NAGM) [43,44]. GM lesions are more prevalent in those developing progressive MS and correlate with accruing disability [45,46] at least as much as, if not more so than, WM lesions [7,47]. One recent study [48] investigated differences between those with RRMS or SPMS 30 years after a CIS and found that the number of GM lesions was what most clearly differed between them.

Unlike RRMS, where the dominant mechanisms driving inflammation appear to be led by the activation of the acquired (adaptive) immune system and infiltration of peripherally-derived lymphocytes and macrophages, in progressive MS greater activation of immune pathways intrinsic to the CNS are thought to be more relevant [14,49]. Microglial activation occurs from the early stages of MS, through increases in its prominence over time [49–51]. There has also been growing interest in inflammation occurring outside brain parenchyma, and how this may influence pathology within the brain. For example, meningeal inflammatory mechanisms have been implicated in contributing to GM lesional pathology and surface-in-gradients of neuronal loss in lesional and extra-lesional GM, as well as in microglial activation [52,53]. Histopathological studies have also shown inflammation and aggregation of lymphoid tissues (consisting of clustered B- and T-cell infiltrates) within the meningeal layers compartmentalized behind an intact or repaired blood-brain barrier (BBB) [54–57]. Given that sustained CNS inflammation may be detectable in the CSF (e.g. through mild lymphocytosis, presence of oligoclonal immunoglobulin-G bands), there has been significant interest in persistent leptomeningeal and perivascular compartmentalized inflammation and the role it plays toward clinical disease progression [58,59]. One hypothesis is that persistent accumulation of inflammatory lymphoid cells within a repaired BBB may sustain intrathecal myelin-specific immune responses [44,52,60–62]. More recently, the discovery of the homeostatic role of the glymphatic system in CNS waste clearance (e.g. soluble proteins and metabolites) [63] has been described in several neurodegenerative conditions including Parkinson's disease and Alzheimer's dementia [64,65], and more recently in MS [66] although its exact effects on clinical disability remains to be determined.



Iron homeostasis within the CNS may also be relevant to neurodegeneration and disease progression in MS, as iron accumulation may lead to neurotoxicity (from metabolic dysfunction, oxidative stress or calcium/glutamate-induced excitotoxicity), altered microglial/macrophage activity and activation of circulating immune cells [67]. Although not necessarily specific to MS, iron deposition in neuropathological specimens of MS patients appears to correspond to regions that undergo neurodegeneration and demyelination [68,69].

## 5. Monitoring and predicting disease progression on MRI (in clinical practice and trials)

### 5.1. WM inflammation

#### 5.1.1. Acute WM inflammation

WM lesions, as seen in conventional structural MRI, are a key part of current diagnostic criteria [11] based on lesion distribution and evolution [70–73] and have been considered in detail in the 2016 SPMS review [12]. Administration of gadolinium-based contrast agents may indicate areas of acute WM inflammation on MRI as a result of a disrupted BBB, with findings enhancing for up to four weeks [12,74]. Studies have repeatedly shown [22,75–77] that early WM lesion accrual is associated with worse clinical disability (as measured using EDSS) [22,75–77], with infratentorial lesions [22,78,79] in particular being a consistent predictor of worse clinical outcomes. Of note, one recent longitudinal study [22] explored the effects of early lesion accrual on clinical outcomes 30 years from first symptom onset, and found that a greater number of baseline lesions predicted greater clinical disability (EDSS >3.5) at 30 years (OR = 1.84 between grouped lesion counts). Compared to other lesion locations, the number of infratentorial lesions at baseline and 1-year, and deep white matter lesions at 1-year were the strongest independent predictors of clinical disability (EDSS >3.5) (ORs 12.4, 11.1, and 10.7, respectively) and SPMS development (ORs 20.3, 19.3, and 14.9) by 30 years, while the number of infratentorial lesions at baseline and 1-year were most predictive of MS-related mortality by 30 years (HR = 3.9 and 5.25 respectively). It is important to note however that, while a greater burden of WM lesion correlates directly with worse disability and greater disease progression, these MRI findings still only explain a proportion of the observed clinical variability of MS outcomes (the ‘clinico-radiological paradox’) [80].

#### 5.1.2. Chronic active WM inflammation

Given that the effects of early accrual WM lesions may take several years to exert maximal effect on brain atrophy and progressive disease [35,36], and that a significant proportion (~30%) of lesions show evidence of chronic inflammatory activity [75] there has been increasing interest in imaging techniques that better characterize chronically active lesions. While the optimal methods of detecting chronic WM lesions are still to be determined, the presence of a susceptibility-weighted rim surrounding WM lesions and measurement of serial lesion expansion both mark chronically active lesions. A susceptibility-weighted rim can be detected using susceptibility-weighted imaging (SWI) MRI [81–84], and reflects iron deposition at the

perimeter of chronically active lesions as a result of microglial and macrophage activation [14,37,85–89]. Slow expansion of lesions, as a marker of chronic lesional activity, can be measured through serial measurement of lesion growth over time [86,90,91].

The presence and increased proportion of slow-expanding lesions is related to greater disability progression over time [86,90,91]. In one study conducted by Elliott and colleagues [86], accumulation of T1 hypointense lesion volume correlated with chronic T2 lesional expansion, rather than the formation of new T2 lesions, and was associated with an increased risk of disability progression at 12 weeks. A more recent study by the same group [90] developed automated heuristic algorithms to detect chronically active, slow expanding lesions through Jacobian analyses of sub-voxel level tissue deformation, and found that chronic slowly expanding lesions were more common and had greater T2 volumes among PPMS patients when compared to relapsing MS, further emphasizing the role of chronic inflammation in progressive disease. In another study [92], Klistorner and colleagues found that chronic lesion volumes were also significantly associated with accelerated brain atrophy and disability accrual (as measured by EDSS) independent of the formation of new WM lesions. Another recent longitudinal cohort study by Preziosa and colleagues [91] also found that a higher proportion of slowly expanding WM lesions and lower MTR values at baseline both independently predicted clinical disability progression (using EDSS) after 9 years.

### 5.2. GM inflammation

#### 5.2.1. Acute GM inflammation

Detecting cortical lesions *in vivo* using MRI is more difficult than identifying WM lesions [93]. Cortical lesions are smaller, generate less contrast (due to the comparative paucity of myelin in the cortex compared with WM) and are spatially more prone to partial volume effects [94]. Demyelinating cortical lesions can be detected on conventional field-strength (1.5T and 3T) MRI using double inversion recovery (DIR) or phase-sensitive inversion recovery sequences (PSIR) [95]. The histopathological-validated sensitivity of DIR and PSIR at 3T with similar resolution (1.2 mm<sup>3</sup> and 1.25 mm<sup>3</sup> respectively) is only about 10% of purely intracortical lesions, albeit with high pathological specificity [96,97]. Ultra-high field strength MRI at 7T, with superior spatial resolution and contrast, increases the sensitivity of cortical lesion detection [98]. Compared with 3T MRI, 7T MRI is able to detect about twice the number of intracortical lesions in clinical MRI sequences (T2-weighted and FLAIR) but a significant proportion of cortical lesions remain undetected, particularly subpial lesions [99–101].

Despite these limitations, MRI studies can identify cortical lesions in most people with MS, even in the earliest stages, and they are rarely seen in healthy controls [40,41,102,103]. Longitudinal studies have shown cortical lesion accrual is greater in SPMS than in RRMS patients and that cortical lesions appear to develop intracortically, independently of WM lesions [104–106]. Cortical lesion loads correlate positively with EDSS and appear to do so more than WM lesion volumes, particularly with increased sensitivity for cortical lesion detection at

7T [102,105,107,108]. In 102 patients with MS, cortical lesion volume, along with disease duration, increased the odds of a higher EDSS score independent of cortical atrophy [108]. Similarly, in 63 people evaluated 30 years after a first demyelinating episode suggestive of MS, cortical lesions were the main correlate of neurological disability measured by EDSS and distinguishing feature of a progressive disease course [48]. In the same study, cortical lesions also had a significant contribution to other clinical outcomes at 30-years in terms of lower limb function (timed 25-ft walk test) and cognitive impairment (symbol digit modalities test) [48]. Cortical lesion number and volume have been found to be higher in patients with cognitive impairment and both correlated with test scores across multiple cognitive domains, while cortical lesion volume appears to be an independent predictor of a composite cognitive impairment index [109]. Similarly, cortical lesion number has been shown to significantly increase the risk of mild cognitive impairment [110], and cortical lesion volume correlates with cognitive impairment independent of WM lesion load and brain volumes [102].

Cortical lesions not only influence current physical and cognitive disability but also seem to be of prognostic value. An early longitudinal study showed that cortical lesion volume predicts subsequent gray matter atrophy and disability progression over 3 years [106]. More recently, baseline cortical lesion volume has been shown to influence both baseline EDSS and subsequent EDSS change (over a mean 1.5-year interval), independent of white matter lesion load and cortical atrophy [105]. Using a gradient-boosted decision tree machine learning algorithm, cortical lesions, particularly leukocortical lesions were among the most influential imaging markers to predict EDSS progression and differentiate between MS disease phenotypes over 3 years [111]. In the longer term, the presence of at least three cortical lesions at diagnosis predicts cognitive impairment at 20 years [112]. Furthermore, the key predictive factors in a machine-learning derived risk score of conversion to SPMS over 10 years included both cortical lesion number at MS diagnosis and increase in cortical lesion volume over the first 2 years, with the latter having the greatest predictive effect barring age [113].

### 5.2.2. Chronic active GM inflammation

Histopathological studies have shown that, as with WM lesions, cortical lesions may be staged into active, inactive and chronic active lesions; the latter is identified by increased presence of activated microglia at the lesion edge or pial surface [55,60,114]. People with chronic active cortical lesions showing rims of activated microglia on postmortem tissue had a less favorable disease course with more active WM inflammation, shorter disease duration and a younger age at death [115]. There was also a correlation between chronic active cortical lesions and the presence of chronic active WM lesions, suggesting that chronic inflammation in WM and GM are related. Chronic active cortical lesions can be identified on T2\* gradient echo MRI sequences by the appearance of a hypointense halo or ring around a hyperintense center [116]. Chronic activity can be seen in all cortical lesion subtypes, although most are leukocortical lesions, and the rim hypointensity correlates with the identification of iron-rich

microglia on immunohistochemical analysis [116]. Similarly, quantitative susceptibility mapping (QSM) can accurately quantify brain iron load and be used to identify chronically active lesions with a paramagnetic rim, related to the presence of iron-laden activated microglia and macrophages [117]. QSM-hyperintense cortical lesions appear to correlate with EDSS in the subset of RRMS patients, although to date an association in SPMS has not been observed (attributed to smaller sample sizes) [111,117]. Positron emission tomography (PET) imaging has been shown to have a useful role to play in identifying chronic inflammatory activity (see review [118]). Using MRI PET and the 11 C-PBR28 radioligand, Herranz et al. [119] were able to show that patients with more active cortical lesions had lower cognitive performance and greater disability.

### 5.3. Microglial activation in chronic inflammation

Activated microglia are seen at the rims of chronically active lesions [37,120] and extra-lesional WM [6]. We have previously discussed the presence of a susceptibility-weighted rim on SWI scans above. Considering extra-lesional tissues, there is currently no MRI technique that is specifically sensitive to microglial activation, although microglial activation does appear to be associated with myelin and axonal pathology that can be assessed using MRI [35]. Here positron emission tomography (PET) has a clear advantage over MRI, with the ability to specifically tag cell types if an appropriate ligand can be found. For microglia, translocator protein ligand (TSPO) PET has shown promise in mapping microglial activity, suggesting that this is apparent in the NAWM preceding radiological features of neurodegeneration measured by enlarging T2-lesions and brain atrophy [121,122].

### 5.4. Leptomeningeal disease

Imaging the leptomeninges is technically challenging, both in terms of distinguishing areas of inflammation from meningeal blood vessels (which also avidly enhance with Gadolinium contrast on T1-weighted images) or due to contrast leakage from surface brain lesions into surrounding CSF spaces [59]. With the ability of 3T and 7T MRI to better detect subpial demyelination and GM lesion formation, several studies have demonstrated leptomeningeal contrast enhancement (LMCE) as a radiological marker of neuroinflammation, which appears to correlate with both subpial demyelination and areas of meningeal inflammation cells [59]. LMCE correlates with greater volume and rate of GM loss, greater disability, and longer disease duration in MS [59,123–125]. In one study, LMCE appeared to be more prevalent among those with MS compared to healthy controls (25% vs 2.7%) [59], while two studies suggested that, among patients with established MS, this finding was also more common in progressive forms (33–85.7%) [59,125]. Using 3T imaging, Zivadinov and colleagues [125] found that LMCE persisted in at least 50% of cases over the 5-year follow-up period, while those with SPMS were more likely to have multiple foci of LMCE. However, in a more recent study [126] which utilized 7T

MRI the investigators found that, while LMCE persisted in approximately 70–85% of the patients after 2 years, there were no observed differences in LMCE between patients that followed progressive and non-progressive courses of MS. The presence of LMCE does not appear to be influenced by DMT use [59,125–128], and two further studies which considered the use of intrathecal rituximab [129] and intravenous ocrelizumab [130] anti-CD20 therapies.

### 5.5. Perivascular disease

A small number of studies have found associations between greater numbers of enlarged perivascular spaces and worse cognitive performance [131] and fatigue [132] clinically, as well as greater numbers of gadolinium-enhancing lesions [133] and lower brain volumes [134]. Considering micro, rather than macro-structural features, Carotenuto and colleagues [66] recently evaluated diffusion tensor imaging along the perivascular space (DTI-APLS) (as a marker of glymphatic function), and found a lower DTI-APLS index among individuals with MS compared to healthy controls (suggesting impairment in glymphatic system function), as well as in those with more progressive forms of MS compared to relapsing-remitting phenotypes. A lower DTI-APLS also correlated radiologically with higher WM and cortical GM lesion volumes, greater GM atrophy (both cortical and deep GM) and reduced fractional anisotropy and increased mean diffusivity in the NAWM, as well as being clinically associated with more severe clinical disability among and greater MS disease duration [66]. This is a newly emerging field, and these findings suggest that there may be value in exploring it further.

### 5.6. Neurodegeneration

#### 5.6.1. Brain and grey matter atrophy

The final pathway of tissue injury from acute and chronic demyelination is neuro-axonal loss [135] although it also occurs independently of lesions [136,137] and is associated with volumetric changes on MRI [138]. Since the 2016 review [12], there is now more of a consensus [139] that brain volume loss occurs from earliest MS, is associated with concurrent disability and predicts future disability throughout the disease course with changes in GM volume being more pronounced and clinically relevant than WM. It has also been shown that people with MS may have ‘silent progression,’ defined as worsening disability in the absence of relapses or white matter lesions, with higher rates of brain atrophy than those with stable disease, although it is not clear if this is driven by GM volume loss [140]. The measurement of whole brain atrophy has been preferred in clinical trials, as it is technically less challenging, but remains difficult to apply to clinical practice [12,139,141].

#### 5.6.2. Regional atrophy

It has been shown that regional linear atrophy measures, even derived from low resolution 0.5T MRI, can independently predict long-term disease progression and disability [23]. Similarly, lateral ventricle volume is a promising metric that correlates with disability progression and may prove more clinically feasible than whole brain volume measurement [141–143]. Brain

atrophy appears fastest in deep GM, being associated with disability progression and baseline deep GM volume predicts time-to-EDSS progression [144]. In deep GM, the cingulate cortex and thalamus show the greatest volume loss and correlate with subsequent disability progression, with baseline thalamic volume predictive of future disability worsening over 2–8 years [145–149]. Thalamic atrophy is better explained by WM lesion volumes than by focal thalamic lesions [149,150] suggesting a network-based neurodegeneration due to progressive structural disconnection and Wallerian degeneration.

#### 5.6.3. Connectivity, disconnectome, and network collapse

The concept that neurodegeneration may also be network-mediated was further suggested by studies using source-based morphometry (SBM) and independent component analysis (ICA). These have shown regions of cortical atrophy are nonrandom and co-vary in distinct anatomical patterns, some consistent with known neural networks, as well as being associated with clinical disability [151]. Indeed, some baseline regional patterns of GM atrophy identified using ICA may better predict disability than single regional or global atrophy measures [152]. SBM has been applied longitudinally to identify covarying patterns of GM atrophy associated with confirmed disability progression over 10 years in RRMS patients [153].

There has been growing interest in comprehensively studying connections between brain regions, by mapping either structural or functional connectivity between different brain GM regions [154]. Using resting state functional MRI, functional connectivity appears to increase early in MS as part of network reorganization [155,156] and decreases with greater disease duration and disability progression [157,158]. Structural connectivity studies have shown that patients with MS have a more random cortical topology [159] which may be associated with cognitive dysfunction [160]. Limited longitudinal analyses of structural cortical networks have so far revealed both adaptive and maladaptive changes in network connectivity, efficiency, and network reorganization that similarly appear to evolve at different timepoints in the disease [161–163], while baseline connectivity disruption may predict worse future cognition [164].

Conversely, ‘disconnectome’ approaches have been employed to assess how WM lesions disrupt WM tracts connecting GM regions. The effects of WM lesions on global network properties, regional connectivity (e.g., the proportion of WM tracts to a given GM region affected by WM lesions) and connectivity between pairs of regions (individual WM tracts most likely affected by WM lesions) can then be derived [164]. Disconnection measures, while directly related to WM lesion volumes, are associated with disability independent of WM lesion volumes [165]. Models combining disconnectome metrics of region-pairs with GM atrophy better predicted future processing speed (symbol digit modalities test) compared with models based on global or regional disconnection with GM atrophy or GM atrophy alone, but overall prognostic associations remain poorly understood [164].

#### 5.6.4. Atrophied lesion volume

Recently, the volume of T2-weighted lesional tissue subsequently replaced by CSF has been posited as an imaging biomarker of disease progression [166]. Although histological

correlation has yet to be confirmed, atrophied T2 lesion volume is associated with both baseline WM lesion volumes and percentage brain volume changes, capturing aspects of both inflammation and neurodegeneration [167]. It is greater in people with progressive MS versus relapse-onset MS and increases with disease duration [166,168]. Furthermore, atrophied T2 lesion volume correlates with disability, explaining addition variance beyond whole brain atrophy and WM lesion volumes [166,169], and differentiates patients showing disease progression better than global and regional atrophy measures [167,168]. Prognostically, atrophied T2 lesion volume has been associated with conversion to SPMS [168] and appears to predict time to disease progression earlier than whole brain, central or cortical atrophy measures [169].

## 5.7. Microstructural disease in the normal appearing brain tissue

Pathology in MS may extend beyond lesion borders into macroscopically normal-appearing brain tissue [114,170], and so quantitative MRI techniques may be useful in detecting subtle microstructural abnormalities [171] not visible on conventional MRI sequences [172,173]. In addition to increased sensitivity to MS pathology in normal-appearing brain tissue, quantitative MRI techniques may help to identify and monitor biological processes occurring *in vivo* by exploring microstructural damage in various tissue components (such as myelin, axons, and iron).

### 5.7.1. Axonal degeneration

Diffusion-tensor imaging (DTI) has been widely used in the research setting and DTI metrics (fractional anisotropy and mean diffusivity) correlate with myelin content and axonal counts in NAWM [174] and axonal density, but not myelin in normal-appearing cortex [91]. Measures of diffusivity have shown deterioration in WM tract integrity in patients with progressive MS [175] and similar worsening of DTI parameters in WM tracts can be seen in patients with no evidence of disease activity, suggesting DTI metrics may be sensitive to an underlying neurodegenerative process [176]. DTI metrics may also have some utility in predicting cognitive decline [177] and disability progression [178]. Although sensitive to pathology, DTI metrics lack biological specificity as they are easily affected by any changes to the underlying tissue microstructure or organization and are difficult to interpret at voxels where fibers or tissue types cross [179].

An emerging technique, neurite orientation dispersion and density imaging (NODDI) overcomes the latter by modeling water diffusion in three different compartments to provide more precise microstructural information, including metrics of intracellular volume fraction, neurite density index (NDI) and orientation dispersion index (ODI) [180]. The utility of these metrics has yet to be fully elucidated. NDI appears to be reduced in NAWM and even more so in WM lesions, with potentially similar findings in NAGM and cortical lesions [180,181]. ODI appears to be more heterogeneous and is dependent on the underlying tissue type, for example being increased in GM relative to WM, which has more compacted fibers. ODI changes could also reflect changes in underlying

pathology; compared to healthy WM, ODI may be increased in NAWM and early lesions due to tissue damage disrupting highly parallel fibers (and increasing dispersion) and decreased in chronic lesional tissue as a result of severe axonal loss [180]. NODDI metrics have been associated with disease severity [182,183] but further work is required to observe the longitudinal evolution of these parameters and evaluate their value in prognosticating disease progression.

### 5.7.2. Iron accumulation

The utility of iron accumulation in identifying chronically active WM lesions has been discussed earlier (see section 4.2.2) but iron accumulation in extralesional tissues may also be relevant. Early MRI studies noted T2-hypointensities, thought to reflect iron deposition, within deep GM structures [184,185], which were subsequently found to correlate with brain atrophy [186,187], disability [187–190] and clinical course [187,189], as well as cognitive impairment [191]. Baseline measure of GM T2-hypointensity were even predictive of future disability progression [192,193] and atrophy [194]. Over the past decade, advanced MRI techniques such as QSM and R2\* have been developed to estimate brain iron load. Histological work has shown that QSM is positively correlated with the paramagnetic properties of iron leading to an increase in susceptibility, while the diamagnetic effects of myelin lead to a decrease in susceptibility and negative correlation; while increases in R2\* signal may be due to increases in iron or myelin concentration [195].

Using these methods, iron accumulation within deep GM structures can be seen in the earliest stages of MS [196] and is increased in the progressive forms of the disease [197]. Higher deep GM R2\* signal has been linked to EDSS and motor scores while higher basal ganglia susceptibility (both reflecting higher iron concentration) has been associated with clinical disability [198]. Interestingly the same study found lower thalamic susceptibility in MS, associated with greater disease duration, disability and SPMS [198]. It has been proposed that there may be thalamic iron deposition in early MS followed by depletion of iron from oligodendrocytes and reduced thalamic susceptibility [199]. Similar low iron concentrations are seen in NAWM in iron-imaging studies of MS consistent with histopathology, where iron depletion also correlated with disease duration [200]. Iron levels within tissues and lesions are not stationary, but subject to fluctuations depending on inflammatory activity [201] and may also be involved in tissue regeneration [202]. Monitoring iron changes to track neurodegeneration is therefore likely to be complex, and more work needs to be done to fully establish the consequences of iron deposition and dysregulation in MS.

### 5.7.3. Myelination

Several MRI techniques have been shown to be sensitive to myelin density [203,204] of which magnetization transfer ratio (MTR) and myelin water fraction (MWF) have the highest correlation with histological verification in clinical studies [203,204]. In both WM and GM, lesional tissue MTR values are abnormally lower than in normal-appearing brain tissue [205], while a more severe baseline NAWM MTR abnormalities also appears to predict poorer clinical outcomes in MS



patients 5 years later [206]. However, in patients with SPMS compared with RRMS, MTR abnormalities in cortical lesions and NAGM are more pronounced and NAGM MTR most consistently associated with clinical outcomes independent of WM lesion volume and brain atrophy [207]. Similarly, normal-appearing cortex MTR can distinguish MS phenotypes and is a significant contributor to long-term cognitive outcomes [48,208]. GM MTR has been shown to correlate with physical disability [209,210] while baseline GM MTR independently predicted disability worsening over 3–8 years [211,212]. In contrast, in another study, MTR within lesions rather than MTR within NAWM and NAGM contributed to concurrent EDSS in a cohort of predominantly RRMS patients, with less overall disability [205]. More recently, Varma and colleagues [213] revised existing MTR methods to develop inhomogenous magnetization transfer ratio (ihMTR) techniques, which are thought to be more sensitive to myelin, and so in quantifying demyelination, than conventional MTR methods alone. Subsequent studies have since demonstrated a greater correlation of ihMTR with EDSS compared to conventional MTR techniques [214], and that may be more sensitive (compared with MTR) to distinguish between WM in controls and NAWM tissue in people with MS [215].

The volume of NAWM deficient in MWF has been shown to correlate with EDSS disability and discriminate SPMS patients from those with RRMS [216]. Myelin-heterogeneity (measured by increased variance of MWF) within the NAWM may be a more sensitive marker of myelin change and has been associated with decreased cognitive processing speed [217] and EDSS [172]. Over time the MWF of NAWM appears to reduce and this may be more in patients with progressive disease (10% decrease over 2 years observed in PPMS patients [218] vs 8% decrease in RRMS patients over 3–5 years [219]). Such changes in NAWM over time are not seen in other neuroinflammatory disorders (such as neuromyelitis optica) and are suggestive of an ongoing neurodegeneration that appears to be specific to MS [220].

#### 5.7.4. Surface-in gradients

Extrasional abnormalities are not uniformly distributed but instead show surface-in gradients in both periventricular WM and cortical GM, with greater abnormality seen the closer the distance from the ventricular surface [53]. Surface-in gradients have been mostly demonstrated on MTR sequences [221–224], but can also be seen on quantitative T1 [225], T2\* [226] and diffusion-weighted imaging [227], while pathological of gradients of neuronal loss and meningeal inflammation have been demonstrated in cortical gray matter [44].

As highlighted in a recent review [53], the cause of surface-in gradients remains unclear, but they are most likely mediated by CSF soluble factors released from meningeal inflammation. However, it is clear that surface-in gradients occur early in MS [222,224] and are most severe in progressive stages [221,224] correlating with disability [225,228–230] and disease duration [229]. Longitudinal studies are lacking, but surface-in gradients appear to in part predict on the risk of future relapses [222], treatment response [231] and a recent study has suggested that baseline gradients may predict future disability in people with early MS [225].

#### 5.8. Tissue sodium accumulation

More recently, sodium ( $^{23}\text{Na}$ ) MRI has been identified as a marker of cellular integrity and tissue viability [232], with an increased sodium concentration (suggestive of axonal damage) within both focal MS lesions on T2 sequences and the NAWM [233–239] that correlates with increased clinical disability and disability progression [237,239]. In a subsequent radiological study conducted by Weber and colleagues [232] comparing lesional and NAWM total sodium concentrations and sodium concentrations were greater among the NAWM and NAGM of MS patients when compared to healthy controls. While total sodium concentrations were similar in both T2 lesions and NAWM, total sodium concentrations were significantly higher in T1 hypointense and isointense lesions compared to T2 lesions.

#### 5.9. Remyelination

Myelin-sensitive MRI metrics can detect longitudinal changes in myelination within lesions. Longitudinal study of MWF changes has shown that while some lesions show decreases in MWF over time, others show increase in MWF over time and capacity for remyelination [240,241]. Similar changes have been observed using MTR, with an increase in MTR observed to correlate with the return to T1 isointensity [242] and the MTR of WM lesions follow different temporal evolutions of demyelination and remyelination [243].

Despite some evidence that active RRMS patients with greater remyelination potential have lower disability levels [244], we still know little about the extent to which remyelination failure contributes to disease progression [245]. Clinical trials of potential remyelinating agents in MS have started to show effects on electrophysiology and MRI (in particular GM lesions) [246,247], but we have not yet identified the right MRI metric that can predict disability worsening within a sufficient time-frame for remyelination clinical trials [248].

#### 5.10. Artificial intelligence and machine learning

Machine learning applications in MS research have been recently reviewed [249], and so will be not discussed in detail here. However, it is worth noting that this is a rapidly advancing area, both in terms of technical developments in machine learning approaches and their applications to MS, including use in the assessment of lesion accrual [250], automating lesion and brain tissue segmentation [251], distinguishing between acute versus chronic lesions [252], and quantifying cortical atrophy [253].

Machine learning techniques may also allow us to derive measures previously only possible using dedicated imaging, for example, synthesizing DIR and PSIR images from standard sequences (such as T1-, T2-weighted and FLAIR images) [254]. In another study, Barnett and colleagues explored the application of AI-based MRI monitoring techniques in MS toward real-world clinical practice and found that these demonstrated superior sensitivity in detecting new, enlarging or contrast-enhancing lesions (subclinical features of MS disease activity) when compared to qualitative reporting techniques [255].

There is also considerable interest in the use of machine learning algorithms for their ability to assemble multiple sources of information to predict clinical disability and future disease progression [256]. Machine learning may also be useful in identifying prognostically relevant features that are otherwise clinically overlooked. For example, in one study conducted by Eshaghi and colleagues [257], unsupervised machine learning was found to be capable of stratifying people with MS based on MRI features (such as the prominence of WM lesion accrual or brain atrophy at a given timepoint) into different subtypes that may better predict disability progression and treatment response than standard clinical phenotypic definitions.

## 6. Conclusion

The potential role of MRI in predicting and monitoring MS progression has increased significantly with the development of new methods seeking to assess specific elements of MS pathology that are not captured by conventional MRI outcome measures such as WM lesion accrual. However, it remains to be shown which of the new MRI measures are of greatest clinical relevance, and it is still proving very challenging to use advanced MRI acquisitions and analysis protocols in clinical practice, although such methods are being adopted as exploratory outcome measures in clinical trials.

## 7. Expert opinion

Our understanding of the mechanisms underlying MS progression lags behind relapses, as do the therapeutic options available to treat it, but over the past decade there have been substantial advances in both areas. MRI research has contributed significantly to this, complementing other lines of investigation such as histopathology and PET imaging, allowing us to assess the evolution of pathology in life and its association with clinical outcomes. Importantly, there has been a clear evolution in the way we view relapses and progressive MS as separate entities to one where they can occur simultaneously, and that progression independent of relapses is a major contributor to disability even in people with relapsing-remitting MS. This has important implications for the way treat MS, suggesting that there may be considerable scope for therapies designed to slow or prevent progression to have meaningful impact on disability long before someone transitions from relapsing-remitting to secondary progressive MS.

Neurodegeneration is thought to ultimately underlie irreversible progressive disability in MS, but the processes leading to it remain unclear. Focal WM inflammation, as assessed by lesion counts or volumes only partially predicts neurodegeneration (as reflected by brain atrophy), however it is now clear that this only captures a fraction of inflammatory activity in MS. Significant progress has been made with methods to assess chronic WM and GM lesion activity, meningeal and perivascular inflammation, and other factors that may promote neuronal damage such as iron and sodium accumulation, and work is ongoing trying to determine how these relate to neurodegeneration and each other. This requires long-term studies, given that the clinical manifestations of progressive MS may take decades to

unfold, and to date there have been very few MRI studies spanning 10 or more years. Longitudinal studies will allow us to map the evolution of different pathological processes over time, as it is likely that multiple mechanisms will have significant contributory effects to disease progression, and these may change over time and differ between people with MS even if they appear to be running the same clinical course. Ultimately, a combined assessment of multiple MRI or other biomarkers capturing different pathogenic processes may well be required to effectively monitor individual disease progression and assess treatment efficacy.

Analyses methods considering the effects of pathology on neural networks (rather than the brain as a whole) have helped bridge the apparent disconnect between MRI measures and clinical outcomes, but to date have mainly considered effects on WM and GM, and structural and functional measures, separately. There is likely to be further value in combining them, although this a far from simple challenge.

There also remain significant technical barriers in translating advanced MRI research tools, often developed using data from a single research scanner, into routine clinical practice, including the availability and harmonization of MRI acquisition sequences across scanners from multiple manufacturers, and the complexity of image post-processing required. For example, while brain atrophy measures were shown to be clinically relevant more than two decades ago, they have yet to become a universal part of clinical practice, in part due to MRI acquisition and processing factors. Translating newer MRI measures into clinically useable tools will still be more difficult, although as with brain atrophy measures, many are now being adopted in clinical trials, and in doing so they are being refined for use in longitudinal studies undertaken using multiple different MRI scanners. Another barrier to adoption is the need for advanced MRI to deliver clinically actionable information, and so we need clear thresholds that would inform decisions, and we need treatments that target the associated pathological processes.

Machine learning, although relatively recently applied to the study of progressive MS, has already shown great promise allowing us to combine data in new ways to identify previously overlooked features that may help us to better explain clinical progression and its genesis, clinical heterogeneity between people with MS, and overcome some of the challenges in deriving advanced MRI measures from clinical MRI. It also has great potential to help interpret and use the results, while being able to distill multiple sources of information to refine prognostic models.

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- **Landmark study highlighting the potential of unsupervised machine learning to identify prognostically relevant features and stratifying people with MS based on MRI pathological features may better predict disability progression than conventional clinical phenotypes.**