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Magnetization transfer ratio abnormalities reflect clinically relevant grey matter damage in multiple sclerosis

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Abstract

Background—In multiple sclerosis, grey matter (GM) damage appears more clinically relevant than either white matter damage or lesion load.

Objective—We investigated if normal-appearing white matter (NAWM) and grey matter tissue changes assessed by magnetization transfer ratio were associated with long-term disability.

Methods—Sixty-nine people were assessed 20 years after presentation with a clinically isolated syndrome (CIS) [28 still CIS, 31 relapsing-remitting multiple sclerosis, 10 secondary progressive multiple sclerosis], along with 19 healthy subjects. Mean magnetization transfer ratio, peak height (PH) and peak location of the normalized magnetization transfer ratio histograms were determined in NAWM and grey matter, as well as, white matter and GM Fraction (GMF) and T₂-weighted lesion load.

Results—Median expanded disability status scale for multiple sclerosis patients was 2.5 (range 1–8). GM-PH, and less so, NAWM mean and peak location, were lower in multiple sclerosis patients ($P = 0.009$) versus controls, relapsing-remitting multiple sclerosis versus CIS ($P = 0.008$) and secondary progressive multiple sclerosis versus relapsing-remitting multiple sclerosis ($P = 0.002$). GM-PH (as well as GMF) correlated with expanded disability status scale ($r_s = -0.49$; $P = 0.001$) and multiple sclerosis functional score ($r_s = 0.51$; $P = 0.001$). GM-PH independently predicted disability with similar strength to the associations of GMF with clinical measures.

Conclusion—Grey matter damage was related to long-term disability in multiple sclerosis cohort with a relatively low median expanded disability status scale. Markers of intrinsic grey matter damage (magnetization transfer ratio) and tissue loss offer clinically relevant information in multiple sclerosis.

Keywords

clinically isolated syndromes; grey matter atrophy; lesion load; magnetization transfer ratio; multiple sclerosis; white matter atrophy

Introduction

In multiple sclerosis (MS), the relationship between the white matter (WM) lesion load, as assessed using conventional magnetic resonance imaging (MKI), and disability is only moderate [1,2]. This has prompted a search for other MKI markers of disease progression that may either better explain clinical outcomes or provide additional clinically relevant information. A variety of MRI techniques have been developed and, of these, brain atrophy measures and magnetization transfer ratio (MTR) have shown particular promise in MS, in particular, tissue-specific estimates of the grey matter (GM) damage. GM atrophy, more so than WM lesion accrual or WM atrophy, may be associated with long-term disability [3-5]; MTR changes in the GM especially in early relapsing-remitting MS (RRMS) and primary progressive MS, have shown promise as predictors of future disability [6,7].

While recent histopathological studies in MS have reported extensive cortical demyelination [8-11] (including deep GM nuclei [10,12-14]), a study in an experimental model of MS found no clear association between regional cortical demyelination and atrophy [15]. This suggests that some elements of intrinsic cortical damage in MS may be at least partly independent of tissue atrophy, or may proceed it [16], and that assessment of both may provide complementary information. It is this that is explored in this work, using tissue-specific MTR as a measure of intrinsic tissue damage [17-19], alongside tissue-specific volumetric measures to assess atrophy [3]. MTR imaging has proven a sensitive marker of tissue damage in MS and, at least in the WM, appears to be mainly influenced by demyelination and axonal loss [19,20] and to a lesser degree by inflammation [20,21], although pathological features other than demyelination may also be important in the determinants of the MTR [22]. MTR abnormalities within normal-appearing (NA) WM and GM have been detected from the earliest clinical stages of MS [23-25], and may increase over time [5,26]. Several studies have reported that MTR changes in NAWM and GM may differ between clinical subgroups and are correlated with disability [6,7,26-30].

By studying a cohort of patients with a long and homogenous disease duration since their first presentation with a clinically isolated syndrome (CIS) suggestive of MS, this work aimed to:

1. Assess how GM and NAWM MTR metrics at 20 years reflect disease subtype [CIS, RRMS, or secondary progressive MS (SPMS)] and their level of disability.
2. Evaluate the relative clinical relevance of the MTR histogram metrics, tissue-specific brain atrophy estimates, and WM lesion load measures.

Methods

Subjects

The patients included in this study are part of a previously described cohort of CIS patients followed up approximately every 5 years for 20 years since their first presentation with a CIS suggestive of MS [1,3]. In 75 out of 107 patients seen at 20 years clinical and MRI data were acquired. Six patients were excluded (one patient developed cerebro-vascular disease in addition to MS; two patients did not complete the full scanning protocol, and the GM-WM segmentation failed in three patients). The remaining 69 patients were included in this

study 145 female and 24 male; mean age 51.4 years, range (39.4–67.5)]. Twenty-eight subjects had remained CIS and 41 had converted to clinically definite MS [31] (31 had RRMS and 10 had evolved to SPMS) [32]. Patients were followed-up a mean of 20.0 years (range 18–27) from their first episode of CIS suggestive of MS. Clinical measures included Expanded Disability Status Scale score (EDSS) [33] and MS functional composite scores (MSFC) [34]. Only two patients were on disease modifying treatment and both had RRMS. MRI data was also obtained in 19 healthy controls [11 females and 8 male; mean age 39.91 (6.53) years, range (30.57–57.30)].

The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee. All study participants gave written informed consent.

Image acquisitions and processing

The following whole brain sequences were acquired in all subjects at the 20-year follow-up time point, using a 1.5-Tesla GE Signa scanner (General Electric, Milwaukee, Wisconsin): 1) 2D interleaved dual spin echo (SE) [repetition time (TR) 1720 ms; echo times (TEs) 30/80 ms]; 28×5 mm slices; matrix 256×256 ; field of view 24×24 cm². Both echoes were acquired with and without a MT presaturation pulse to calculate a MTR map [35]. The saturating MI pulse was 1 kHz off-water resonance with an on-resonance equivalent flip angle of 1430° ; 2) 2D dual-echo proton density (TE 17 ms) and T₂ (TE 103 ms)–weighted fast SE [TR 2000 ms; 28×5 mm slices; field of view 24×18 cm²; in-plane resolution of 1.1 mm]; 3) 3D axial T₁–weighted, inversion-prepared, fast-spoiled gradient recall [TR 10.9 ms; TE 4.2 ms; inversion time 450 ms; 124×1.5 mm slices; imaging matrix 256×160 , interpolated to a final in-plane resolution of 1.1 mm; flip angle 20°].

The long TE images of sequences 1) and 2) were coregistered using FMRIB's Linear Image Registration Tool (FLIRT) (<http://www.fmrib.ox.ac.uk/fsl/>), and the same transformation was applied to the short echo images. Lesions were outlined using a semiautomated method as previously described [36]. T₂-lesion volumes (T₂LL) were obtained using the proton density-weighted scans (short echo) of sequence 2 and 3D T₁–weighted lesion load was computed from sequence 3. SPM2 <http://www.nmrgroup.ion.ucl.ac.uk/atrophy> [37] was used to segment the long echo images from sequence 1 into GM, WM (both NAWM and lesions), and CSF. (In the three cases where segmentation failed the T₂LL was very large, which is the reason for the failure). These segmentations were combined to obtain WM, GM, and whole brain masks. Lesions were then removed to obtain NAWM and GM masks, which were applied to the calculated MTR maps. A 10 percentage unit (p.u.) lower threshold was applied as were two successive erosions of WM and a single erosion of the GM to minimize partial volume effects. Brain volume–normalized NAWM and GM histograms were generated with a bin width of 0.1 p.u. and a smoothing window of ± 0.3 p.u. The peak height (PH), peak location (PL), and mean MTR were extracted for NAWM and GM.

WM, GM, and brain parenchymal fraction (WMF, GMF, and BPF) were obtained from sequence 3 using SPM2 (Wellcome Department of Cognitive Neurology, London, UK), corrected for lesion misclassification as GM [3,38].

Statistical analyses

Z-scores for MSFC subtests were calculated using our sample as a reference and used to derive MSFC scores [39].

Cross-sectional group comparisons of the MTR parameters were performed using linear regression with group indicator, and age, gender, and BPF as covariates. To assess the associations between the MTR histogram parameters and T₂LL, brain-volume

measurements and clinical outcomes, due to non-Normality of the variables as was shown by normal probability plots, Spearman's rank correlation was used.

To assess the relative contribution of the MTR histogram parameters, tissue-specific brain volumes and T₂LL to accrued disability: 1) ordinal logistic regression was used for EDSS, categorized as follows: 1.5; >1.5 and 3; >3 and 6; >6, and 2) linear regression was used for MSFC and its components: 9-hole peg test (9HPT); Paced Auditory Serial Addition Test (PASAT) and timed walk (the inverse of timed walk was used as it was more normally distributed). EDSS and MSFC (and its components) were modeled as response variables, with MTR parameters, tissue volumes, lesion load, age, and gender as covariate predictors. Lesion load was log transformed to improve normality before inclusion in the regression models. Where the T₂LL was zero (10 subjects), the log volume was given a value of 0.01 to include these subjects.

For each response variable, MRI covariates were entered together and removed singly by manual backwards stepwise exclusion until all model predictors were significant at $P < 0.1$ (a less stringent P -value threshold was used to take a more conservative approach in detecting potential confounds). To minimize the number of model covariates, a multistage approach was used. First, GM and NAWM MTR histogram parameters were modeled separately and then the best predictors from the two (GM and NAWM) models combined to obtain the best overall MTR model. After establishing the best MTR predictors, T₂LL and tissue volume (GMF and WMF) measurements were added to obtain a final model. Age and gender were added to the final models but omitted if the adjusted coefficients were both nonsignificant and not materially different from unadjusted coefficients.

The data were analyzed using Stata 9.2 (Stata Corporation, College Station, Texas). Statistical significance was taken at $P < 0.05$.

Results

The median EDSS for all patients (MS patients and those who had remained CIS) was 2.5 (range 0–8) and for MS patients only, 3.0 (range 1–8).

Group comparisons

The mean, median, and standard deviation (SD) of the GM and NAWM MTR histogram metrics for all patients and healthy subjects are presented in Table 1.

Group comparisons are presented in Table 2 and Figure 1. When age and gender were included as covariates, GM PH was found to be significantly lower in the following: 1) MS patients (SPMS and RRMS) versus controls; 2) SPMS and RRMS versus those subjects remaining CIS; and 3) SPMS versus RRMS. In the NAWM, mean MTR and PL were significantly lower in the following: 1) MS patients (SPMS and RRMS) versus controls; 2) SPMS and RRMS versus those subjects remaining CIS; but not between 3) SPMS versus RRMS. WM PH was lower in SPMS compared to all other groups. There were no differences between controls and those remaining CIS in any MTR metrics.

When BPF was also included as covariate (along with age and gender), the only significant differences observed were as follows: lower GM PH in SPMS versus 1) CIS [age and gender adjusted mean difference (B) = -0.88 ; $P = 0.011$] and 2) RRMS ($B = -0.66$; $P = 0.036$), and lower NAWM PH in SPMS versus RRMS ($B = -1.28$; $P = 0.053$).

Univariate correlations of MTR parameters with clinical outcomes and other MRI measures are presented in Table 3 and Figures 2 and 3.

Regression models (Table 4)

EDSS—Of the MTR parameters, GM PH was the only independent predictor of disability: there was an estimated 76% ($P = 0.001$) reduction in odds of a patient having greater disability per 1 SD higher GM PH.

GM PH remained the only independent predictor, even after adding T_2 LL and WMF measures to the best MTR predictors. Because of the strong correlation between GM PH and GMF ($r_s = 0.71$; $P < 0.001$) their independent contribution could not be estimated in the same model (inclusion of both GM PH and GMF in the same model rendered them both statistically nonsignificant); however, substituting GM PH with GMF, there was an estimated 66% ($P = 0.005$) reduction in the odds of a patient having greater disability per 1 SD higher GMF.

MSFC—Of the MIR parameters, GM PH was the only independent predictor of disability: there was a 0.86 ($P = 0.001$) increase in z-MSFC per 1 SD higher GM PH.

GM PH remained the only independent predictor, even after adding T_2 LL and WMF to the best MTR predictors. Because of the strong correlation between GM PH and GMF ($r_s = 0.71$; $P < 0.001$) their independent contribution could not be estimated in the same model; however, substituting GM PH with GMF, there was an estimated 0.67 ($P < 0.001$) increase in MSFC per 1 SD higher GMF.

Similar observations were evident when investigating 9HPT and inverted timed walk (Table 4). None of the MRI parameters predicted PASAT.

Discussion

This study builds on our previous work [3] with this cohort in two ways: it characterizes intrinsic tissue-specific changes, as measured by MTR, in a group of people with long and homogeneous disease durations not markedly confounded by the potential effects of disease modifying treatments, and it explores the relative contribution of GM and WM MTR, and atrophy, to clinical outcomes in MS. The main observations were as follows: 1) MTR abnormalities can be found in GM and NAWM; 2) both are associated with clinical outcomes, although GM more so than NAWM; 3) GM MTR PH and GM atrophy (GMF) measures explain similar degrees of variability in disability scores; and 4) such measures are more clinically relevant in the longer term than T_2 LL estimates.

MTR parameters (especially PH in GM and less so, mean MTR and PL in NAWM) were generally lower the more clinically advanced a patient's MS had become following a consistent stepwise pattern: they were lower in SPMS than in RRMS, and lower in RRMS than in healthy controls and those remaining classified as CIS, but there were no differences between CIS and healthy controls. These results suggest that MTR abnormalities in GM and NAWM – but more so in GM – may mark ongoing disease activity, rather than reflecting any residual effects of a CIS.

Volume-normalized MTR histogram measures are principally influenced by three factors: the average MTR values within a tissue, within tissue variability, and skew. This means for two tissues with similar mean MTR, an increase in tissue heterogeneity will lead to a reduction in PH. For tissues with different mean MTR values, an increase in tissue heterogeneity will tend to mask such differences. It is, therefore, worth considering a given MTR histogram parameter in the context of its SD. The PL relative to the mean MTR provides some insight into the skew of the histogram. A PL lower than the mean MTR, suggests the histogram is skewed towards higher values.

In our study, we see that the main disease effects in GM appear to be an increase in tissue heterogeneity, with greater skew towards lower MTR values (PL significantly increases, while mean MTR marginally reduces) when compared to healthy controls. In the NAWM tissue heterogeneity also increases but not to a degree that this masks a reduction of the mean MTR values (as well as reduction in concurrent PL). This differential disease effect may in part be due to the much greater ability using current MRI techniques to detect (and therefore exclude) WM lesions. Hence, the GM is more likely to contain demyelinated lesions than the NAWM, and so be more heterogeneous. Further, given its relatively small myelin content (compared to the WM) a larger proportional reduction in GM myelination is probably required to be detected using MTR. In summary, it is plausible that the GM MTR findings reflect a greater mixture of lesional and nonlesional cortex – the latter constituting the majority of GM tissue – with the results being a combination of reduced mean MTR and increased PL, whereas NAWM MTR findings reflect a more subtle nonlesional diffuse abnormalities (e.g., a combination of microglial activation [9], inflammation, demyelination, astrogliosis, and axonal loss) with reductions in both the mean and PL.

In a previous report on a larger subset of the same cohort of patients, we showed that GM but not WM atrophy measurements correlated with disability [3]. However, in this study the association between MTR measures and clinical outcomes appears to be less tissue-specific than for atrophy. While GM MTR was more closely related to clinical outcomes, NAWM MTR parameters were also correlated with clinical scores: GMF, but not WMF, correlated with clinical outcomes. This disparity may, in part, reflect differences in the nature of GM and WM pathology, in particular noting that WM lesions appear more inflammatory than those in GM [40]. If this holds true for NA tissues, we may expect that inflammation associated edema will tend to compensate for atrophy associated with cell loss more in the WM more than GM, while simultaneously diluting cell densities more in the WM than GM, which in turn may influence the strength of associations between tissue-specific MRI measures with clinical outcomes.

A recent histopathological study of an experimental model of MS has suggested that cortical demyelination and atrophy may not be closely linked [15]. In contrast in our study, we found that GMF and GM MTR PH were strongly correlated ($r_s = 0.71$). While the above discrepancy may represent known difficulties to translating findings from animal models of MS into human disease and vice-versa, if we assume that the substrates of MTR change in the GM are similar to those in the WM (i.e., weighted to a degree towards myelination, but not purely so [19]), our findings would suggest a link between GM demyelination and atrophy; if not, it would suggest that MTR changes in the GM, compared with the WM, at least in long-term MS, are less weighted towards demyelination and perhaps share another common substrate such as neuronal and or axonal loss.

While a correlation of brain atrophy and MTR has been evident in previous studies looking at early RRMS patients [41,42], MTR especially of the GM, appeared to be independent of brain atrophy when distinguishing MS patients from controls [24,42,43], this was not the case in our study. Given that disease associated atrophy is generally more marked, and spans a greater range, in the present cohort (disease duration ~20 years) compared with people with shorter disease duration, this observation may be the result of greater power to detect correlations rather than true biological differences. It may also relate to partial volume effects, which tend to increase at tissue volumes decrease. While measures were taken to limit this, we cannot entirely discount this possibility. However, it may also represent a true pathological link between intrinsic tissue damage and atrophy with connected features including demyelinating lesions and neuronal loss.

Correlation between T₂LL and NAWM MTR was stronger than with GM MTR. However, at best such correlations accounted for about 50% of shared variability, suggesting that global WM and more particularly GM MTR changes are at least partly independent of focal WM lesion formation. In addition, GM PH was a better predictor of clinical outcomes than T₂LL, reinforcing the conclusion from previous work that GM pathology is an important determinant of disability in MS [3].

When considering these results, in addition to those noted above, several other limitations should be kept in mind. First, studies have reported mean GM MTR [24] and the others have reported PH [6] as better correlated with disability, but differences in MTR sequences across different scanners and centers [44] and variation in processing methodologies [43,45,46], may influence the relative sensitivity of the various MTR metrics to pathology. Second, the cohort of patients presented here has a bias towards those with lower disability (benign-MS) of all who were seen at 20 years (it was not possible to scan some of the more disabled patients), potentially limiting the scope to fully investigate associations between MRI measures and disability. Third, current image techniques have limited ability to detect cortical lesions [47,48]; thus there is uncertainty to what extent such lesions account for the GM MTR change seen. Future MR hardware (e.g., high field scanners at 3 Tesla and above) and sequence developments (e.g., double inversion recovery, phase-sensitive inversion recovery) should focus on better detection of GM lesions [49,50]. Finally, no assumption can be made about the longitudinal changes in MTR and atrophy in predicting disability. While a subgroup of the patients had similar sequences acquired at 14 year follow-up, a major scanner hardware upgrade rendered it difficult to directly compare measurements from earlier scanning with that obtained at 20 years.

Notwithstanding these limitations, this study shows that GM damage – as marked by MTR changes – is related to disability in MS, and is a better predictor of clinical outcomes than NAWM MTR, WM lesion load or WM atrophy in patients with longstanding MS.

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Figure 1.

MTR histogram profiles for the GM and NAWM. The average histogram profiles for the GM (left) and NAWM (right) for all subgroups: controls (solid line), CIS (dot dash line), RRMS (dashed line), and SPMS (dotted line). The peak location is the modal MTR value in p.u.; the peak height is the number of normalized brain units at the modal MTR value. GM, grey matter; NAWM, normal-appearing white matter; CIS, clinically isolated syndrome; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive MS; p.u., percentage unit.

Figure 2.

GM peak height plotted against GMF (top left), T_2 lesion load (top right), EDSS (bottom left) and MSFC (bottom right). GM, grey matter; GMF, grey matter fraction; EDSS, expanded disability status scale; MSFC, multiple sclerosis functional score.

Figure 3. NAWM mean MTR (left) and peak location (right) plotted against multiple sclerosis functional score and T₂-lesion load.

Table 1

Mean and median (SD) of the MTR histogram metrics

MTR histogram metrics	Mean; Median (SD)			
	Controls (N = 19)	CIS (N = 25)	RRMS (N = 31)	SPMS (N = 10)
GM				
Mean MTR (p.u.)	32.65; 32.66 (0.44)	32.41; 32.34 (0.55)	32.30; 32.27 (0.82)	31.83; 31.63 (0.82)
PL MTR (p.u.)	33.31; 33.40 (0.37)	33.29; 33.40 (0.30)	33.68; 33.50 (0.99)	33.37; 33.25 (1.00)
PH % volume/p.u.	12.10; 12.54 (1.20)	11.27; 11.15 (1.24)	10.64; 10.60 (0.99)	9.24; 8.86 (1.49)
NAWM				
Mean MTR (p.u.)	38.56; 38.52 (0.38)	38.49; 38.56 (0.41)	37.99; 38.24 (0.91)	37.77; 37.90 (0.84)
PL MTR (p.u.)	38.71; 38.80 (0.38)	38.66; 38.70 (0.52)	38.25; 38.50 (0.78)	38.00; 38.25 (0.69)
PH % volume/p.u.	19.62; 19.86 (2.28)	18.84; 18.85 (1.75)	19.01; 19.30 (1.80)	16.8; 17.87 (3.17)

CIS, clinically isolated syndrome; MS, multiple sclerosis; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; GM, Grey Matter; NAWM, normal-appearing white matter; MTR, magnetization transfer ratio; PL, peak location; PH, peak height; p.u., percentage unit.

Table 2
Age- and sex-adjusted mean difference (with *P*-values in brackets) [95% CI] of the MTR histogram metrics between patient subgroups and control subjects

Subgroups	GM			NAWM		
	Mean [p.u.]	PL [p.u.]	PH % volume/p.u.	Mean [p.u.]	PL [p.u.]	PH % volume/p.u.
MS – controls	–0.27 (0.205) [–0.71 to 0.15]	0.47 (0.049) ^a [0.002 to 0.94]	–0.92 (0.009) ^b [–1.60 to –0.24]	–0.65 (0.005) ^b [–1.10 to –0.19]	–0.47 (0.027) ^a [–0.89 to –0.05]	–0.55 (0.350) [–1.73 to 0.62]
CIS – controls	–0.03 (0.861) [–0.48 to 0.40]	0.16 (0.499) [–0.32 to 0.65]	0.05 (0.876) [–0.64 to 0.75]	–0.09 (0.694) [–0.56 to 0.37]	–0.002 (0.992) [–0.43 to 0.42]	–0.07 (0.896) [–1.29 to 1.13]
MS – CIS	–0.23 (0.141) [–0.55 to 0.08]	0.30 (0.082) [–0.03 to 0.65]	–0.97 (<0.001) ^b [–1.48 to –0.47]	–0.55 (0.001) ^b [–0.89 to –0.22]	–0.47 (0.003) ^b [–0.77 to –0.16]	–0.47 (0.278) [–1.34 to 0.39]
SPMS – Controls	–0.55 (0.054) ^c [–1.11 to 0.01]	0.28 (0.369) [–0.33 to 0.90]	–1.79 (<0.001) ^b [–2.64 to –0.94]	–0.81 (0.008) ^b [–1.40 to –0.21]	–0.65 (0.019) ^a [–1.20 to –0.10]	–1.71 (0.026) ^a [–3.21 to –0.21]
RRMS – Controls	–0.19 (0.389) [–0.63 to 0.25]	0.53 (0.032) ^a [0.04 to 1.02]	–0.65 (0.056) ^c [–1.32 to 0.01]	–0.60 (0.013) ^a [–1.07 to –0.13]	–0.41 (0.058) ^c [–0.84 to 0.01]	–0.19 (0.739) [–1.38 to 0.98]
SPMS – CIS	–0.50 (0.037) ^a [–0.98 to –0.03]	0.11 (0.654) [–0.40 to 0.64]	–1.83 (<0.001) ^b [–2.55 to –1.11]	–0.71 (0.006) ^b [–1.22 to –0.21]	–0.64 (0.007) ^b [–1.11 to –0.18]	–1.61 (0.013) ^a [–2.89 to –0.34]
RRMS – CIS	–0.14 (0.383) [–0.48 to 0.18]	0.37 (0.050) ^a [–0.01 to 0.74]	–0.69 (0.008) ^b [–1.20 to –0.18]	–0.50 (0.006) ^b [–0.86 to –0.14]	–0.41 (0.015) ^a [–0.73 to –0.08]	–0.09 (0.828) [–1.00 to 0.80]
SPMS – RRMS	–0.35 (0.136) [–0.83 to 0.11]	–0.25 (0.337) [–0.77 to 0.26]	–1.14 (0.002) ^b [–1.85 to –0.42]	–0.20 (0.410) [–0.71 to 0.29]	–0.23 (0.307) [–0.69 to 0.22]	–1.51 (0.019) ^a [–2.78 to –0.25]

MS, multiple sclerosis; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; CIS, clinically isolated syndrome; GM, grey Matter; NAWM, normal-appearing white matter; MTR, magnetization transfer ratio; PL, peak location; PH, peak height; p.u., percentage unit.

^aIndicates significance level at 0.01 < *P* 0.05.

^bIndicates significance level at *P* 0.01.

^cIndicates significance level at 0.05 < *P* 0.1.

Table 3Correlations of MTR histogram parameters with T₂LL, tissue-specific brain volumes, and disability (MS group only)

MTR histogram metrics	T ₂ LL	GMF	WMF	EDSS	MSFC
<i>r_s (P-value)</i>					
GM					
Mean	-0.04 (0.780)	0.12 (0.435)	0.43 (0.005) ^a	-0.29 (0.060)	0.30 (0.064)
PL	0.33 (0.035) ^b	-0.15 (0.350)	0.23 (0.141)	-0.12 (0.428)	0.12 (0.448)
PH	-0.47 (0.002) ^a	0.71 (<0.001) ^a	0.01 (0.921)	-0.49 (0.001) ^a	0.51 (0.001) ^a
NAWM					
Mean	-0.69 (<0.001) ^a	0.36 (0.019) ^b	0.30 (0.051) ^b	-0.27 (0.079)	0.34 (0.037) ^b
PL	-0.64 (<0.001) ^a	0.35 (0.024) ^b	0.20 (0.196)	-0.25 (0.107)	0.33 (0.040) ^b
PH	-0.31 (0.045) ^b	0.38 (0.013) ^b	-0.002 (0.992)	-0.25 (0.113)	0.17 (0.287)

GM, grey matter; NAWM, normal-appearing white matter; MTR, magnetization transfer ratio; PL, peak location; PH, peak height; T₂LL, T₂-lesion load; WMF, WM fraction; GMF, GM fraction; EDSS, expanded disability status scale; MSFC, multiple sclerosis functional score.

^aIndicates significant level at $P < 0.01$.

^bIndicates significant level at $0.01 < P < 0.05$.

Table 4
Independent predictors in regression models in MS group only (*N* = number of patients shown)

Variables ^a	EDSS (<i>N</i> = 41)	MSFC (<i>N</i> = 38)	9HPT (<i>N</i> = 39)	Inverted timed walk <i>N</i> = 37	PASAT (<i>N</i> = 39)
MTR metrics only	GM-PH (<i>P</i> = 0.001)	GM-PH (<i>P</i> = 0.001)	GM-PH (<i>P</i> = 0.001)	GM-PH (<i>P</i> < 0.001) and gender (<i>P</i> = 0.018)	None
GM-PH; GMF/WMF; T ₂ LL	Either, GM-PH (<i>P</i> = 0.001) or GMF (<i>P</i> = 0.005)	Either, GMF (<i>P</i> < 0.001) or GM-PH (<i>P</i> = 0.001)	Either, GM-PH (<i>P</i> = 0.001) or GMF (<i>P</i> = 0.015) and T ₂ LL (<i>P</i> = 0.007)	Either, GMF (<i>P</i> < 0.001) or GM-PH and gender (<i>P</i> = 0.041)	None

GM, grey matter; GMF, GM fraction; WMF, white matter fraction; PH, peak height; MTR, magnetization transfer ratio; T₂LL, T₂-weighted lesion load; EDSS, expanded disability status scale; MSFC, multiple sclerosis functional composite score; 9HPT, 9-hole peg test; PASAT, paced auditory serial addition test.

^a Age and gender were used as covariates on all models.