Spinal cord quantitative MRI discriminates between disability levels in multiple sclerosis

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ABSTRACT

Objective: The clinicoradiologic paradox, or disconnect between clinical and radiologic findings, is frequently encountered in multiple sclerosis (MS), particularly in the spinal cord (SC), where lesions are expected to cause clinical impairment. We aimed to assess whether quantitative diffusion tensor and magnetization transfer imaging measures in the SC can distinguish MS cases of comparable lesion burdens with high and low disability.

Methods: One hundred twenty-four patients with MS underwent 3-T cervical SC MRI and were categorized into 4 subgroups according to SC lesion count and disability level. Regions of interest circumscribed the SC cross-section axially between C3 and C4. Cross-sectional area, fractional anisotropy (FA), mean diffusivity (MD), perpendicular diffusivity ($\lambda_{\perp}$), parallel diffusivity ($\lambda_{\parallel}$), and magnetization transfer ratio (MTR) were calculated. Differences between patient subgroups were assessed using t tests and linear regression.

Results: FA, MD, $\lambda_{\perp}$, $\lambda_{\parallel}$, MTR, and SC cross-sectional area were more abnormal in the high- vs low-disability subgroup of patients with low lesion counts ($p < 0.05$). MRI measures (except $\lambda_{\parallel}$ and MTR) were more abnormal in the high- vs low-disability subgroup of patients with high lesion counts ($p < 0.05$). In age- and sex-adjusted comparisons of high- vs low-disability subgroups, all MRI measures retained differences in the low-lesion subgroup, except $\lambda_{\parallel}$, whereas only FA, MD, and $\lambda_{\perp}$ retained differences in the high-lesion subgroup.

Conclusions: In this cross-sectional study of patients with MS, quantitative MRI reflects clinically relevant differences beyond what can be detected by conventional MRI. Our findings support the utility of quantitative MRI in clinical settings, where accurate measurement of disease burden is becoming increasingly critical for assessing treatment efficacy. *Neurology*® 2013;80:540-547

GLOSSARY

BPF = brain parenchymal fraction; **CSA** = cross-sectional area; **DTI** = diffusion-tensor imaging; **EDSS** = Expanded Disability Status Scale; **FA** = fractional anisotropy; $\lambda_{\parallel}$ = parallel diffusivity; $\lambda_{\perp}$ = perpendicular diffusivity; **MD** = mean diffusivity; **MS** = multiple sclerosis; **MSFC** = multiple sclerosis functional composite; **MT** = magnetization transfer; **MTR** = magnetization transfer ratio; **ROI** = region of interest; **SC** = spinal cord; **TE** = echo time; **TR** = repetition time.

The practicing neurologist frequently encounters the phenomenon of the clinicoradiologic paradox, in which a substantial disconnect between spinal cord (SC) lesions detected with conventional MRI and physical disability in multiple sclerosis (MS) is observed.¹

This disconnect is particularly surprising in the SC, because of its compact structural organization. Anatomically, a strong correlation between MRI measures of lesion load in the SC and clinical dysfunction is expected—yet many studies confirm the lack of such a correlation.^{2,3} These observations, coupled with the tight anatomical organization of the SC and the propensity for SC lesions to occur in MS,^{4,5} make the SC an opportune structure within which to study the clinicoradiologic paradox.

Supplemental data at
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To study a real-world example of the clinico-radiologic paradox, we categorized a sample of patients with MS into 4 subgroups based on clinical disability level and MRI lesion count. Because of the sensitivity of diffusion-tensor imaging (DTI) and magnetization transfer (MT) imaging to microstructural tissue properties,^{6,7} we hypothesized that DTI and MT imaging indices would detect differences in individuals with differing disability levels, regardless of overall lesion count. The ability to detect clinically relevant microstructural changes in the SC with MRI is a necessary prerequisite to more effectively utilize MRI in clinical settings and to better understand MS disease mechanisms.

METHODS **Standard protocol approvals, registrations, and patient consents.** This study was approved by the institutional review boards of Johns Hopkins University and the Kennedy Krieger Institute. All participants provided written informed consent.

Study participants. Patients with relapsing-remitting MS, secondary progressive MS, and primary progressive MS were recruited from the Johns Hopkins MS Clinic by convenience sampling between 2007 and 2009. Because of the exploratory nature of this cross-sectional study, a sample size calculation was not performed. MS diagnosis was confirmed by the treating neurologist, according to the 2005 revised McDonald criteria.⁸ Within 30 days of MRI, MS functional composite (MSFC) scores were obtained and Expanded Disability Status Scale (EDSS) scores were determined by a Neurostatus-certified examiner. EDSS and MSFC were chosen as clinical measures over column-specific clinical measures because EDSS and MSFC have the benefits of familiarity and clinical interpretability by most neurologists, and because regions of interest (ROIs) encompassing the SC cross-section rather than specific columns were used.

For comparative analyses between patients with similar lesion loads but differing disability levels, patients were stratified into 2 groups according to MRI lesion count. Those with ≤ 2 lesions were classified as the “low-lesion” group, whereas those with ≥ 3 lesions were classified as the “high-lesion” group. A lesion-count cutoff of 2 was selected for this dichotomization because this was the median value across all patients and ensures adequate subgroup sample sizes. Patients were further dichotomized according to disability level using an EDSS cutoff score of 6. This particular EDSS cutoff was chosen a priori because it represents an important functional milestone regarding clinical disability, signifying the transition from ambulating independently for 100 m to requiring intermittent/constant unilateral assistance.⁹ Accordingly, MS patients with EDSS scores < 6 were categorized as the “low-disability” subgroup, whereas those with EDSS scores ≥ 6 were categorized as the “high-disability” subgroup.

Cervical SC MRI. Cervical SC MRIs were performed on all participants using a 3-T Intera scanner (Philips Medical Systems, Best, the Netherlands) using body coil excitation and 2-element phased array surface coil reception.

MT-weighted images were acquired using a T2*-weighted, 3-dimensional, gradient-echo sequence with an MT prepulse and a

multishot echo-planar readout (echo-planar imaging factor = 3, parallel imaging factor = 2, repetition time [TR]/echo time [TE]/ α = 121 milliseconds/12.5 milliseconds/9°), yielding 30 contiguous 3-mm axial slices spanning vertebral levels C2–6; nominal in-plane resolution: 0.6×0.6 mm². To calculate MT ratio (MTR), scans were acquired with (MT_{on}) and without (MT_{off}) a 1.5-kHz off-resonance sinc-gauss-shaped radiofrequency saturation pulse. MT_{on} was registered to MT_{off} using a 6 df, rigid-body procedure implemented in FLIRT (Oxford Centre for Functional MRI of the Brain's Linear Imaging Registration Tool, Oxford, UK). MTR was calculated using the following formula: (MT_{off} – MT_{on})/MT_{off}.

DTI data were obtained on all participants using a multislice spin-echo sequence with a single-shot echo-planar readout (parallel imaging factor = 2, TR/TE = 4,727 milliseconds/63 milliseconds). Axial fat-suppressed, diffusion-weighted images were obtained in 16 non-coplanar gradient directions with $b = 500$ s/mm², 1 minimally diffusion-weighted acquisition ($b_0 \sim 33$ s/mm²), 3-mm slice thickness, and nominal in-plane resolution of 1.5×1.5 mm².

Additional image sequences included a sagittal, multislice turbo spin-echo (factor = 20, parallel imaging factor = 2) short-tau inversion recovery (field of view = 250 mm, acquired resolution $1 \times 1 \times 2$ mm³ [anterior to posterior, foot to head, right to left], TR/TE/inversion time = 4,227 milliseconds/68 milliseconds/200 milliseconds).

Each diffusion-weighted image was registered to the initial $b = 0$ volume using a 6 df, rigid-body registration implemented in FLIRT using JIST (Java Image Science Toolkit).¹⁰ The diffusion tensor and maps of fractional anisotropy (FA), mean diffusivity (MD), perpendicular diffusivity ($\lambda_{\perp}$), and parallel diffusivity ($\lambda_{\parallel}$) were generated. The $b = 0$ image was deformably registered to the MT and the information applied to the diffusion-weighted images.^{10,11} Windowed sinc interpolation was used for resampling and rigid/affine transformation, and trilinear interpolation for deformable transformation. DTI indices were calculated from eigenvalues of the diffusion tensor.¹²

An automated reproducible segmentation protocol was applied to the MT_{off} images to delineate ROIs encompassing the axial cross-section of the SC across segments C3–4 and transferred to the MRI index maps (figure 1).¹³ SC column-specific ROIs were not used because of a high degree of anatomical distortion on DTI maps, making it difficult to accurately localize anatomical tracts. ROIs were manually adjusted as necessary on DTI maps with residual distortion. Average values of SC cross-sectional area (CSA), FA, MD, $\lambda_{\parallel}$, $\lambda_{\perp}$, and MTR were calculated from the ROIs of each MRI index map across all axial slices from C3 to C4.

Cervical SC lesions were counted between segments C2 and C6 on the axial MT and sagittal short-tau inversion recovery sequences by an experienced observer blinded to clinical status (J.O.).

Brain MRI. Full details of our brain MRI acquisition have been described previously.^{14,15} DTI was used to calculate supratentorial brain and CSF volumes.¹⁵ Brain parenchymal fraction (BPF) was calculated using the following formula: BPF = brain volume/(brain volume + CSF volume).

Statistical analysis. Statistical calculations were performed using STATA version 11 (StataCorp, College Station, TX). Student *t* tests were used for group comparisons of SC MRI indices. Because of the exploratory nature of this study, adjustment for multiple comparisons was not performed.¹⁶ Pearson product-moment coefficients were used to assess correlations between MRI indices. Multivariable linear regression was used to assess differences in MRI indices between patient subgroups, adjusting for age, sex, BPF, and SC CSA.

Figure 1 (A) Axial section of cervical spinal cord on high-resolution magnetization transfer sequence (B) with superimposed region of interest encompassing spinal cord cross-sectional area

Statistical significance was defined as $p < 0.05$. The discriminatory capacity of combinations of MRI indices was assessed using stepwise forward selection in a logistic regression model with high/low disability as the dependent variable and MRI indices, SC CSA, age, and sex included as covariates ($p < 0.10$ to remain in model).

RESULTS This study included a total of 124 patients with MS (69 relapsing-remitting MS, 36 secondary progressive MS, and 19 primary progressive MS). The patients were predominantly female (64%) and had a mean age of 45 years. Average MS disease duration was 11 years, and 69% of patients were receiving disease-modifying treatments (interferon- β : 40%; glatiramer acetate: 30%; natalizumab: 25%; and other medications: 5%) (table 1). When stratified by lesion

load, 69 patients fulfilled criteria for the low-lesion subgroup, and 55 patients for the high-lesion subgroup. Within subgroups stratified by lesion count, individuals with lower disability were younger, had shorter disease durations, were predominantly of the relapsing subtype, and were more likely to be receiving disease-modifying treatment than those with higher disability. Comparisons of equivalent disability subgroups between patients with high vs low lesion counts showed remarkably similar proportions of relapsing patients and distributions of EDSS scores (table 1).

Summary statistics for all MRI measures, including quantitative MRI indices (FA, MD, $\lambda_{\perp}$, $\lambda_{\parallel}$, MTR), SC lesion count, and SC CSA, are given in

Table 1 Comparisons of clinical characteristics and MRI measures in patient subgroups, stratified by lesion load

	All patients	Low lesion			High lesion		
		Low EDSS score	High EDSS score	p Value ^a	Low EDSS score	High EDSS score	p Value ^a
Subjects, n	124	55	14	NA	31	24	NA
Age at MRI scan, y (SD)	45.2 (11.1)	42.2 (11.9)	51.3 (6.5)	0.008 ^b	43.1 (10.3)	51.2 (8.6)	0.003 ^b
Female, %	63.7	78.2	64.3	0.28	45.2	54.2	0.50
Disease duration, y (SD)	10.9 (9.3)	8.4 (9.0)	19.4 (10.0)	0.0002 ^b	8.7 (6.6)	14.7 (8.5)	0.005 ^b
Median EDSS score (IQR)	3.5 (2–6)	2.5 (2.0–3.5)	6.5 (6.0–6.5)	<0.001 ^b	2.5 (1.4–4.0)	6.5 (6.0–6.5)	<0.001 ^b
Receiving disease-modifying treatment, %	69.4	81.8	50.0	0.01 ^b	76.7	41.7	0.008 ^b
RRMS, %	56.5	78.2	7.1	<0.001 ^b	71.0	12.5	<0.001 ^b
Lesion count (SD)	2.2 (1.5)	1.1 (0.9)	1.4 (0.6)	0.18	3.5 (0.7)	3.8 (0.9)	0.20
Spinal cord cross-sectional area, mm ² (SD)	76.9 (9.3)	80.1 (8.5)	67.4 (9.4)	<0.001 ^b	78.2 (8.0)	73.5 (7.7)	0.03 ^b
FA (SD)	0.61 (0.06)	0.61 (0.06)	0.57 (0.07)	0.03 ^b	0.63 (0.06)	0.59 (0.06)	0.02 ^b
MD, $\mu\text{m}^2/\text{ms}$, (SD)	1.27 (0.16)	1.25 (0.15)	1.41 (0.23)	0.003 ^b	1.22 (0.12)	1.31 (0.17)	0.02 ^b
$\lambda_{\perp}$, $\mu\text{m}^2/\text{ms}$, (SD)	0.76 (0.16)	0.74 (0.14)	0.90 (0.23)	0.003 ^b	0.70 (0.13)	0.81 (0.16)	0.01 ^b
$\lambda_{\parallel}$, $\mu\text{m}^2/\text{ms}$, (SD)	2.22 (0.21)	2.19 (0.19)	2.34 (0.26)	0.02 ^b	2.19 (0.21)	2.24 (0.21)	0.35
MTR (SD)	0.30 (0.04)	0.31 (0.04)	0.27 (0.05)	0.003 ^b	0.30 (0.03)	0.28 (0.06)	0.17

Abbreviations: EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; IQR = interquartile range; $\lambda_{\parallel}$ = parallel diffusivity; $\lambda_{\perp}$ = perpendicular diffusivity; MD = mean diffusivity; MTR = magnetization transfer ratio; NA = not applicable; RRMS = relapsing-remitting multiple sclerosis.

^aThe p values were derived from comparisons of low vs high EDSS score in subgroups stratified by lesion count.

^b p Value < 0.05.

table 1. DTI maps from 8 patients and the MTR map from 1 patient were not included because of inadequate image quality. Eighty-five percent of patients had at least 1 SC lesion, which is consistent with prior literature.^{4,17} Of all identified lesions, 93% occupied ≤ 1 vertebral level, whereas 1% occupied ≥ 3 vertebral levels.

In patients with low lesion counts, all MRI measures were more abnormal in those with high vs low disability. Similarly, in patients with high lesion counts, all MRI measures were more abnormal in those with high vs low disability, with the exception of $\lambda_{\parallel}$ and MTR (table 1, figures 2 and 3).

In age- and sex-adjusted comparisons of patients with low lesion counts, all MRI measures still retained a difference in comparisons of those with high vs low disability, with the exception of $\lambda_{\parallel}$. Similarly, in patients with high lesion counts, FA, MD, and $\lambda_{\perp}$ remained different in comparisons of patients with high vs low disability after adjusting for age and sex, whereas SC CSA, $\lambda_{\parallel}$, and MTR were not different (table 2).

Additional analyses adjusting for BPF and SC CSA, and using an EDSS cutoff score of 4 and the MSFC as a measure of disability, also demonstrated that MRI indices were able to discriminate between MS patients with high/low disability (tables e-1 to e-6 on the *Neurology*® Web site at www.neurology.org). Correlations between individual MRI indices are presented in table e-7. The clinical discriminatory capacity of combinations of MRI indices was assessed in a forward selection model (table e-8). In patients with a low lesion load, MTR and SC CSA were the only covariates retained in the model, whereas in patients with a high lesion load, only FA was retained, suggesting that MRI indices are highly correlated and that specific MRI indices have better discriminatory capacity than others in settings of different lesion loads.

DISCUSSION Weak correlations between SC lesion load, as estimated with conventional MRI, and disability status in patients with MS limit the utility of lesion-based measurements in the clinical setting, and on a larger scale in clinical trials. In this study, we found consistent differences in quantitative MRI indices between patients with substantially different levels of disability, despite having similar lesion counts, even after controlling for age and sex. These findings support the concept that microstructural changes undetectable by conventional lesion count contribute substantially to clinical disability in MS, and suggest that quantitative MRI measures have the ability to provide clinically relevant information beyond that which may be gleaned from measures of MRI lesion load alone.

Figure 2 Comparisons of MRI measures in low- vs high-disability subgroups in patients with low lesion load

Boxplots depict median, interquartile range, and upper and lower fences of each MRI index. EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; MD = mean diffusivity; MTR = magnetization transfer ratio.

Figure 3 Comparisons of MRI measures in low- vs high-disability subgroups in patients with high lesion load

Boxplots depict median, interquartile range, and upper and lower fences of each MRI index. EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; MD = mean diffusivity; MTR = magnetization transfer ratio.

Regardless of lesion load, FA, MD, and $\lambda_{\perp}$ were consistently able to discriminate MS patients with high and low levels of disability. FA was consistently lower, MD higher, and $\lambda_{\perp}$ higher in individuals with high disability levels, as compared with those with low disability levels. In practice, FA measures the proportion of water diffusion along rather than perpendicular to axonal fibers, $\lambda_{\parallel}$ represents diffusion along axonal fibers, $\lambda_{\perp}$ represents diffusion perpendicular to axonal fibers, MD is a measure of mean diffusion,⁷ and MTR is a measure sensitive to myelin content.⁶ These quantitative MRI indices provide complementary information regarding the structural integrity of SC tissue.

Our demonstration of robust differences in quantitative MRI indices of the SC in a large, diverse cohort of patients with high and low levels of MS disability, regardless of SC lesion count, expands on prior studies that have shown correlations between FA and $\lambda_{\perp}$ and disability in MS^{18,19} and attests to the additive clinical value of quantitative MRI indices over conventional MRI measures. Recent DTI studies of ex vivo human SCs have demonstrated that $\lambda_{\perp}$ is highly sensitive to tissue microstructural changes but not specific to particular pathologic processes,²⁰ findings that are consistent with those reported in animal studies of acute axonal transection.²¹ Similarly, in the optic nerve, changes in $\lambda_{\perp}$ have been linked to both demyelination and axonal loss, based on correlational analyses with visual evoked potentials and optical coherence tomography.²² Overall, the observed differences in MRI indices between disability subgroups in this study are likely to reflect a combination of pathologic processes, including demyelination, axonal loss, inflammation, and gliosis.

When comparing differences in quantitative MRI indices between patients with high and low levels of disability (adjusted for age and sex), all MRI measures with the exception of $\lambda_{\parallel}$ were different in patients with low lesion counts, whereas only FA, MD, and $\lambda_{\perp}$ were different in patients with high lesion counts. This finding is of interest because it suggests that in settings of low lesion count, greater perturbations in microstructural changes, likely corresponding to a greater spectrum of pathologic processes, contribute to increased disability. However, in individuals with high lesion counts, the panel of quantitative MRI indices that showed a clear difference between disability levels was more restricted, with MTR not demonstrating a difference. Because MTR is a measure sensitive to myelin content,⁶ this finding suggests that demyelination may be less relevant in associations with clinical disability in patients with high SC lesion counts, with axonal degeneration likely having a dominant role, whereas demyelination and axonal pathology both seem to have a substantial role in

Table 2 Age- and sex-adjusted differences in MRI measures and effect size in patient subgroups, stratified by lesion load^a

	Low lesion			High lesion		
	Adjusted difference between low/high EDSS subgroups	Effect size	p Value	Adjusted difference between low/high EDSS subgroups	Effect size	p Value
Spinal cord cross-sectional area, mm ²	12.11	0.20	<0.001 ^b	3.18	0.032	0.18
FA	0.046	0.073	0.03 ^b	0.046	0.10	0.02 ^b
MD, $\mu\text{m}^2/\text{ms}$	-0.15	0.11	0.008 ^b	-0.10	0.084	0.04 ^b
$\lambda_{\perp}$, $\mu\text{m}^2/\text{ms}$	-0.16	0.12	0.005 ^b	-0.11	0.11	0.02 ^b
$\lambda_{\parallel}$, $\mu\text{m}^2/\text{ms}$	-0.13	0.053	0.07	-0.055	0.013	0.41
MTR	0.033	0.078	0.02 ^b	0.011	0.012	0.43

Abbreviations: EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; $\lambda_{\parallel}$ = parallel diffusivity; $\lambda_{\perp}$ = perpendicular diffusivity; MD = mean diffusivity; MTR = magnetization transfer ratio.

^a The p values were derived from comparisons of low vs high EDSS score in subgroups stratified by lesion count; adjusted differences were calculated using the following formula: (MRI measure from low-disability subgroup) – (MRI measure from high-disability subgroup); effect sizes estimate the proportion of variance in MRI indices attributable to disability categorization.

^b p Value <0.05.

patients with low lesion counts. Alternatively, this finding may suggest that in patients with high lesion loads, the degree of demyelination is so extensive that it can no longer distinguish between different disability levels, or that additional pathologic processes contribute to alterations in MTR. Although the cross-sectional nature of this study precludes definitive interpretation, our observations suggest that different pathologic processes underlying clinical disability may be at play depending on the magnitude of SC lesion load. If substantiated in longitudinal studies, this finding may have clinical implications for treatment selection and disease monitoring in patients with MS who have higher lesion loads in the SC.

Interestingly, SC CSA, a measure of general tissue loss, was different between the high- and low-disability subgroups in patients with low lesion loads, perhaps consistent with early myelin and axonal loss in the more disabled patients. Importantly, some low lesion counts may have occurred in part because of dissolution of abnormal-appearing tissue. However, in individuals with high lesion loads, SC CSA was unable to differentiate between high and low disability levels after adjusting for age and sex. These findings suggest that in patients with high lesion load, it is not the magnitude of tissue loss, but the structural integrity of remaining tissue that is related to disability, highlighting the utility of quantitative MRI indices in these settings.

Our findings, which demonstrate the ability of quantitative MRI indices to differentiate between modest sample sizes of patients with MS who had similar lesion counts, but differing disability levels, are encouraging. If confirmed prospectively, these techniques may have clinical utility in a variety of realms,

including monitoring therapeutic efficacy, predicting disability progression, and as a surrogate outcome measure in clinical trials. The need for predictive measures of disease progression is apparent as the clinical practice of MS continues to evolve and the choice of treatments with vastly different risk-benefit profiles continues to expand.²³

A few prior studies have assessed the clinical predictive value of quantitative MRI indices. A recent study found that baseline cervical spine $\lambda_{\perp}$ was predictive of recovery from an SC relapse in patients with MS.²⁴ Another study found that baseline FA was predictive of clinical progression but did not find a relationship between longitudinal change in MRI indices and disability progression.¹⁸ Finally, the ability of a “snapshot” cervical SC MTR measure to predict short-term relapse rate has also been reported.²⁵ In our study, a variety of quantitative MRI measures were able to detect differences in disability on a cross-sectional level, suggesting that these measures are sensitive to clinically relevant microstructural changes, and support the potential use of a baseline MRI scan to provide valuable information on both short-term and long-term disability progression. A longitudinal extension of this study will be of substantial interest in this regard.

This study has a number of limitations. First, the ability to distinguish between individuals with high/low disability in our study is limited by the constraints of the EDSS, and is thus heavily weighted toward ambulatory disability.²⁶ In the SC, however, the motor system is a highly relevant functional system, thus the use of a scale weighted toward ambulation may be appropriate in this setting. Second, to

dichotomize individuals into high/low disability levels, and high/low lesion counts, EDSS and lesion-count cutoffs had to be chosen. Although the designated cutoff points were carefully chosen based on a clear rationale, they may still be regarded as arbitrary given the lack of prior studies determining the most appropriate cutoff points for these measures. Third, the use of ROIs encompassing the SC CSA resulted in the inclusion of both white and gray matter, likely resulting in a dilution of the observed clinicroadiologic relationships. In addition, the inclusion of lesional and nonlesional tissue might have contributed to diminished specificity of quantitative MRI indices in identifying microstructural changes; however, it is also possible that important information can be derived from normal-appearing SC tissue. Fourth, there was a discrepancy between SC segments included for assessment of MRI indices vs lesion counting. The segment of SC analyzed for MRI indices was limited to C3-4 because image quality was consistently highest between these segments likely because of the least amount of distortion from motion artifact. For lesion counting, we included a larger segment of the cervical SC to promote the most accurate characterization of patients into high/low lesion count. Notwithstanding these limitations, we were still able to demonstrate consistent and robust differences between differing levels of disability with our methodology.

Finally, our assessment of conventional lesion load was limited to lesion counting, which does not take into account the volume of lesioned tissue. However, lesion counting still represents a reasonable method for quantifying lesion load, because individuals with more lesions tend to have larger volumes of lesioned tissue, particularly in our study population, in which 93% of lesions occupied ≤ 1 vertebral level. Accordingly, it is unlikely that our interpretations would have changed substantially with a more quantitative approach of lesion quantification. Furthermore, in clinical practice, lesion counting is routinely used, making this measurement of practical use.

Our findings illustrate that microstructural changes undetectable by conventional MRI contribute to observed differences in clinical disability in patients with MS. These findings promote not only the utility of quantitative MRI indices in being able to provide important insight into the microstructural changes contributing to disability, but also suggest that with further development, these measures could be of clinical utility in both the management of individual patients and as a surrogate outcome measure in clinical trials. Further studies are needed to assess the relationships of lesion counts, quantitative MRI indices, and clinical disability progression longitudinally, and to evaluate the relationships of these indices with more detailed characterizations of clinical disability in MS.

AUTHOR CONTRIBUTIONS

Conceptualization of the study: Jiwon Oh, Peter A. Calabresi, Daniel S. Reich. Pulse sequence design/implementation and quality control: Seth A. Smith, Craig Jones, Peter C.M. van Zijl, Daniel S. Reich. Analysis/interpretation of the data: Jiwon Oh, Min Chen, Shiv Saidha, Daniel S. Reich, Peter A. Calabresi.

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