

Ongoing microstructural changes in the cervical cord underpins disability progression in early primary progressive multiple sclerosis

Rosa Cortese¹, Carmen Tur¹, Ferran Prados^{1,2,3}, Torben Schneider⁴, Baris Kanber^{1,2,9}, Marcello Moccia^{1,5}, Claudia A.M. Gandini Wheeler-Kingshott^{1,6,7}, Alan J. Thompson¹, Frederik Barkhof^{1,8,9}, Olga Ciccarelli^{1,9}

Affiliations:

1. Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, University College London, Russell Square, London WC1B 5EH, UK
2. Center for Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College of London, London.
3. Universitat Oberta de Catalunya, Barcelona, Spain.
4. Philips United Kingdom, Guilford, Surrey, United Kingdom
5. MS Clinical Care and Research Centre, Department of Neuroscience, Federico II University, Naples, Italy
6. Brain MRI 3T Research Center, C. Mondino National Neurological Institute
7. Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy
8. Department of Radiology and Nuclear Medicine, MS Centre Amsterdam, VU Medical Centre Amsterdam, the Netherlands
9. National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, London

Address for correspondence:

Dr Rosa Cortese, Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, University College London, Russell Square, London WC1B 5EH, UK. Email: r.cortese@ucl.ac.uk.

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Abstract:

Background: Pathology in the spinal cord of patients with primary-progressive MS (PPMS) contributes to disability progression. We previously reported abnormal Q-space imaging (QSI)-derived indices in the spinal cord at baseline in patients with early PPMS, suggesting early neurodegeneration.

Objective: To investigate whether changes in spinal cord QSI over 3 years in the same cohort are associated with disability progression and if baseline QSI metrics predict clinical outcome.

Methods: 23 PPMS patients and 23 healthy controls recruited at baseline were invited for follow-up cervical cord 3T-MRI and clinical assessment after 1 and 3 years. Cord cross-sectional area (CSA) and QSI measures were obtained, together with standard brain MRI measures. Mixed-effect models assessed MRI changes over time and their association with clinical changes. Linear regression identified baseline MRI indices associated with disability at 3 years.

Results: Over time, patients deteriorated clinically, and showed an increase in cord QSI indices of perpendicular diffusivity that was associated with disability worsening, independently of the decrease in CSA. Higher perpendicular diffusivity and lower CSA at baseline predicted worse disability at 3 years.

Conclusion: Increasing spinal cord perpendicular diffusivity may indicate ongoing neurodegeneration which underpins disability progression in PPMS, independently of the development of spinal cord atrophy.

Main text

Introduction

Primary progressive multiple sclerosis (PPMS) is characterised by disability progression from disease onset, with faster rate of deterioration in the early stages of the disease^{1,2}. The main underlying mechanism of progression is neurodegeneration, which includes a loss of neuronal function and structure. Neurodegeneration in the spinal cord has been shown to be an important determinant of disability progression in PPMS³.

Recently, there has been increased interest in implementing advanced diffusion models to characterise in vivo spinal cord microstructure and reflect specific tissue properties. High b-value Q-space imaging (QSI) is an advanced model-free diffusion weighted imaging technique⁴, which has higher sensitivity for detecting changes in neuro-axonal structure in brain lesions and normal appearing white matter when compared with standard diffusion tensor imaging⁵. The main QSI metrics are derived from the displacement probability density function, which is the average probability of a spin moving a certain distance during a given diffusion time, and include the full-width of half-maximum (FWHM) and P0, that represent the width and the height of the displacement probability density function and are computed for both perpendicular (xy) and parallel (z) directions. Increased FWHM_{xy} and ADC_{xy} and reduced P0_{xy} reflect increased movement of water perpendicular to the main cord axis, which indicates an increased perpendicular diffusivity⁵. The application of QSI to the spinal cord has the potential to characterize in vivo microstructural damage⁶.

We previously demonstrated that QSI-derived indices of perpendicular diffusivity are increased in patients with early PPMS compared to healthy controls at baseline, even in the

absence of spinal cord atrophy⁷. We have invited all the patients who were recruited at baseline to come back for follow-up scan at 1 and 3 years, to investigate whether changes in the QSI indices over this period are associated with disability progression and if baseline QSI metrics predict clinical disability at three years.

Materials and Methods

Study participants

Twenty-three patients with a diagnosis of PPMS⁸ within 6 years from disease onset and twenty-three healthy controls recruited into the baseline study⁷, were invited for a follow-up assessment at 1 and 3 years. Patients were clinically assessed on the day of the MRI at each time point.

The baseline and 1-year data concerning the spinal cord cross-sectional area measurements of this cohort of PPMS patients have been reported in a previous study which was aimed to calculate the optimal sample size for clinical trials⁹.

All participants provided written informed consent prior to taking part in the study, which was approved by the local research ethics committee (REC reference: 10/H0713/74, dated 23/03/2011).

Clinical Assessments

All patients were assessed at each time point using the same scales used at baseline⁷.

Conventional scales included: Expanded Disability Status Scale (EDSS)¹⁰, 9-Hole Peg Test (9-HPT)¹¹ and 25-Foot Timed Walk Test (TWT)¹². For the purpose of statistical analysis, z-

scores were calculated for 9-HPT and TWT from normative values displayed in the National Multiple Sclerosis Society Task Force database¹³.

Other clinical measures, which can reflect spinal cord pathology, were tested including:

American Spinal Injury Association (ASIA) motor and sensory scale¹⁴, Multiple Sclerosis Walking Scale–12 (MSWS–12)¹⁵ and Modified Ashworth Scale (MAS)¹⁶, grip strength from upper limbs (Sammons Preston, Incorporated, Bolingbrook, IL, USA), vibration perception thresholds (VPTs), (Bio – medical Instrument Company, Newbury, Ohio) and postural stability¹⁷.

MRI data acquisition

The MRI protocol used for the baseline study⁷ was repeated at 1 and 3 years follow-up. All scans were performed using a 3T Achieva system (Philips Medical Systems, Best, Netherlands). To reduce motion artefacts during scanning and to improve image quality, an MR compatible cervical collar was worn by all subjects¹⁸. The parameters of the sequences acquired are given as supplemental material (**Supplementary material 1**). The full protocol has been previously described⁷.

Imaging post-processing

Brain T2 lesion volume was calculated by outlining lesions on T2-weighted images using a semi-automated edge finding tool (JIM v.6.0). The presence (or absence) of T2-hyperintense lesions at C2–C3 cord level was recorded by reviewing the axial FFE images at each time point; because of the low contrast between lesions and non-lesional tissue on the spinal cord images, lesion contouring was not feasible.

The mean cross-sectional area (CSA) of the cord at each time point was calculated at C2-C3 using the 3D-FFE images and the active surface model¹⁹ (JIM v.6.0).

To avoid segmentation errors due to white matter lesions, when calculating brain volumes, an automated lesion-filling technique of brain T1 lesions was employed²⁰. Whole-brain tissue segmentation and parcellation were obtained for each timepoint using geodesic information flows method (GIF)²¹ and brain parenchymal fraction (BPF) was calculated to be used in the model as potential confounder. Structural Image Evaluation using Normalization of Atrophy (SIENA) was applied in order to estimate the Percent Brain Volume Change (PBVC) between baseline and year 3²².

With regard to QSI, the diffusion displacement probability density function (dPDF), which is the average probability of a spin moving a certain distance during a given diffusion time, was computed in each voxel for both xy and z directions. The processing pipeline for the diffusion data was previously described⁷ and is illustrated in **Figure 1**.

To look at differences in QSI metrics, the full length (60mm) of the cervical spinal cord was initially extracted, excluding the CSF and other tissue types. A region of interest was manually created outlining the whole cord on the average b0 image on each axial slice, using the ROI tool in JIM 6.0. The mean whole cord ADC and QSI indices for both directions were computed.

To assess the inter and intra-rater variability of the CSA and the whole cord region-of-interest outlined on b0 images, we obtained the Intraclass Correlation Coefficients (ICC) for each

measure using 5 randomly selected patients. ICC was greater than 0.90 for all MRI measures, indicating excellent reliability (see **Supplemental Material 2** for details).

Statistical Analysis

Analyses were performed in Stata 14.2 statistical software (Stata Corporation, College Station, Texas, USA). All the analyses were corrected for potential confounders such as age, sex, **disease duration**, presence of cervical cord lesions at C2/C3 and atrophy measures in the brain and the spinal cord, when appropriate. Statistical significance was considered when p-values were < 0.05 .

Participant demographics and characteristics

For each timepoint, age, sex and clinical measures were compared between PPMS and healthy controls, using linear regression tests.

Clinical and MRI changes over 3 years

To assess changes over 3 years in clinical variables in the patient group, linear mixed effect regression models were used: EDSS, TWT and 9-HPT z-scores, grip strength, VPTs and ASIA scores recorded at each time point (baseline, 1 and 3 years) were used as a response variable, and time was entered as a predictor. Although not all patients attended all the time points, the use of these models allowed us to consider all the data acquired maximising the efficient use of all available data.

Changes over 3 years in spinal cord MRI (CSA and QSI indices) and brain MRI (BPF, PBVC and T2 lesion load) were also assessed using linear mixed effect regression models. Each

MRI measure (recorded at baseline, 1 and 3 years) was used as a response variable, with time as predictor. A subject type indicator and 'type × time' interaction terms were used.

Relationship between QSI changes and clinical deterioration over 3 years

Associations between QSI changes and clinical changes over time in patients were assessed using linear mixed effect regression models. Values of the clinical measures (one at a time) were considered as the dependent variable. Time, measured in years, was considered as the main explanatory variable together with the changes over 3 years in the MRI measures (one at a time) and the interaction term 'time x change in MRI'. Whenever the variable time was significant ($p < 0.05$), we considered that there was a significant change over time in the clinical variable. Whenever the interaction term was significant, we considered that the change in the MRI measure over time influenced the rate of change in the clinical variable, indicating a relationship between changes in clinical and MRI measures. This model used all the available timepoints (baseline, 1 year and 3 years).

Baseline MRI predictors of clinical outcome at 3 years

To identify predictors of clinical outcome, multiple linear regression models were fitted, where clinical scores at 3 years were the dependent variable, and, age, sex, baseline clinical measures, QSI indices, CSA and the presence of lesions at C2-C3 at baseline were used as explanatory variables.

Results

Participant demographics and characteristics

Of 23 patients recruited at baseline, 20 and 16 patients underwent both clinical and MRI assessments at 1 year and 3 years follow-up, respectively. At 3 years, an additional 6 patients were clinically assessed either in person (two patients, who did not undergo an MRI scan because they had a pacemaker implanted) or on the phone with a telephone EDSS (four patients, who were too disabled to attend the hospital for visit or scan). One patient died of causes unrelated to MS. None of the patients was taking disease-modifying medication or steroids throughout the study.

Of the original 23 healthy controls, 14 attended the 3 years follow-up visit (9 subjects moved away).

The number of participants studied at each time point and their demographic and radiological characteristics are shown in **Table 1**.

Clinical and MRI changes over 3 years

During the 3 years follow-up, patients deteriorated clinically, as shown by an increase in the EDSS (annual rate of change: 0.31, 95% confidence interval [CI]: 0.18 to 0.45, $p < 0.001$) and a worsening in the other clinical scales (z-score TWT, z-score 9-HPT, grip strength and ASIA-motor scores) (**Table 2**). In particular, 11 out of 16 PPMS patients had EDSS progression over 3 years (defined as at least 1-point increase in EDSS in patients with baseline EDSS ≤ 5.5 or at least 0.5-point increase in EDSS in patients with baseline EDSS > 5.5).

When looking at the QSI rate of change, there was an increase in the ADC_{xy} and a decrease in the P0_{xy} in the spinal cord in patients over time, whilst no changes were observed in

healthy controls (**Table 3**). The rate of P0xy decrease over the follow-up was greater in patients than controls (by -0.017 per year, 95% CI: -0.032 to -0.003 p=0.020) (**Table 3**, **Figure 2**).

Patients showed a greater decline of spinal cord CSA than healthy controls (by -0.961 mm² per year, 95% CI: -1.510 to -0.144, p=0.001). Over 3 years, the CSA decreased (by -1.092 mm² per year, 95% CI: -1.468 to -0.176, p<0.001) whereas no change was observed in the healthy controls group (**Table 3**).

In both patients and controls, there were no differences in the rate of changes of the QSI metrics and CSA over time between males and females. Age did not have any effect on these rates.

Patients did not show new lesions at C2-C3 over time.

There was no significant change in BPF, PBVC and brain T2 lesion load in patients over time.

Relationship between MRI changes and clinical changes over 3 years

In patients, an increase in QSI indices of perpendicular diffusivity over time correlated with disability progression. More specifically, for each 0.1 $\mu\text{m} \times 10^2$ increase in the change over three years in cord FWHMxy there was a decrease of the yearly rate of change in 9-HPT z-score of -2.98 (95% CI: -5.19 to -0.78, p=0.007) and a decrease of the yearly rate of change in TWT z-score of -5.67 (95% CI: -10.88 to -0.46, p=0.033) (**Table 4**). For each 0.1 a.u. decrease per year in cord P0xy there was a decrease of the yearly rate of change in 9-HPT z-score of 3.65 (95% CI: 0.93 to 6.38, p=0.008) (**Table 4**) (**Figure 3**). CSA, the presence of cervical cord lesions at C2/C3 and BPF did not significantly contribute to the final model,

which only included age and sex as potential confounders. Changes in CSA over time did not correlate with clinical changes.

Baseline MRI predictors of clinical outcome at 3 years

In patients, there was an association between higher QSI-derived perpendicular diffusivity at baseline and increasing disability at follow-up; in particular, higher cord ADC_{xy} , higher $FWHM_{xy}$ and lower PO_{xy} at baseline were associated with more abnormal postural stability tests, greater vibration dysfunction (i.e., vibration perception thresholds) and spasticity (Modified Ashworth Scaler), respectively (**Table 5**).

Lower cord cross-sectional area at baseline was associated with greater gait impairment, as measured by lower TWT z-scores, at 3 years follow-up (**Table 5**).

Discussion

This study provides new insights into the mechanisms of progression in PPMS and suggests that ongoing neurodegeneration in the cord, as reflected by increased QSI measures of perpendicular diffusivity over time, underpins clinical progression independently of brain and spinal cord atrophy occurring during the same follow-up. We found that higher QSI indices of perpendicular diffusivity, **suggesting increased movement of water perpendicular to the main cord axis**, at baseline were associated with clinical disability at 3 years. In the baseline assessment of the same cohort we detected an increased perpendicular diffusivity in patients with early PPMS than healthy controls, indicating reduced structural integrity of neurons and demyelination, and we have now extended these finding by showing that QSI metrics of perpendicular diffusivity continued to change over time and reflected neurodegenerative processes which are relevant to disability worsening.

Existing data from animal studies demonstrated that myelin has a significant effect on changes in QSI-derived perpendicular diffusivity^{5,4}, while cellular infiltrates, or inflammation, may reduce the specificity of the indices of parallel diffusivity to axonal damage in chronic MS^{23,24}. Therefore, in a complex disease such as PPMS, which includes inflammation, demyelination and axonal damage, the pathological features that QSI indices reflect are likely to be multifactorial, whereas increased perpendicular diffusivity may specifically indicate neurodegenerative processes due to demyelination and axonal membranes disruption.

Identification of increased perpendicular diffusivity over time in patients and not in controls were also reported in QSI indices in the cervical spinal cord in patients with relapse-onset MS²⁵. Such consistency of both cross-sectional and longitudinal results raises the possibility that QSI indices may be used as biomarkers of spinal cord involvement at any stage of PPMS⁷ and can reveal occult changes in neuronal integrity over time. Interestingly, in patients with PPMS, QSI changes seemed to be widely independent from the reduction of CSA and the presence of spinal cord lesions. This supports the concept that, although global measures on conventional scans, such as cord atrophy, can capture morphological changes, they cannot reveal the underlying MS-related microstructural abnormalities, which can be revealed by quantitative MRI indices instead²⁶.

Another key observation in our study was that higher cord QSI perpendicular diffusivity indices at baseline were independent predictors of motor disability (measure gait, balance and strength) at 3 years and correlated with a worsening in clinical measures.

The relationship between MRI indices at baseline and system-specific measures of disability is essential to improve our understanding of the structure-function relationship in MS, which is an important step towards the development of targeted treatments and the use of these measures in monitoring therapeutic efficacy. Recently, an increasing number of studies have focused on the use of spinal cord atrophy as an imaging surrogate of axonal loss²⁷. Indeed, atrophy is the only spinal cord imaging measure that has been used as exploratory outcome measure in phase 2 and phase 3 clinical trials in patients with progressive MS²⁸, though with variable treatment benefit on this metric^{29,30}. These negative results could be not only related to the inefficacy of the drug, but also to methodological difficulties and the variability in the measurement techniques³¹. Therefore, the development of new and more sensitive imaging approaches, like QSI, may be of benefit to identify new surrogate endpoint markers for the evaluation of the safety and efficacy of new therapeutic intervention.

As expected, patients developed cord atrophy over time, which was not detected in healthy controls. In contrast with recent studies reporting a strong association between the development of cord atrophy and disability progression in PPMS^{32,33} we did not observe a correlation between change in CSA and clinical deterioration. This discordance may be due to the small sample size of our study. In support of this, a sample size calculation with 80% power, at 5% significance, requires an n of 147 to detect a significant difference in CSA changes between patients with and without EDSS progression, which is substantially higher than the sample recruited into this study. An additional explanation for the lack of agreement between our findings and previous studies, comes from the heterogeneity in techniques to detect atrophy. Indeed, Tsagkas et al. demonstrated a correlation between the EDSS increase over time and upper cervical spinal cord volume measured using a 3D T1-weighted

magnetization-prepared rapid gradient-echo (MPRAGE) in PPMS³², which is different from our methodology.

The main limitation of this longitudinal study is the small sample size with only 70% of patients being scanned at 3 years follow-up. Unfortunately, the sample size cannot be increased because our scanner underwent a major software and hardware upgrade.

Replication in larger cohorts is required before these findings can be used clinically. In addition, QSI is a technique that need long acquisition times to acquire a large number of data points, limited directional resolution, and difficulty in interpreting the probability density function. Although we used mixed effects models to minimise the bias resulting from excluding patients at different timepoints, the inclusion of patients who could not attend for high level of disability, might have added information. **Finally, we did not adjust the analysis of lesions outside C2-C3, and, therefore, we could not assess the effects of distant lesions on cord atrophy.**

In conclusion, increasing spinal cord perpendicular diffusivity over time, which may indicate ongoing neurodegeneration, was associated with progressive and irreversible neurological disability in MS, independently from spinal cord atrophy. As the use of advanced MRI techniques to detect microstructural changes remains technically challenging, future work should therefore aim to acquire standardised, high-quality data across scanner manufacturers and sites and reduce acquisition times. The ultimate goal is to apply these new MRI parameters into clinical trials when testing new neuroprotective agents.

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TABLE 1: Cohort description

	Baseline		1 Year		3 Years	
	PPMS	HC	PPMS	HC	PPMS	HC
No.	23	23	20	18	22 ^a	14
Mean age, years, mean (SD)	51 (9.1) ^b	44 (12.6)	52 (9.3) ^b	46 (11.9)	53 (8.8) ^b	46.3 (12.3)
Sex (M:F)	11:12	5:18	10:10	5:13	10:12	5:9
Disease duration, years, mean (SD)	3.4 (1.7)	NA	4.5 (1.8)	NA	6.4 (1.7)	NA
CSA, mm ² , mean (SD)	76.99 (9.58) ^b	81.65 (8.62)	75.41 (9.40) ^b	81.42 (8.59)	73.23 (8.31) ^{b, c}	81.59 (9.11)
N. of patients with lesions at C2-C3	12/23	NA	10/20	NA	9/16	NA
BPF, mean (SD)	0.744 (0.741) ^b	0.757 (0.756)	0.742 (0.666)	0.753 (0.683)	0.740 (0.683)	0.754 (0.753)
Brain T2 lesion volume, mm ³ , mean (SD)	10.10 (8.82)	NA	11.81 (10.06)	NA	10.62 (10.38)	NA
Annualised PBVC, mean (SD)	NA	NA	-1.37 (2.09) ^d	-0.19 (0.79) ^d	-1.02 (0.64) ^e	-0.34 (0.74) ^e

^a 16/22 completed MRI and clinical assessment, 2/22 completed clinical assessment only,
4/22 telephone EDSS

^b $P < 0.05$, obtained using linear regression, to compare PPMS patients and HC

^c Faster reduction in CSA in PPMS patients than HC

^d Annualised PBVC between 1 year and baseline

^e Annualised PBVC between 1 and 3 years

Note: 4 patients were too disabled to attend the 3-year follow-up and did not contribute to annualised PBVC between Y3 and Y1. No differences between the rates of annualised atrophy were found, considering that the error of the method (SIENA) is 0.2-0.3%³⁵

Abbreviations: BPF: brain parenchymal fraction, CSA: cord cross-sectional area, HC: healthy controls, NA: not applicable, PBVC: percent brain volume change PPMS: primary progressive multiple sclerosis.

TABLE 2: Clinical characteristics of patients at baseline, 1 year and 3 years follow-up and clinical changes over time

	Baseline	1 Year follow-up	3 Years follow-up	Annualised rate of change (analysed from BL to 3 Years) ^a		
				RC ^b	95%CI	p-value
Median (range) EDSS	5.5 (2.5-6.5)	6 (4.5-7)	6.5 (3.5-8)	0.31	0.18 to 0.45	<0.001
Mean (SD) TWT, z-score	0.28 (0.20)	0.18 (0.33)	-1.36 (1.54)	-0.53	-0.75 to -0.31	<0.001
Mean (SD) 9-HPT, z-score	-0.61 (1.10)	-0.99 (1.16)	-1.26 (1.20)	-0.190	-0.36 to -0.02	0.027
Mean (SD) grip strength, lbs force	54.93 (25.97)	40.22 (24.81)	14.76 (9.65)	-10.61	-14.10 to -7.12	<0.001
Mean (SD) vibration perception threshold	13.07 (8.76)	15.95 (7.86)	20.28 (13.40)	2.52	-0.57 to 5.62	0.110
Mean (SD) ASIA-motor	96.22 (4.57)	89.47 (8.72)	77.33 (18.65)	-5.89	-8.88 to -2.89	<0.001
Mean (SD) ASIA-light touch	108.50 (13.15)	111.67 (1.29)	106 (9.47)	-0.94	-2.51 to 0.63	0.243
Mean (SD) ASIA-pin prick	108.44 (13.11)	110.53 (2.80)	105.89 (9.59)	-0.89	-2.47 to 0.68	0.267
Mean (SD) summated MAS	3.22 (8.91)	5.81 (6.39)	6.77 (7.28)	0.26	-0.96 to 1.48	0.675
Mean (SD) MSWS-12	47.63 (15.58)	73.86 (18.36)	46.64 (13.03)	-1.74	-5.07 to 1.59	0.305
Mean (SD) sway, 32cm, EO, deg/sec	0.62 (0.29)	0.73 (0.27)	0.59 (0.20)	-0.02	-0.07 to 0.04	0.595
Mean (SD) sway, 32cm, EC, deg/sec	0.74 (0.33)	0.92 (0.41)	0.77 (0.25)	0.01	-0.08 to 0.08	0.969
Mean (SD) sway, 4cm, EO, deg/sec	0.72 (0.29)	0.78 (0.29)	0.84 (0.25)	0.04	-0.03 to 0.10	0.285

Mean (SD) sway, 4cm, EC, deg/sec	0.88 (0.41)	0.85 (0.37)	0.46 (0.32)	0.03	-0.06 to 0.11	0.561
Mean (SD) Romberg 32cm, deg/sec	1.27 (0.32)	1.28 (0.44)	1.33 (0.22)	0.001	-0.06 to 0.07	0.082
Mean (SD) Romberg 4cm, deg/sec	1.21 (0.22)	1.19 (0.24)	1.23 (0.57)	-0.02	-0.16 to 0.11	0.730

^a Mixed-effects model was used to assess changes over time.

^b RC (95% CI), regression coefficient (given as unit change/year) (95% CI), which represents the annual change of each unit.

Abbreviations: 9-HPT: 9-hole peg test, ASIA: american spinal injury association, EDSS: expanded disability status scale EC: eyes closed, EO: eyes open, MAS: modified ashworth scale, MSWS: multiple sclerosis walking scale, TWT: 25-foot timed walk test.

TABLE 3: Rate of changes in MRI measures over 3 years different between patients and controls

	Rate of annualised change using mixed-effect models (95% CI), p-value		
	Patients	Controls	Patients vs. controls, interaction term (95% CI), p-value
Cord ADCxy	0.207 (0.023 to 0.390) mm ² /ms/year, p=0.027^a	0.012 (-0.081 to 0.305) mm ² /ms/year, p=0.256	0.095 (-0.172 to 0.361) p=0.484
Cord P0xy	-0.007 (-0.022 to -0.004 to -0.022) a.u./year, p=0.042^a	-0.019 (-0.051 to 0.013) a.u./year, p=0.247	-0.017 (-0.020 to -0.005) p=0.020^a
CSA	-1.092 (-1.468 to -0.176) mm ² /year, p<0.001^a	-0.756 (-0.532 to 0.269) mm ² /year, p=0.519	-0.967 (-1.510 to -0.441) p<0.001

^a Corrected for age and sex.

Abbreviations: ADC: apparent diffusion coefficient, CSA: cord cross-sectional area, P0: zero displacement probability.

TABLE 4: Summary of significant associations between changes in QSI indices and changes in clinical disability scores.

Cord QSI indices	Clinical measure	Interaction term ^{a,b}	95%CI	p-value ^c	Yearly rate of change in clinical score in patients with no change in MRI measures over 3 years ^b		
					RC	95%CI	p-value
FWHM _{xy}	9-HPT z-score	-2.98 z-score/year/ $\mu\text{m} \times 10^2$	-5.19 to -0.78	0.007	-0.24	-0.36 to -0.11	<0.001
P0 _{xy}	9-HPT z-score	3.65 z-score/year/ a.u./year	0.93 to 6.38	0.008	-0.34	-0.46 to -0.22	<0.001
FWHM _{xy}	TWT z-score	-5.67 z-score/year/ $/\mu\text{m} \times 10^2/\text{year}$	-10.88 to -0.46	0.033	-0.46	-0.76 to -0.16	0.003

^a The interaction term indicates the yearly rate of change in clinical measure per each unit of change in the QSI indices

^b Mixed-effects model was used to assess changes over time.

^c Corrected for age and sex.

Note: 2 patients did not show change in FWHM_{xy} over time and 1 patient in P0_{xy}.

Abbreviations: 9-HPT: 9-hole peg test, FWHM: full width of the displacement probability density function, P0: zero displacement probability, QSI: q-space imaging, TWT: 25-foot timed walk test.

TABLE 5: Baseline MRI predictors of clinical outcome at 3 years.

MRI predictors (at Baseline)	Dependent Variable (at 3 years)	RC^a	95%CI	p-value^b
ADC _{xy}	32 cm instability, eyes open	2.14 units of sway/mm ² /ms	0.48 to 3.80	0.035
	32 cm instability, eyes closed	1.99 units of sway/mm ² /ms	0.08 to 3.91	0.043
	4 cm instability, eyes open	3.49 units of sway/mm ² /ms	1.05 to 5.92	0.012
	4 cm instability, eyes closed	2.71 units of sway/mm ² /ms	0.23 to 5.20	0.036
FWHM _{xy}	VPTs	353.37 seconds/mm ² /ms	12.10 to 694.63	0.044
P0 _{xy}	MAS	-3.70 units/a.u.	-19.42 to -1.43	0.048
CSA	TWT z-score	0.09 units/mm ²	0.001 to 0.184	0.045

^a Regression coefficient from linear regression

^b Corrected for age and sex.

Abbreviations: ADC: apparent diffusion coefficient, CSA: cord cross-sectional area, FWHM: full width of the displacement probability density function, MAS: modified ashworth scale, P0: zero displacement probability, TWT: 25-foot timed walk test, VPTs: vibration perception thresholds.