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ORIGINAL COMMUNICATION

Joint assessment of brain and spinal cord motor tract damage in patients with early RRMS: predominant impact of spinal cord lesions on motor function

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Abstract

Background In patients with MS, the effect of structural damage to the corticospinal tract (CST) has been separately evaluated in the brain and spinal cord (SC), even though a cumulative impact is suspected.

Objective To evaluate CST damages on both the cortex and cervical SC, and examine their relative associations with motor function, measured both clinically and by electrophysiology.

Methods We included 43 patients with early relapsing–remitting MS. Lesions were manually segmented on SC (axial T2*) and brain (3D FLAIR) scans. The CST was automatically segmented using an atlas (SC) or tractography (brain). Lesion volume fractions and diffusion parameters were calculated for SC, brain and CST. Central motor conduction time (CMCT) and triple stimulation technique amplitude ratio were measured for 42 upper limbs, from 22 patients.

Results Mean lesion volume fractions were 5.2% in the SC portion of the CST and 0.9% in the brain portion. We did not find a significant correlation between brain and SC lesion volume fraction ($r=0.06$, $p=0.68$). The pyramidal EDSS score and CMCT were both significantly correlated with the lesion fraction in the SC CST ($r=0.39$, $p=0.01$ and $r=0.33$, $p=0.03$), but not in the brain CST.

Conclusion Our results highlight the major contribution of SC lesions to CST damage and motor function abnormalities.

Keywords T2 lesions · Electrophysiology · MRI · Spinal cord · Multiple sclerosis

Introduction

The secondary progressive phenotype MS usually presents as a worsening pyramidal syndrome of both lower and upper limbs, suggesting strong corticospinal tract (CST) involvement [1]. However, quantifying focal and diffuse CST damage from the motor cortex to the spinal cord (SC) using MRI presents data-acquisition and data-processing challenges. Thus, the whole CST has not yet been explored in patients with MS.

Conversely, a substantial number of studies have focused on the brain portion of the CST. Diffusion tensor imaging (DTI) is a tool of choice for this exploration, as it allows white-matter (WM) tracts to be extracted and tissue integrity to be characterized. In particular, DTI-derived metrics extracted from the brain CST have been shown to correlate to several clinical scores [2–4]. Moderate associations between motor function and T2 lesion volume in the CST have been reported [5]. Finally, CST T2 lesion volume has

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been shown to correlate with DTI metrics in normal-appearing CST [6], suggesting that focal damage plays a role in both the lesion and Wallerian degeneration.

By contrast, only a limited number of studies have evaluated the impact of CST damage in the SC. For a start, the precise location of the lesions had not been fully explored, owing to technical limitations [7], including the small size of the WM tract in the SC and the need for systematic whole-cord axial acquisitions with high in-plane resolution and large coverage [7]. Nevertheless, even without a specific assessment of lesion location, the SC T2 lesion load has been shown to be associated with disability [8], and to have a strong prognostic value [9, 10]. A few studies have also highlighted the involvement of diffuse SC CST damage in motor disabilities. In particular, magnetization transfer imaging metrics in the lateral column of the SC have been found to be correlated with ankle flexion strength [11], and diffusion imaging metrics with scores on the Expanded Disability Status Scale (EDSS), 9-Hole Peg Test (9HPT) and Timed 25-Foot Walk (T25FW) [12].

In the present study, we took advantage of advances in SC MRI acquisition and post-processing to assess CST structural integrity in both the cortex and the cervical SC, and examine their relative associations with motor function in a population of patients with early relapsing–remitting MS (RRMS). Structural integrity was assessed using T2 lesion delineations and DTI quantitative measurements in the brain and cervical SC. In addition to standard clinical scores, which are usually slightly impacted at this stage of the disease [13], we also assessed upper limb motor functions by electrophysiology in a subset of patients. More specifically, we recorded the central motor conduction time (CMCT) using transcranial magnetic stimulation, which increase suggests demyelination [14] or loss of rapidly conducting corticospinal fibres, as well as the triple stimulation technique (TST) amplitude ratio, which decrease suggests central conduction block or axonal loss [15, 16].

Methods

Participants

We included 44 patients with early RRMS in this single-center study. All patients underwent an MRI evaluation, and 24 also underwent an electrophysiological evaluation (on a voluntary basis). They were part of a multicenter longitudinal study (EMISEP; ClinicalTrials ID: NCT02117375) approved by the relevant institutional review board. Written informed consent was obtained from all participants. The main inclusion criteria were (1) age 18–45 years, (2) RRMS diagnosis according to 2010 criteria [17] < 48 months, (3) initial MRI severity > 9 T2 lesions on brain MRI and/or initial myelitis documented on spinal cord MRI, and (4) no relapse and no corticosteroids in the month before inclusion. Healthy controls were also included for brain ($n = 16$) and spinal cord MRI ($n = 19$) assessment. The demographic characteristics of patients and controls are summarized in Supplementary Table 1.

Study design

The study design is described below and summarized in Fig. 1.

MRI acquisitions

Imaging was performed using a 3-tesla MRI scanner (MAGNETOM Verio (VB17), Siemens). Details of acquisition parameters are given in Supplemental Material. Briefly, (1) for SC lesion identification, axial T2*w and sagittal T2 TSE from C1 to C7; (2) for SC diffusion measurement, diffusion-weighted EPI sequence (30 directions); (3) for brain lesion identification, axial T2w, axial PD, and 3D FLAIR; and (4) for brain CST identification and diffusion measurements, diffusion-weighted EPI sequence (30 directions) and 3DT1 MPRAGE.

MRI processing

Processing was performed using the Spinal Cord Toolbox (SCT Version 3.0) [18] and the Anima toolbox [19]. Details of image analysis are given in Supplemental Material and are summarized below for the patients' scans. The same steps were applied to the controls' scans, except for those concerning lesion identification and alignment.

Spinal cord MRI processing

Lesion volume fractions First, two neurologists (RC, AK) manually delineated cervical cord lesions on the axial T2*w images, using sagittal T2w images to help identify the lesions. Second, the SC was segmented and the vertebrae labelled on the T2*w images. Third, the left and right lateral and ventral components of the CST were extracted using the MNI-Poly-AMU template (Fig. 2). Fourth, the lesion volume fraction was computed as (lesion volume in region of interest)/(ROI volume), with ROIs in the cervical cord defined as right CST, left CST, whole CST, and whole cord. CST sides were named according to their functional lateralization (e.g., the right CST related to motor function on the right side of the body). Level C7 (bottom of the acquisition slab) was removed from this analysis, owing to the difficulty of precisely aligning them on the template.

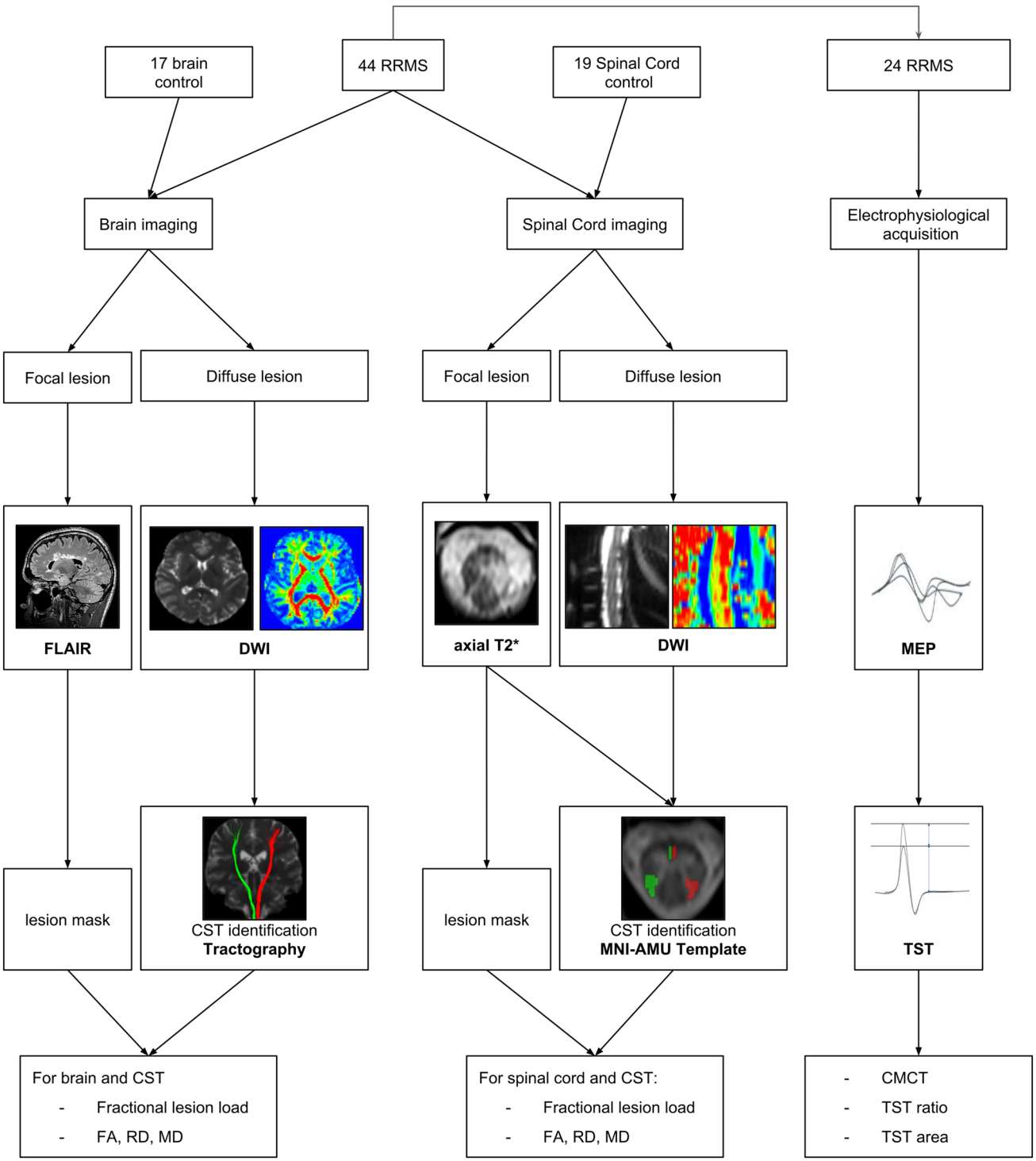

Fig. 1 Study design. *RRMS* relapsing–remitting multiple sclerosis, *DWI* diffusion-weighted imaging, *CST* corticospinal tract, *MEP* motor evoked potential, *TST* triple stimulation technique, *CMCT* central motor conduction time, *FA* fractional anisotropy, *RD* radial diffusivity, *AD* axial diffusivity

Scalar diffusion parameters First, we corrected the diffusion images for motion and distortion. Second, we applied cord segmentation, level labelling and ROI extraction to the mean diffusion B0 images to locate the left and right lateral CST components in the diffusion acquisition frame. Because of the low resolution of our DTI data, ventral CST components were not extracted, to avoid a detrimental partial volume effect. Third, we

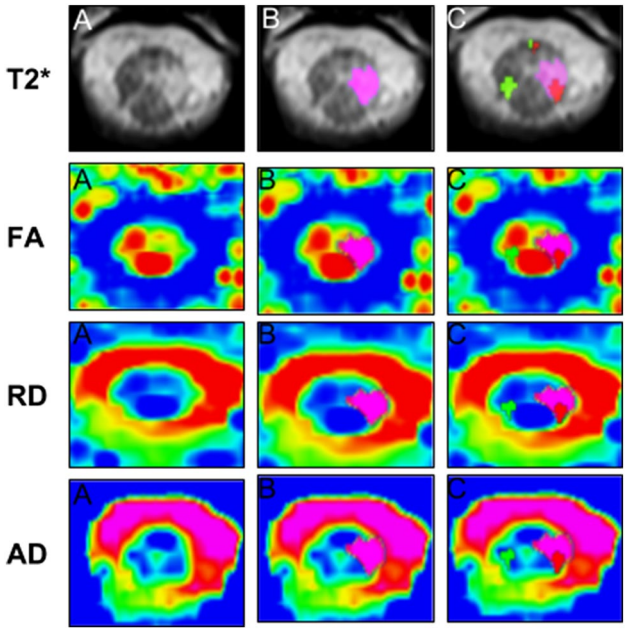

Fig. 2 Example of spinal cord MRI in a patient with RMMS. First row: axial T2*. Other rows: DTI parameter maps. **a** Native image; **b** segmented lesion in pink; **c** masks of corticospinal tract crossing the lesion (left CST in red, right CST in green). *FA* fractional anisotropy, *RD* radial diffusivity, *AD* axial diffusivity

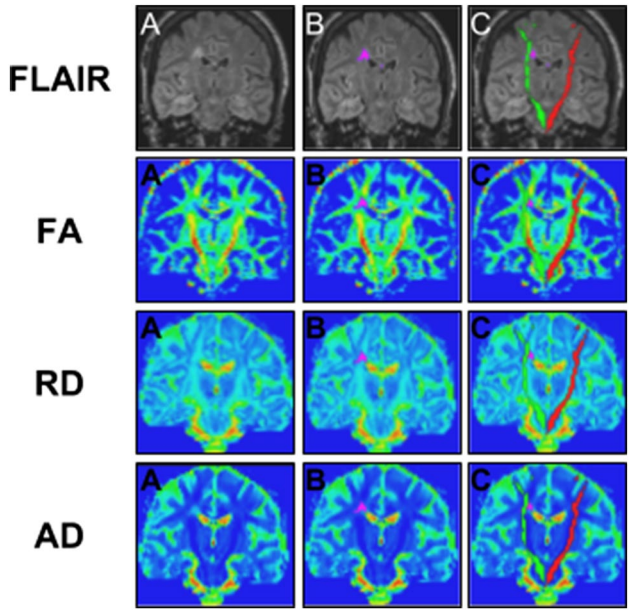

Fig. 3 Example of brain MRI in patient with RRMS. First row: FLAIR acquisition registered on b0 image. Other rows: parametric maps. **a** Native images, **b** segmented lesion in pink, **c** masks of corticospinal tract crossing the lesion (left CST in red, right CST in green), *FA* fractional anisotropy, *RD* radial diffusivity, *AD* axial diffusivity

extracted the fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD) maps. Finally, for each participant, the mean values of diffusion parameters for the CST, spine and lesions were extracted for the C2–C4 ROI. We selected this ROI because we judged it to be the least prone to strong geometric distortion and variability in terms of DTI parameters in our control group.

Brain MRI processing

Lesion volume fractions First, two neurologists (RC, AK) manually performed lesion delineation on the 3D-FLAIR images, using T2w and PD images to help lesion identification. Second, diffusion acquisitions were corrected for motion and distortion. Third, lesion masks were rigidly aligned to the diffusion acquisitions. Fourth, the WM mask was extracted. Fifth, brain portions of the left and right CSTs were identified after masking out WM lesions, using probabilistic tractography and a set of filtering ROIs (Fig. 3). Finally, for each patient, we computed the lesion volume fractions in the right CST, left CST, whole CST, and whole brain. Lesion fractions were also computed on similar ROIs combining lesion volumes from both the brain and SC.

Scalar diffusion parameters The FA, RD and AD parameters were then extracted from the diffusion acquisitions. Finally, for each participant, each of these DTI parameters was averaged on the brain CST, WM, normal-appearing WM, and lesions.

Electrophysiological acquisitions

The electrophysiological acquisition protocol is fully described in Supplemental Material. Briefly, motor evoked potentials (MEPs), TST amplitude ratio and area measurements were performed on the first dorsal interosseous muscle on each side, using surface electrodes and standard protocols [20, 21]. Values > 8 ms for the CMCT, < 33% for the MEP ratio, < 93% for the TST ratio, and < 92% for the TST area were considered as abnormal [15, 20].

Clinical data

The clinical assessment included the (1) EDSS and pyramidal EDSS, (2) 9HPT, (3) T25FW, (4) 6-Minute Walking Test (6MWT), and (5) MS Walking Scale (MSW12).

Statistical analysis

Statistical analysis was performed in R (Version 3.4.4) [22]. We used a 0.05 testwise significance level (no correction for multiple comparisons).

Differences in mean DTI metrics between patients and controls for the different ROIs and diffusion parameters and differences in mean electrophysiological scores between sides with and without pyramidal signs were tested by computing the p value associated with the equality of means using Welch's two-sample t test.

Correlations between lesion volume fractions in the brain and cord were assessed using the Pearson correlation coefficient. The associated p values for $r=0$ are also given.

Correlations between characteristics of CST lesion fractions and electrophysiological scores were calculated using the Spearman correlation coefficient in two different ways. First, we computed the correlations between lesion fractions in the CST (brain, cord and brain + cord) and the quantities from the matching side. Second, to assess the specificity of the lateralization, we also computed correlations between overall nonlateralized variables [whole brain, whole cord, whole central nervous system (CNS) when appropriate] and mean electrophysiological scores. The associated p values for $r=0$ are also given.

Correlations between MRI metrics, electrophysiology and clinical scores were assessed using the Spearman correlation coefficient. The associated p values for $r=0$ are also given.

Results

Clinical characteristics

We included 44 patients with RRMS. Their clinical characteristics are summarized in Table 1. Two of these patients had a motor deficit, and 17 had an isolated pyramidal syndrome with no motor deficit.

MRI characteristics

Lesion volume fractions

One patient was excluded from this analysis because motion artifacts on the spinal cord T2*w images prevented precise delineation of the lesions. The mean lesion number was 2.5 in the SC (range 0–8; 6 patients had no spinal cord lesion) and 30 in the brain (range 2–71). The mean lesion fraction was 5.64% (SD = 10.61) in the whole cervical SC and 0.26% (SD = 0.21) in the whole brain. Regarding the CST, mean absolute T2 lesion volumes were 52.5 mm^3 in the SC and 121.9 mm^3 in the brain. After normalizing for region volume, mean lesion fraction was 5.18% (SD = 10.05) in the SC CST and 0.88% (SD = 1.45) in the brain CST. Two patients had no CST lesions. Detailed results are provided in Table 2. Lesion volume fractions in the whole SC and the SC CST were strongly correlated ($r=0.96$, 95% CI [0.93, 0.98], $p<e-16$). We also observed a similar, albeit less pronounced, correlation in the brain ($r=0.49$, 95% CI [0.22, 0.69], $p=0.001$). By contrast, we did not find any evidence of a correlation between the lesion volume fractions in the brain and SC ($r=0.06$, 95% CI [− 0.24, 0.36], $p=0.68$).

DTI metrics in patients and controls

Table 3 gives the results of FA, RD and AD metrics for the SC and brain for patients and controls. In the whole cervical cord, we found evidence of differences between controls and patients for FA and RD, even after excluding lesions. When we focused on the CST, evidence of significant differences between the two groups vanished. In the whole brain and brain CST, we found no evidence of differences between

Table 1 Clinical characteristics of patients

Clinical characteristics ($N=44$)		
Age (years)	Mean ± SD	30.7 ± 6.4
Sex	(F/M)	28/16
Disease duration (months)	Mean ± SD	21.1 ± 11.40
EDSS	Median (range)	1 (0–3)
Pyramidal EDSS	Median (range)	0 (0–2)
9-HPT right (s)	Mean ± SD (range)	19.1 ± 4.4 (13.9–40.6)
9-HPT left (s)	Mean ± SD (range)	19.7 ± 5.7 (14.5–54.1)
6MWT (m)	Mean ± SD (range)	540 ± 95 (324–822)
T25FW (min)	Mean ± SD (range)	4.9 ± 0.8 (3.8–7.8)
MSW12	Mean ± SD (range)	17.2 ± 10.7 (12–54)
Right pyramidal signs	(Yes/no)	8/36
Left pyramidal signs	(Yes/no)	9/35
Disease-modifying drugs	Fingolimod $n=9$; interferon $n=10$; glatiramer acetate $n=11$; teriflunomid $n=6$; dimethyl fumarate $n=3$, other $n=4$ (Rituximab, Natalizumab, Mycophenolic acid, Alemtuzumab), no DMD $n=1$	

DMD disease-modifying drugs, *EDSS* Expanded Disability Status Scale, *T25FW* Timed 25-Foot Walk Test, *9HPT* 9-Hole Peg Test, *6MWT* 6-Minute Walking Test, *MSW12* MS Walking Scale

Table 2 Brain, spinal cord and corticospinal tract lesion volume

	WHOLE		CST	
	Lesion volume in ROI (mm^3)	Percentage of lesions in ROI	Lesion volume in ROI (mm^3)	Percentage of lesions in ROI
Spinal cord				
Mean ± SD (min, max)	**425.20 ± 790.48 (0.00, 4160.23)**	*5.64 ± 10.61 (0.00, 57.00)*	**52.54 ± 99.67 (0.00, 568.16)**	*5.18 ± 10.45 (0.00, 62.44)*
Brain				
Mean ± SD (min, max)	**3668.84 ± 3,292.29 (187.45, 16 916.51)**	*0.26 ± 0.21 (0.01, 1.00)*	**121.86 ± 214.08 (0.00, 976.00)**	*0.88 ± 1.45 (0.00, 5.44)*
Spinal cord + brain				
Mean ± SD (min, max)	**4094.04 ± 3435.63 (187.45, 17 080.47)**	*0.28 ± 0.23 (0.01, 1.00)*	**174.40 ± 241.30 (0.00, 1207.26)**	*1.23 ± 1.71 (0.00, 7.60)*

Bold: mean, standard deviation and range for lesion volume in each ROI (in mm^3). Italics: mean, standard deviation and range for lesion volume fraction in each ROI (i.e., percentage of lesions in ROI)

Table 3 Mean (standard deviation) diffusion parameter values for patients and controls and *p* values associated with no differences between patients and controls

	Controls (spinal cord: $n = 18$, Brain $n = 16$)	Patients ($n = 43$)	*p* value for no control-to-patient difference
Spinal cord			
FA			
Whole spinal cord	0.719 (0.054)	0.664 (0.079)	0.009
NASC	–	0.661 (0.081)	0.002
CST	0.746 (0.078)	0.712 (0.093)	0.180
Lesion	–	0.655 (0.115)	–
RD (×1000)			
Whole spinal cord	0.406 (0.076)	0.483 (0.119)	0.014
NASC	–	0.492 (0.127)	0.002
CST	0.366 (0.114)	0.408 (0.138)	0.258
Lesion	–	0.473 (0.149)	–
AD (100×)			
Whole spinal cord	0.158 (0.014)	0.158 (0.014)	0.946
NASC	–	0.159 (0.014)	0.760
CST	0.159 (0.014)	0.158 (0.016)	0.800
Lesion	–	0.156 (0.018)	–
Brain			
FA			
WM	0.346 (0.025)	0.341 (0.020)	0.451
NAWM	0.346 (0.025)	0.342 (0.020)	0.518
CST	0.480 (0.025)	0.469 (0.024)	0.139
Lesion	–	0.311 (0.038)	–
RD (1000×)			
WM	0.610 (0.045)	0.613 (0.046)	0.791
NAWM	0.610 (0.045)	0.611 (0.046)	0.914
CST	0.548 (0.048)	0.556 (0.039)	0.533
Lesion	–	0.870 (0.103)	–
AD (×100)			
WM	0.105 (0.003)	0.105 (0.004)	0.623
NAWM	0.105 (0.003)	0.104 (0.004)	0.427
CST	0.120 (0.005)	0.120 (0.005)	0.679
Lesion	–	0.139 (0.014)	–

FA fractional anisotropy, *RD* radial diffusivity, *AD* axial diffusivity, *NA* normal appearing

controls' and patients' diffusion parameters. Moreover, we do not observe evidence of correlations between lesion fraction in the spinal cord and values of DTI metrics in the spinal cord (Supplementary Table 2).

Electrophysiological scores

We collected electrophysiological data from 44 sides (21 right side and 23 left side). Four patients declined the electrophysiological assessment on the one side, and one patient was excluded from the TST analysis because of repolarization abnormalities. The electrophysiological assessments are detailed in Supplementary Table 3. Twelve of the 24 patients (19 of the 44 sides) had at least one abnormal value (7/44 CMCT, 9/42 MEP ratio, and 15/42 TST ratio). Sides associated with pyramidal signs experienced lower mean TST ratio scores than sides without pyramidal signs (74.44, SD = 24.40 versus 95.34, SD = 11.13, $p = 4e{-}04$, Table 4).

Associations between MRI metrics and clinical scores

Lesion volume fractions and clinical scores

Detailed correlations are provided in Table 5. EDSS was correlated with the lesion fraction of the whole SC ($r = 0.41$, $p = 0.007$). Pyramidal EDSS was positively correlated with the lesion fractions of the SC CST ($r = 0.39$, $p = 0.01$), whole SC ($r = 0.34$, $p = 0.02$) and brain + spine CST ($r = 0.41$, $p = 0.007$).

DTI parameters and clinical scores

We did not observe significant correlations between diffusion parameters and clinical data. (Supplementary Table 4).

Table 4 Mean (standard deviation) electrophysiological scores for sides without pyramidal signs and with pyramidal signs, as well as the *p* values associated with no differences between the two groups

	Sides without pyramidal signs ($n = 31$)	Sides with pyramidal signs ($n = 11$)	*p* value for no difference between the two groups
CMCT	6.29 (1.44)	7.54 (3.32)	0.09
TST ratio	98.30 (9.32)	75.46 (20.62)	1.3e−05
TST area	95.34 (11.13)	74.44 (24.40)	4.4e−04

CMCT central motor conduction time, *TST* triple stimulation technique

Table 5 Correlation coefficients and *p* values between lesion volume fractions and clinical scores

	EDSS	pyEDSS	MSWS12	9HPT	6MWT	25FTW
Spinal cord						
CST	$r = 0.25$ $p = 0.11$	**$r = 0.39$** **$p = 0.01$**	$r = 0.10$ $p = 0.52$	$r = 0.26$ $p = 0.09$	$r = -0.22$ $p = 0.15$	$r = 0.11$ $p = 0.50$
Whole spinal cord	**$r = 0.41$** **$p = 0.007$**	**$r = 0.34$** **$p = 0.02$**	$r = 0.26$ $p = 0.09$	$r = 0.20$ $p = 0.20$	$r = -0.16$ $p = 0.32$	$r = 0.16$ $p = 0.32$
Brain						
CST	$r = 0.08$ $p = 0.62$	$r = 0.16$ $p = 0.30$	$r = 0.01$ $p = 0.95$	$r = 0.18$ $p = 0.26$	$r = -0.05$ $p = 0.72$	$r = -0.06$ $p = 0.72$
Whole brain	$r = 0.004$ $p = 0.98$	$r = 0.09$ $p = 0.54$	$r = 0.08$ $p = 0.59$	$r = 0.08$ $p = 0.57$	$r = 0.07$ $p = 0.64$	$r = -0.03$ $p = 0.87$
Spinal cord + brain						
CST	$r = 0.24$ $p = 0.12$	**$r = 0.41$** **$p = 0.007$**	$r = 0.16$ $p = 0.32$	$r = 020$ $p = 0.20$	$r = -0.04$ $p = 0.79$	$r = 0.04$ $p = 0.79$
Whole	$r = 0.10$ $p = 0.50$	$r = 0.23$ $p = 0.14$	$r = 0.12$ $p = 0.46$	$r = 0.12$ $p = 0.43$	$r = -0.01$ $p = 0.93$	$r = -0.01$ $p = 0.93$

Significant results are indicated in bold

EDSS Expanded Disability Status Scale, *T25FW* Timed 25-Foot Walk Test, *9HPT* 9-Hole Peg Test, *6MWT* 6-Minute Walking Test, *MSW12* MS Walking Scale, *AMSQ* Arm Function in MS Questionnaire

Lateralized associations between MRI metrics and electrophysiology

Detailed correlations are provided in Table 6. CMCT was correlated with lesion fraction in the spine CST ($r=0.33$, $p=0.03$) and CNS ($r=0.49$, $p=0.04$). TST amplitude ratio and TST area were correlated with the lesion fraction in the brain CST ($r=-0.34$, $p=0.03$ and $r=-0.40$, $p=0.01$). Both these electrophysiological parameters were also associated with the lesion fraction in the brain + spine CST ($r=-0.39$, $p=0.01$ and $r=-0.48$, $p=0.002$). Detailed correlations between clinical metrics and electrophysiology are provided in Supplementary Table 5.

Discussion

The main contribution of our study was to perform a description of CST damage from the primary motor cortex to the low cervical cord, quantifying both focal lesion load and diffuse tissue damage, as well as in the brain and SC. Moreover, we precisely assessed the impact of CST structural damage on patients' motor functions, by combining clinical tests and electrophysiology. The main conclusions of this work are threefold.

First, CST focal lesions were frequent, concerning 42 of the 44 patients with early RRMS. This result is in line with the literature [5, 23] although previous studies only quantified brain CST lesion load. More importantly, we found that the lesion load was not homogeneously distributed along the CST. The T2 absolute lesion volume was about twice as high in the brain portion of the CST as in its SC portion. However, the volume of the cervical cord CST was also much lower than the volume of the brain CST. Thus, after normalization for each ROI volume, the focal damage proved to be far more pronounced in the SC portion of the CST than in the brain portion, indicating that the SC portion of the CST is vulnerable to lesions. Moreover, the lesion fractions in the SC CSTs were more closely correlated with pyramidal EDSS scores and CMCT than those in the brain CST, or even the brain + spine CST, emphasizing the highly functional aspect of the SC. We also found a close correlation between the SC CST lesion fraction and the whole cord lesion fraction. Owing to the small size of the spinal cord, a focal lesion is highly likely to impact the CST. Consequently, there was very little added value in specifically studying the CST lesion fraction compared with the whole SC lesion fraction in our study.

Second, we found evidence of differences in SC diffusion parameters between patients and controls, illustrating the presence of measurable focal as well as diffuse damage in the SC at the beginning of the disease. These results confirm a recent study where similar conclusions were reached using magnetization transfer ratio imaging [24]. By contrast, we did not observe any significant differences in brain WM diffusion parameters between patients and controls. Like the lack of correlation between the SC and brain lesion fractions, this result illustrates the value of not limiting damage analysis to the brain portion of the CNS to characterize patients' pathophysiological state. Previous studies [5, 6, 25] have reported evidence of patient-to-control differences on various diffusion parameters in brain WM, but these involved patients with more advanced disease (mean EDSS = 4, 2.8 and 1.5, compared with 0.8 in our population). When we specifically focused on the SC portion of the CST, we did not observe any significant differences in diffusion parameters between patients and controls. This result can probably partly be explained by the low resolution of our DTI spinal cord imaging ($2 \times 2 \times 2$ mm^3) resulting in a notable partial volume effect and more variable DTI measurements.

Third, despite the high occurrence of CST structural damage in our cohort, only 50% of patients had electrophysiologically measurable functional consequences, 38% had a pyramidal syndrome, and 5% had a motor deficit. This can probably be explained by the varying degrees of demyelination and axonal loss in focal MS lesions reported in

Table 6 Correlations between electrophysiological data and lesion fractions in spinal cord, brain and central nervous system

	Lesion fraction					
	Spinal cord		Brain		Brain + spinal cord	
	ALL	Lateralized CST	ALL	Lateralized CST	ALL	Lateralized CST
CMCT	$r=0.35$ $p=0.15$	**$r=0.33$** **$p=0.03$**	$r=0.29$ $p=0.23$	$r=-0.02$ $p=0.89$	**$r=0.49$** **$p=0.04$**	$r=0.21$ $p=0.20$
TST ratio	$r=-0.15$ $p=0.54$	$r=-0.23$ $p=0.15$	$r=-0.07$ $p=0.79$	**$r=-0.34$** **$p=0.03$**	$r=-0.07$ $p=0.80$	**$r=-0.39$** **$p=0.01$**
TST area	$r=-0.17$ $p=0.50$	$r=-0.25$ $p=0.12$	$r=-0.11$ $p=0.66$	**$r=-0.40$** **$p=0.01$**	$r=-0.12$ $p=0.63$	**$r=-0.48$** **$p=0.002$**

Significant values are indicated in bold

Lateralized CST corresponding functional corticospinal tract, *CMCT* central motor conduction time, *TST* triple stimulation technique

anatomopathological studies [26], leading to differing consequences in terms of conduction time or conduction block. In the present study, we used both CMCT [14], which reflects demyelination or loss of rapidly conducting corticospinal fibres, and the TST amplitude ratio, which reflects a conduction failure resulting from either central conduction block or axonal loss [15, 16]. Accordingly, the TST ratio abnormalities were associated with pyramidal signs, whereas no association was found with the CMCT. These results were in line with a previous study [13]. However, the correlations between lesion fractions in the CST and electrophysiological parameters are more difficult to interpret, as lesion fraction does not specifically reflect demyelination or axonal loss. It would be worthwhile carrying out a precise quantification of lesion severity using quantitative MRI techniques such as submillimetric axial MT imaging in future studies to better explain the link between MRI and electrophysiological parameters.

Limitations

First, our analysis did not include the thoracic segment of the SC. To date, the acquisition and postprocessing of thoracic SC images have proved more challenging than for the cervical portion [7]. Second, CST delineation is only an approximation, even using state-of-the-art techniques such as tractography for the brain and an atlas for SC [27]. Third, our sample consisted of 43 patients with early RRMS, and 16 controls for the brain and 19 for the SC acquisitions. This moderate sample size was nonetheless sufficient to highlight the stronger involvement of SC lesions in CST damage and motor function abnormalities, compared with brain lesions. Fourth, we only included patients with early RRMS in our study. Consequently, only two patients had a motor deficit, thus preventing us from evaluating the link between CST lesion load and clear motor disability. While this was beyond the scope of the present study, it would be worthwhile including patients with different MS phenotypes and more advanced disease in future studies. Moreover, our population consisted of patients who met criteria for disease severity (> 9 brain lesions and/or myelitis). Thus, we cannot exclude the possibility that these inclusion criteria introduced a bias toward an over-representation of focal SC lesions in our cohort. It will be important to reproduce these results in other cohorts.

Conclusions and perspectives

Our study described both the structural and functional involvement of the CST in the brain and cervical SC. Our results highlight the high frequency of focal CST damage even in the first few years of RRMS, as well as the major contribution of SC lesions to CST damage and motor function abnormalities. The link between early CST lesion volume fraction and subsequent motor disability will be evaluated in an ongoing longitudinal study.

Compliance with ethical standards

Conflicts of interest R Chouteau, B Combès, E Bannier, JC Ferré, G Edan, C Barillot, and A Kerbrat have nothing to disclose related to this study. R Chouteau received a scholarship from ARSEP.

Ethical standards The subjects included in the study were part of a multicenter longitudinal study (EMISEP; ClinicalTrials ID: NCT02117375) approved by the relevant institutional review.

Informed consent Written informed consent was obtained from all participants in compliance with ethical standards.

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