Published in final edited form as:

Mult Scler. 2013 April ; 19(4): 427–435. doi:10.1177/1352458512456614.

Multiparametric MRI correlates of sensorimotor function in the spinal cord in multiple sclerosis

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Abstract

Background—Spinal cord (SC) pathology is a major contributor to clinical disability in multiple sclerosis (MS). Conventional magnetic resonance imaging (MRI), specifically SC-MRI lesion load measures that include lesion count and volume, demonstrate only a modest relationship with the clinical status of MS patients. Although SC cross-sectional area (CSA) correlates better with clinical dysfunction than MRI lesion count, SC atrophy likely signifies irreversible tissue loss. Using quantitative MRI indices sensitive to early and late microstructural changes in the spinal cord, we searched for the presence of better correlations between MRI measures and clinical status in MS.

Objectives—We investigated whether diffusion-tensor imaging indices and the magnetization-transfer ratio (MTR) were better associated with the clinical status of MS patients than conventional SC-MRI measures.

Methods—A total of 129 MS patients underwent 3-tesla cervical SC-MRI and quantitative sensorimotor function testing, using the Vibratron-II and dynamometer. Regions-of-interest circumscribed the SC on axial slices between C3-C4. We calculated SC-CSA, fractional anisotropy (FA), mean diffusivity (MD), perpendicular diffusivity ($\lambda_{\perp}$), parallel diffusivity ($\lambda_{\parallel}$) and MTR. We used multivariable linear regression to determine if there were any associations between MRI indices and clinical measures of dysfunction.

Results—All MRI indices were significantly different in subjects with MS versus healthy controls, and between the progressive versus relapsing MS subtypes, with the exception of $\lambda_{\parallel}$. In multivariable regression models that were adjusted for age, sex, brain parenchymal fraction, and

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Conflict of interest

The authors declare that there are no conflicts of interest.

SC-CSA, the MRI indices independently explained variability in hip flexion strength (p -values: MD, $\lambda_{\perp}$, $\lambda_{\parallel} < 0.001$; FA = 0.07), vibration sensation threshold (p -values: FA = 0.04; MTR = 0.05; $\lambda_{\perp} = 0.06$), and Expanded Disability Status Scale scores (p -values: FA = 0.003; MD = 0.03; $\lambda_{\perp} = 0.005$; MTR = 0.02).

Conclusions—In a large, heterogeneous MS sample, quantitative SC-MRI indices demonstrated independent associations with system-specific and global clinical dysfunction. Our findings suggest that the indices studied may provide important information about microstructural SC changes and the substrates of limb disability in MS. The identified structure-function relationships underpin the potential utility of these measures in assessments of therapeutic efficacy.

Keywords

MRI; multiple sclerosis; spinal cord; cross-sectional area; diffusion-tensor imaging; magnetization-transfer ratio; fractional anisotropy; diffusivity; clinical dysfunction

Introduction

The spinal cord (SC) is a common site for lesions in multiple sclerosis (MS), with SC pathology likely contributing substantially to clinical disability in patients. Pathological and imaging series demonstrate SC lesions in over 80% of MS patients, even early in the disease course.^{1–3} Anatomically, the SC is a compact structure that is organized into discrete functional columns. Taken together, these factors make the SC a useful area to study structure-function relationships in MS.

The SC has been difficult to evaluate by magnetic resonance imaging (MRI) due to considerable technical limitations. The small size of the SC makes it susceptible to motion artifact from physiologic cardiac and respiratory cycles, as well as image distortions resulting from field inhomogeneities from the surrounding bone and cartilage.^{4,5} In addition, conventional MRI suffers from the “clinico-radiological paradox,” which refers to the inability of conventional MRI measures to establish strong correlations with clinical dysfunction. There are a variety of reasons for the clinico-radiological paradox, including insufficient sensitivity and specificity of conventional MRI techniques toward underlying tissue histopathology, as well as difficulties in accurately quantifying neurological dysfunction.⁶

Because diffusion-tensor imaging (DTI) and magnetization-transfer imaging (MTI) are MRI techniques that are sensitive to microstructural tissue properties, we applied them to assess the SC in MS patients. DTI uses information contained in the orientation and magnitude of water diffusion in tissue, which provides insight into the microstructural integrity of underlying tissue. The MTI technique relies on the communication between rotationally-restricted protons within macromolecules, which in white matter are typically associated with myelin, and surrounding, free water protons. The degree of magnetization transfer (MT), measured here as the magnetization transfer ratio (MTR), is sensitive to myelin content.⁷ To accurately quantify patients’ neurological dysfunction for this study, we obtained quantitative measures of sensory and motor dysfunction using the Vibratron II and dynamometer devices, both validated for use in MS patients.⁸

We hypothesized that using DTI and MTI in conjunction with quantitative clinical measures would probe the structure-function relationships of SC pathology in MS more accurately than conventional MRI. By using complementary MRI techniques, this study expands on previous work where we demonstrated a relationship between MTR abnormalities and sensorimotor impairment,⁹ which will enable greater insight into the microstructural basis of clinical dysfunction in MS.

Methods

Study participants

This study was approved by the institutional review boards of Johns Hopkins University and the Kennedy Krieger Institute. All participants provided written informed consent.

The study population consisted of individuals with relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and healthy controls (HCs) (Table 1). To perform our comparative analyses between those with high versus low inflammatory MS, patients with RRMS were subcategorized as the “relapsing” subgroup, while those with SPMS and PPMS were the “progressive” subgroup. MS patients were recruited from the Johns Hopkins MS Clinic by convenience sampling. Their MS diagnoses were confirmed by the treating neurologist, according to the 2010 revised McDonald criteria.¹⁰ Their Expanded Disability Status Scale (EDSS) scores were determined by a certified neurostatus examiner within 30 days of MRI. Hip strength and vibration sensation thresholds were measured within 2 weeks of MRI. Patients’ medical records were reviewed to determine their disease duration and treatment status. HCs were recruited from the Johns Hopkins University community.

Magnetic resonance imaging

Cervical SC MRI—Cervical SC MRIs were performed on all participants using a 3-tesla 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, 3D gradient-echo sequence with a magnetization-transfer prepulse and a multi-shot echo-planar readout (echo planar imaging (EPI) factor = 3) with a parallel imaging factor of 2 (repetition time (TR)/echo time (TE)/α = 121ms/12.5ms/9°). The scan yielded 30 contiguous 3 mm axial slices of SC between the C2–C6 vertebrae, with a nominal in-plane resolution of 0.6 mm × 0.6 mm². To calculate the MTR, scans were acquired with (MT_{on}) and without (MT_{off}) a 1.5 kHz off-resonance sinc-gauss-shaped radiofrequency saturation pulse. The MT_{on} was registered to the MT_{off} using a 6-degree-of-freedom, rigid-body procedure implemented in FLIRT (Oxford Centre for Functional MRI of the Brain’s Linear Imaging Registration Tool, Oxford, UK (FMRIB)). MTR was calculated according to the formula in equation (1).

$$(MT_{off} - MT_{on})/MT_{off} \quad (1)$$

DTI data were obtained on all participants by using a multi-slice spin-echo sequence with a single-shot echo-planar readout and a parallel imaging factor of 2 (TR/TE = 4727ms/63ms). We obtained axial fat-suppressed diffusion-weighted images in 16 non-coplanar gradient directions with $b = 500 \text{ s/mm}^2$ and we obtained one minimally diffusion-weighted acquisition ($b_0 \sim 33 \text{ s/mm}^2$). Slice thickness was 3 mm and the nominal in-plane resolution $1.5 \times 1.5 \text{ mm}^2$.

Additional image sequences obtained included a sagittal, multi-slice turbo spin echo (TSE; factor 20, parallel imaging factor 2), short-tau inversion recovery (STIR) with field of vision (FOV) = 250mm, acquired resolution of $1 \times 1 \times 2 \text{ mm}^3$ (anterior-to-posterior (AP), foot-to-head (FH), right-to-left (RL)) with TR/TE/TI = 4227ms/68ms/200ms. Four averages gave a total scan time of 3 minutes.

Each diffusion-weighted image was registered to the initial $b = 0$ volume, using a 6-degree-of-freedom, rigid-body registration, implemented in FLIRT using the Java Image Science Toolkit (JIST Baltimore, MD/Jerry Prince laboratory at Johns Hopkins University, USA.),¹¹ which was also used to generate the diffusion tensor and maps of fractional anisotropy (FA), mean diffusivity (MD), perpendicular diffusivity ($\lambda_{\perp}$), and parallel diffusivity ($\lambda_{\parallel}$) seen in Figure 1. The $b = 0$ image was deformably registered to the MT and the information applied to the diffusion weighted (DW) images.^{12,13} All DTI indices were calculated from the eigenvalues of the diffusion tensor.⁴

An automated, reproducible segmentation protocol was applied to the MT_{off} images, to delineate regions-of-interest (ROIs) encompassing the axial SC cross-sections across segments C3–C4, which were transferred to the DTI and MTR maps¹⁴ in Figure 2. SC tract-specific ROIs were not utilized, due to a high degree of partial volume averaging on the DTI maps, which made it difficult to accurately localize anatomical tracts. Segments between C3–C4 were chosen for analysis, as this region of the cervical SC had minimal image quality degradation due to motion artifacts. The average values (weighted by ROI volume) of SC cross-sectional area (CSA), FA, MD, $\lambda_{\perp}$, $\lambda_{\parallel}$, and MTR were calculated within the ROIs on each MRI index map, across all axial slices from C3–C4. Segments from C3–C4 included an average of 11 slices per case.

The cervical SC lesions were identified and counted on the axial MT and sagittal STIR sequences by an experienced observer.

Brain MRI—Full details of our brain MRI acquisition process were described previously.^{15,16} The spin echo-echo planar DTI sequence was acquired on a 3-tesla Philips scanner with 2.2 mm isotropic voxels and the following scan parameters: TE = 69 ms; TR = shortest (automatically calculated); 60 slices; SENSE factor = 2.5; 32 diffusion directions (Philips “overplus high” scheme, Philips Medical Systems, Best, The Netherlands); $b_0 \sim 33 \text{ s/mm}^2$; $b = 700 \text{ s/mm}^2$; repetitions = 2.

DTI images were used to calculate the supratentorial brain and cerebrospinal fluid (CSF) volumes, as described previously.¹⁶ DTI-based brain volume segmentation was used, as this method has lower variability than alternate methods using SIENAX or lesion-TOADS

software, despite susceptibility-induced data distortions.¹⁷ Brain parenchymal fraction (BPF) was calculated using the formula in equation (2).

$$\text{BPF} = \text{brain volume} / [\text{brain volume} + \text{CSF volume}] \quad (2)$$

Quantitative clinical measures

Vibration sensation thresholds for the right and left great toes were quantified using the Vibratron II (Physitemp, Huron, NJ, USA). For strength measurements, we averaged two maximal hip flexion efforts at each hip, using a Microfet2 handheld dynamometer (Hoggan Health Industries, West Jordan, UT). Both devices are described in detail elsewhere and were previously validated for use in MS patients, to reliably detect and quantify sensorimotor dysfunction.⁸ MS patients that were scanned within 3 months after a clinical relapse were excluded.

Statistical analysis

Statistical calculations were performed using STATA Version 11 (StataCorp, College Station, TX, USA).

Student's *t*-tests were used for group comparisons of the SC-MRI indices. Due to the exploratory nature of this study, which aims to describe relationships between MRI indices and clinical measures, adjustments for multiple comparisons were not performed.¹⁸

Multivariable linear regression models were used to assess the relationship between clinical measures and MRI indices, with the clinical measure set as the dependent variable, and the MRI index as the independent variable of interest. Potentially confounding covariates of age, gender, BPF, and SC-CSA were included in each model. In the models using quantitative clinical measurements, bilateral measurements were included for each individual. Therefore, robust standard error estimations were utilized in the regression models, to account for within-subject correlations.^{19,20} Stepwise regression models including all of the quantitative MRI measures as covariates were assessed, but we found substantial instability in these models, likely due to the large number of covariates; thus, we adopted a hypothesis-driven approach that included one MRI index of interest within separate regression models. Adjusted variable plots were utilized to visually depict the adjusted relationship between a quantitative clinical measure and an individual MRI index (adjusted for all other variables in the regression model). We used Spearman's rank correlations coefficient to assess correlations between various MRI indices. Statistical significance was defined as $p < 0.05$.

Results

This study included 74 RRMS patients, 36 SPMS patients, 19 PPMS patients and 14 HCs. The MS patients were 65% female and had a mean age of 45 years, with an average MS disease duration of 11 years. A total of 69% of the MS patients were on disease-modifying therapies: interferon- β , 40%; glatiramer acetate, 30%; natalizumab, 25%; and other medications, 5%. In comparison to RRMS, the progressive patients were significantly older,

had longer disease durations, and had more severe clinical dysfunction (Table 1). The mean vibration sensation threshold and hip flexion strength measures in MS patients were less than the 1st percentile, as compared to a normal reference population.⁸ Table 2 contains summary statistics for all of the study participants' MRI measures, including MRI indices (FA, MD, $\lambda_{\parallel}$, $\lambda_{\perp}$, MTR), SC lesion count, SC-CSA and BPF. DTI maps from nine patients and the MTR map from one patient were not included in our analyses, due to an inadequate image quality related to artifacts.

All MRI measures assessed were significantly different in the MS patients versus HCs, with the exception of both FA and $\lambda_{\parallel}$, although FA did trend towards significance ($p = 0.07$). When comparing the MS subgroups, all MRI indices were significantly different between the progressive and relapsing subtypes, with the exception of $\lambda_{\parallel}$ ($p = 0.16$), as seen in Table 2.

Multivariable linear regression analyses adjusted for age, sex, SC-CSA, and BPF were performed to assess for independent relationships between functional system-specific measures of clinical disability (such as hip flexion strength and vibration sensation threshold) and global disability (EDSS), with the MRI indices. A separate model was constructed for each individual MRI index.

In the hip flexion strength model: MD, $\lambda_{\perp}$, and $\lambda_{\parallel}$ all demonstrated significant independent associations ($p < 0.001$) with motor dysfunction, while FA showed a trend towards an independent association ($p = 0.07$). In the vibration sensation threshold model, FA and MTR showed significant independent associations ($p = 0.04$ and $p = 0.05$, respectively), while $\lambda_{\perp}$ showed a trend towards an independent association ($p = 0.06$) (Table 3, Figure 3). In the EDSS model, all MRI indices tested showed significant independent associations with EDSS ($p = 0.003$, $p = 0.03$, $p = 0.005$, $p = 0.02$ for FA, MD, $\lambda_{\perp}$ and MTR, respectively), with the exception of $\lambda_{\parallel}$ ($p = 0.5$) (Table 3).

The imaging models that we constructed were able to explain up to 38% of the variability in hip flexion strength, 20% of the variability in vibration sensation threshold, and 41% of the variability in EDSS scores (Supplemental Table 4). The percentage by which individual MRI indices that retained significant independent associations with clinical measures added to explaining clinical variability ranged from 6.1%–8.0% in the model of hip flexion strength, 2.0%–2.6% in the model of vibration sensation threshold, and 2.5%–4.8% in the EDSS model. Interestingly, although BPF was included as a covariate in each model to account for the effects of distant brain pathology, this measure did not contribute towards explaining clinical variability in hip flexion strength or vibration sensation threshold in any of the models (Supplemental Table 5). On the other hand, SC-CSA retained significant independent relationships with clinical variables in all of the multivariable models ($p < 0.01$). SC lesion count failed to significantly explain variability in either the hip flexion strength or vibration sensation threshold models (Table 3). We present adjusted variable plots in Figure 3 to visually depict the magnitude of the adjusted relationship between each quantitative clinical measure and each MRI index.

Finally, we assessed our patient data for correlations between the MRI measures of atrophy in the brain and SC. We found that in the progressive patients, there was no correlation between SC-CSA and BPF ($\rho = 0.017$, $p = 0.90$); but in the relapsing patients, there was a correlation found between SC-CSA and BPF ($\rho = 0.24$, $p = 0.04$).

Discussion

Improved correlations between clinical dysfunction and imaging abnormalities in patients with MS are a necessary prerequisite for MRI measures to be useful in understanding the pathological substrate of clinical dysfunction. In this study, we investigated the relationships between quantitative MRI indices, conventional MRI measures, two functional system-specific measures of clinical dysfunction, as well as global disability. In a cross-sectional sample of MS patients that would be considered large relative to other similar studies, and that had adequate representation of the different MS disease subtypes, we demonstrate that quantitative MRI indices relating to the SC maintain significant independent relationships with system-specific measures of clinical dysfunction, as well as global disability, and that combinations of these MRI indices provide important *in vivo* information about the underlying tissue microstructure of the SC in MS patients.

Both motor and sensory systems are particularly relevant functional systems in the SC, because a large portion of the SC is comprised of ascending and descending white matter tracts mediating these functions. In a previous study, we showed significant relationships occur between SC CSF-normalized magnetization-transfer (MTCSF) and quantitative clinical measures.⁹ Thus far, the relationships between DTI indices of the SC and measures of clinical dysfunction have only been explored in a few studies. Univariate correlations between FA, $\lambda_{\perp}$ and clinical dysfunction have been previously reported.^{21,22} In multivariable models, SC FA has been shown to independently influence EDSS scores,²³ while $\lambda_{\perp}$ has been found to independently predict recovery from SC relapses.²⁴ Here, we expand upon previous findings by demonstrating that there are significant relationships between a spectrum of MRI indices and both system-specific and global measures of disability. In our study, the constructed models were able to explain up to 38% of the variance in hip flexion strength, 20% of the variance in vibration sensation threshold, and 41% of the variance in EDSS scores of MS patients, with the contribution of individual MRI indices ranging from 2.0%–8.0% of the clinical variance. For each model studied, we found a panel of MRI indices that maintained independent relationships with hip flexion strength, vibration sensation threshold, and EDSS; even after adjusting for age, sex, BPF, and SC-CSA, which suggests that these MRI indices are capturing tissue microstructural abnormalities that are not reflected by the other covariates in the models.

Moreover, our results expand on previous observations that measures of SC atrophy relate to clinical disability, by showing that SC-CSA not only associates with global clinical dysfunction, but also with motor and sensory system-specific measures of disability.^{25,26}

Taken together, our findings strongly support the utility of quantitative SC-MRI indices in the assessment of clinically-relevant microstructural SC changes, and highlight the potential

advantage of use of these indices over conventional measures of SC atrophy, which reflect tissue loss that is probably irreversible.

Our comparisons of SC-MRI measures between MS and HCs, and between progressive and relapsing MS subtypes showed significant differences in all MRI indices, except $\lambda_{\parallel}$. This is consistent with previous studies that found differences in various DTI indices and MTR in MS patients versus HCs,^{21,23,27,28} and in MTR and FA in progressive versus relapsing patients.^{23,29} We expand on these findings by demonstrating that there are significant differences in FA, MD, $\lambda_{\perp}$, and MTR in progressive versus relapsing patients. These observations suggest that microstructural tissue damage in the SC may be an important factor in the evolution of disease from the relapsing to progressive phases, meriting further longitudinal investigations.²⁹

Although reductions in $\lambda_{\parallel}$ have been shown to be sensitive to axonal damage in models of acute axonal transection,^{30,31} DTI studies in *ex vivo* human SCs have consistently shown increased $\lambda_{\parallel}$.^{32,33} This may be due to a variety of factors, including partial volume effects and the dynamic nature of $\lambda_{\parallel}$ in chronic MS. On the other hand, $\lambda_{\perp}$ appears to be highly sensitive to microstructural changes in SC tissue, but not specific to particular pathological processes in *ex vivo* human SCs,^{32,33} a finding that is consistent with models of acute axonal transection.^{30,31} In practice, $\lambda_{\perp}$ and $\lambda_{\parallel}$ represent water diffusion perpendicular to and along intact axonal fibers, respectively, and FA measures the extent to which water diffuses along those fibers rather than perpendicular to them. MD is an overall measure of water diffusion,³⁴ whereas MTR is a measure sensitive to myelin content⁷ and axonal density,³⁵ as well as overall tissue water content.³⁶ Thus, these quantitative MRI indices have the ability to provide complementary information on the structural integrity of SC tissue in MS patients.

In our study, the direction of the relationship of each MRI index (with the exception of $\lambda_{\parallel}$) with clinical dysfunction corresponded to what was expected from models of tissue damage such as that found in MS, with positive relationships found between FA and MTR and better clinical functionality, and negative relationships between better clinical functionality and MD and $\lambda_{\perp}$ (Table 3). The pathological features these MRI indices reflect are likely to be combinations of processes, including demyelination, axonal loss, inflammation and gliosis. We believe that a longitudinal assessment of the direction and magnitude of change in these measures, and their relationship with clinical progression of MS will be of substantial interest.

In this heterogeneous MS sample, $\lambda_{\perp}$ appeared to most reliably distinguish MS patients from HCs and contributed toward explaining clinical variability in all three models that we examined. This observation is consistent with a recent study that found baseline $\lambda_{\perp}$ of utility in predicting recovery after SC relapses, and that demonstrated dynamic changes in $\lambda_{\perp}$ over time.²⁴ Our findings support the recent proposal that $\lambda_{\perp}$ is a useful marker of overall tissue integrity,³² thus a longitudinal extension of this current study will help determine the clinical utility of $\lambda_{\perp}$ measurements in predicting disability progression.

Poor correlations between brain and SC measures of atrophy were previously described,^{21,25} and we similarly observed this for progressive MS, with no demonstrable correlation between BPF and SC-CSA. Furthermore, BPF did not significantly contribute toward explaining clinical variability in either of the models of functional system-specific disability (vibration sensation threshold and hip flexion strength) that are considered of anatomic relevance in the SC. In contrast, BPF did contribute, along with most of the MRI indices, to explaining variability in EDSS, which is in keeping with the existing literature regarding relationships between brain atrophy and EDSS.³⁷ Taken together, we can postulate that neurodegenerative pathological processes in the brain and SC may occur semi-independently, and that this divergence may be more relevant in patients with progressive MS disease. Our findings underscore the need to further characterize SC-specific pathological processes, particularly within the progressive subtypes, as SC pathology is a well-described contributor to disability in this subset of patients.^{3,29} In other words, further study of the SC may provide a unique platform for improving our understanding of the neurodegenerative mechanisms underlying progressive disability in MS, which are relevant to all MS subtypes, but particularly the progressive forms of the disease.

This study has a number of limitations. First, the small number of HCs likely limited our power to compare MRI indices in the MS patients versus HCs. Despite this, we showed there were significant differences in MRI indices between MS patients and HCs, which suggests that given a larger HC sample, this difference might be more pronounced. Secondly, we did not have clinical measures for our HCs, preventing comparisons of clinical-radiological correlations in MS patients versus HCs; however, given the apparent baseline differences in MRI indices between HCs and MS patients, in addition to the fact that HCs are unlikely to have clinical impairments, it is improbable that obtaining this information would have changed our conclusions significantly. Third, because we only evaluated a discrete segment (C3–4) of the cervical SC, any other upstream or downstream pathological changes that could contribute to clinical dysfunction were not taken into account. Furthermore, the use of the ROIs encompassing the SC-CSA, rather than specific columns, likely resulted in a dilution of any observed structure-function relationships. Notwithstanding these limitations, we were still able to demonstrate consistent and robust structure-function relationships with our employed methodology.

In conclusion, the current study demonstrates significant independent relationships between quantitative SC-MRI indices, particularly $\lambda_{\perp}$, and various measures of clinical dysfunction (both system-specific and of global disability), after adjusting for confounding variables, in a large and diverse sample of MS patients. Our findings highlight the utility of quantitative SC-MRI indices in improving our understanding of the structure-function relationships in MS, which is an important stepping-stone towards utilizing these measures in monitoring therapeutic efficacy and in developing targeted treatments. A longitudinal extension of this dataset will examine the evolution of microstructural changes in the SC, and will ascertain the degree to which these changes might affect the clinical status of MS patients over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank our MS patients for devoting their valuable time to participate in this study. We also thank Terri Brawner, Kathleen Kahl, Ivana Kusevic, Joe Gillen, and Joseph Wang for their assistance with this project.

Funding statement

This work was supported by the Multiple Sclerosis Society of Canada Postdoctoral Fellowship (to JO); National Institutes of Health/National Institute of Child Health and Development (K01 grant number HD049476, to KZ); a Dana Foundation grant (to KZ); National Multiple Sclerosis Society (grant number TR 3760-A-3, to PAC); Braxton Debbie Angela Dillon and Skip (DADS) Donor Advisor Fund (to PAC); EMD-Serono Grant (to PAC); National Institutes of Health/National Institute of Biomedical Imaging and Bioengineering (grant number EB009120, to SAS); National Institutes of Health/National Center for Research Resources/National Institute of Biomedical Imaging and Bioengineering (grant number P41EB015909, to PCMV); and the Intramural Research Program of the National Institute of Neurological Disorders and Stroke (to DSR).

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Figure 1.
Color-coded DTI map derived from fractional anisotropy and the principal eigenvector. Blue represents tracts running in the rostrocaudal axis; green, anteroposterior; and red, mediolateral. The oblique angles are represented by a mixture of colors.
DTI: Diffusion-tensor imaging

Figure 2.

(a) Axial section of cervical spinal cord on high-resolution MT sequence (b) with the superimposed region-of-interest encompassing the spinal cord cross-sectional area.

MT: magnetization-transfer.

Figure 3.

Graphical representation of adjusted relationships between MRI indices and quantitative clinical measures in separate multivariable models.

MRI: Magnetic resonance imaging.

Table 1

Demographics and clinical characteristics.

	All MS	RRMS	Progressive (SPMS and PPMS)	HCs
Subjects, <i>n</i>	129	74	55	14
Age at MRI scan, years (SD)	44.7 (11.4)	39.3 (10.6)	52.0 (7.8) ^{*‡}	40.0 (9.3)
% Female	65	70	58	71
Disease duration, years (SD)	10.8 (9.2)	7.1 (5.6)	15.6 (10.7) [‡]	n/a
Median baseline EDSS (IQR)	3.5 (2–6)	2.5 (1.5–3.5)	6 (4–6.5) [‡]	n/a
% on disease-modifying treatment	69	88	44 [‡]	n/a
Vibration sensation threshold, microns (SD)	15.1 (22.4)	8.1 (13.5)	24.8 (28.1) [‡]	n/a
Hip flexion strength, pounds (SD)	39.4 (18.5)	46.4 (15.6)	29.3 (18.0) [‡]	n/a

EDSS: Expanded Disability Status Scale; HCs: healthy controls; IQR: interquartile range; MRI: magnetic resonance imaging; n/a: not applicable; RRMS: relapsing–remitting multiple sclerosis; SD: standard deviation; SPMS: secondary-progressive multiple sclerosis.

Disease duration was defined as the time since first symptoms attributable to MS.

* $p < 0.05$ for comparison against HCs

[‡] $p < 0.05$ for comparison against RRMS

Table 2

Comparison of average MRI measures between subtypes of MS patients and control subjects.

	All MS patients	RRMS	Progressive patients (SPMS and PPMS)	HCs	All MS patients vs. HCs		Progressive vs. RRMS	
					Mean difference [MS vs. HCs]	p-value	Mean difference [RRMS vs. Progressive]	p-value
Subjects	129	74	55	14	n/a	n/a	n/a	n/a
Cord cross-sectional area, mm ² (SD)	76.9 (9.2)	79.6 (8.4)	73.3 (8.9)	83.1 (9.2)	-6.19	0.02	6.32	<0.001
Lesion count, number (SD)	2.2 (1.5)	2.0 (1.5)	2.5 (1.3)	0	2.18	<0.001	-0.55	0.03
Brain parenchymal fraction (SD)	0.86 (0.05)	0.88 (0.05)	0.83 (0.05)	0.90 (0.04)	-0.038	0.01	0.046	<0.001
FA, (SD)	0.61 (0.06)	0.62 (0.06)	0.59 (0.07)	0.64 (0.04)	-0.032	0.07	0.024	0.03
MD [$\mu\text{m}^2/\text{ms}$], (SD)	1.28 (0.17)	1.25 (0.15)	1.32 (0.19)	1.20 (0.10)	0.076	0.02	-0.067	0.03
$\lambda_{\perp}$ [$\mu\text{m}^2/\text{ms}$], (SD)	0.77 (0.17)	0.74 (0.15)	0.81 (0.18)	0.67 (0.09)	0.097	0.03	-0.070	0.02
$\lambda_{\parallel}$ [$\mu\text{m}^2/\text{ms}$], (SD)	2.22 (0.21)	2.20 (0.20)	2.26 (0.23)	2.16 (0.16)	0.065	0.27	-0.055	0.16
MTR, (SD)	0.30 (0.05)	0.31 (0.04)	0.28 (0.05)	0.31 (0.02)	-0.014	0.04	0.028	<0.001

FA: fractional anisotropy; HCs: healthy controls; MD: mean diffusivity; MTR: magnetization transfer ratio; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary–progressive multiple sclerosis; $\lambda_{\perp}$: perpendicular diffusivity; $\lambda_{\parallel}$: parallel diffusivity.

p-values < 0.05 are indicated in boldface.

Table 3
Relationships between MRI indices and clinical measures in multivariable regression models.

	Hip Flexion Strength		Vibration Sensation Threshold		EDSS	
	Regression coefficient	<i>p</i> -value [*]	Regression coefficient	<i>p</i> -value [*]	Regression coefficient	<i>p</i> -value [‡]
FA	43.43	0.07	-46.78	0.04	-8.17	0.003
MD	-33.49	<0.001	13.62	0.16	2.23	0.03
$\lambda_{\perp}$	-30.92	<0.001	17.79	0.06	2.96	0.005
$\lambda_{\parallel}$	-23.46	<0.001	3.57	0.64	0.54	0.5
MTR	56.41	0.12	-74.68	0.05	-9.37	0.02
Lesion count	-1.43	0.13	1.27	0.25	0.26	0.02

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

^{*} *p*-values correspond to the regression coefficient for each MRI index generated in multivariable linear regression models adjusting for age, sex, spinal cord cross-sectional area, and brain parenchymal fraction, using robust standard error estimations to account for within-subject correlations

[‡] *p*-values correspond to the regression coefficient for each MRI index generated in multivariable linear regression models adjusting for age, sex, spinal cord cross-sectional area, and brain parenchymal fraction.

p-values < 0.05 are indicated in boldface.