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Cervical cord area measurement using volumetric brain magnetic resonance imaging in multiple sclerosis

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Abstract
Background: In multiple sclerosis (MS), recent work suggests that cervical cord atrophy is more consistently correlated with physical disability than brain white matter lesion load and atrophy. Although spinal cord imaging has not been routinely obtained in many clinical trial and research studies, brain volumetric imaging usually has and includes the upper cervical cord.
Objectives: Using volumetric T1-weighted brain images, we investigated cross-sectional area measures in the uppermost cervical cord and compared them with areas at the standard C2/3 level.
Methods: Using T1-weighted brain scans from 13 controls and 37 people with MS, and an active surface technique, cross-sectional area was measured over 5 mm and 1 mm cord segments at C2/3, below the level of odontoid peg, and 2 cm and 2.5 cm below the pons. Brain volume was also measured.
Results: Cord area measurements were most reliable in a 5 mm segment 2.5 cm below the pons (inter-rater coefficient of variation 1.5%, intraclass correlation coefficient 0.99). Cord area at this level correlated more with that at C2/3 area than with brain volume (r=0.811 with C2/3, r=0.502 with brain volume).

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Conclusion: Whereas the standard C2/3 level is often not within the field of view on brain images, the level 2.5 cm below the pons usually is, and measurement at this level may be a good way to investigate upper cervical cord atrophy when only brain images are available.

1. Introduction

In people with multiple sclerosis (MS), combined clinical and MRI studies have shown that neurological disability cannot be explained by brain white matter (WM) lesions alone, and that brain and cervical cord atrophy both independently correlate with clinical impairments (Bonati et al., 2011; Cohen et al., 2012; Kearney et al., 2014a; Lukas et al., 2013). Further, throughout the clinical course of relapsing remitting (RR) and secondary progressive (SP) MS, cervical cord cross-sectional area at the C2/3 level appears to be more consistently and strongly associated with disability than either brain WM lesion load or brain atrophy (Bonati et al., 2011; Cohen et al., 2012; Kearney et al., 2014a; Lukas et al., 2013). Measurement of spinal cord cross-sectional area has developed using dedicated volumetric spinal cord MRI. Due to time and cost constraints, and in the absence of a compelling reason to measure cervical cord area, such scans have not been routinely collected in many research studies or therapeutic trials. However, cord atrophy remains an outcome measure of interest if monitoring pathological changes that contribute to irreversible motor disability or testing treatments that aim to prevent this.

Volumetric brain MRI scans are often obtained as part of research studies in MS, and these scans usually include the brainstem and the upper cervical cord. Recent work in people with traumatic cord injuries has shown that it is possible, using the method developed by Losseff et al. (1996), to obtain comparable C2/3 cord cross-sectional area measures from volumetric cord and brain imaging (Freund et al., 2010). However, while C2/3 is the usual landmark for cord area measures, less than half of routinely acquired brain images, in our experience, will include this level in the field of view. If measures representative of the cord could be robustly obtained at higher (rostral) levels, then this would increase the chances that brain volumetric imaging could be used for this purpose. Previous work employing a manual segmentation method has found that medulla oblongata volume is correlated with upper cervical cord volume (Pearson $r=0.67$) and brain parenchymal fractional volume ($r=0.45$); however these correlations did not significantly differ i.e. medulla oblongata volume was not significantly more representative of the cervical cord than the brain (Liptak et al., 2008). Cord area measures are also usually assessed over a 1.5 cm segment (Losseff et al., 1996; Kearney et al., 2014b), but the longer the segment used the smaller the chance it will have been included in brain imaging. Therefore, it would be of interest to know if shorter segments could be used.

The aims of this study were (1) to determine if a recently implemented active surface model (Horsfield et al., 2010) used to measure cord cross-sectional area at C2/3 could be reliably used at higher levels in short (0.5 cm and 0.1 cm) segments; and (2), if these measures were more representative of the spinal cord area obtained at the standard C2/3 level rather than the brain volume.

2. Materials and methods

2.1. Subjects

From a previously recruited cohort of 32 healthy controls and 89 people with MS (RRMS 45, SPMS 29, PPMS 15), 50 volumetric brain scans included the C2/3 level. These data, from 13 healthy controls (mean age 40.5 (standard deviation (SD) 14.1) years, and 9 females) and 37 people with MS (mean age 48.8 (10.1) years, 26 females, 17 RRMS, 15 SPMS and 5 PPMS), were used in this study. In the MS cohort the median expanded disability status scale (EDSS (Kurtzke, 1983)) was 6.0, range 1.0–8.5. As part of MS functional composite score assessments (Cutter et al., 1999), Timed Walk Test (TWT) and 9 Hole Peg Test (HPT) scores were obtained, and z-scores calculated as per Fischer et al. (2001). This study was approved by our local ethics committee. Written informed consent was obtained from participants.

2.2. MRI protocol

A *T*1-weighted (*T*1w) brain volume scan was acquired with a 3 T Philips Achieva system (Philips Healthcare, Best, The Netherlands) using a 32-channel head coil and multi-transmit technology. The sequence used was a 3D inversion-prepared (TI=824 ms) fast field echo (FFE) sequence (TR/TE=6.9/3.1 ms), flip angle (α)=8°, $1\times1\times1$ mm^3. This was acquired per our routine for brain imaging, and not specifically modified to include the spinal cord.

2.3. Selection of cord levels for area measurement

We measured cord area at four levels. Landmarks were identified on sagittal reconstructions of the *T*1w brain scan. The first was centred on the conventional C2/3 disc landmark, the middle of the anterior border of the disc. The second started at the top of odontoid peg (OP), the highest cervical bony landmark that we could identify, and extended caudally. As the spinal cord can move significantly relative to surrounding bony structures with head flexion or extension (Reid, 1996), we also used the inferior margin of pons as a rostral marker. The average length of medulla oblongata is about 2.5 cm (Gilman and Newman, 1996), but the boundary between it and the spinal cord is indistinct, so we measured cord cross sectional area caudally from 2 cm to 2.5 cm below the inferior margin of pons (labeled P2 and P2.5).

2.4. Image analysis

Mean cervical cord cross-sectional area was measured on 5 contiguous 1 mm thick slices and in the single slice nearest to the reference landmark (for C2/3 it was the middle slice, and for all other measures, the most rostral one). The volumetric *T*1w brain images were reorientated so that axial slices orthogonal to the cord could be extracted. For the C2/3 cord area measures, the *T*1w brain images were reoriented at the middle level of C2/3 intervertebral disc. For the cord area measures of the OP, P2 and P2.5 levels, the *T*1w brain images were reoriented at the level of the inferior margin of pons. Five $1 \times 1 \times 1\,mm^3$ axial slices perpendicular to the long axis of the cord were extracted using the multi-planar reconstruction tool in JIM (version 6, Xinapse Systems) at the OP, P2 and P2.5 levels separately. Using the cord finder tool in JIM, which implements an active surface model (Horsfield et al., 2010), seed points were manually placed in the centre of the cord, and the cord was then automatically contoured. These contours were reviewed for accuracy, and when necessary manually edited. Fig. 1 shows examples of P2.5 and C2/3 sagittal and coronal cord images after reorientation, and the first axial cord section.

2.5. Reproducibility

Intra- and inter-rater reproducibilities were assessed using MRI data from 5 healthy controls and 5 MS patients who were selected randomly from the study population. To evaluate the intra-rater reproducibility, one investigator (ZL) performed the measurement three times in each subject. Inter-rater reproducibility was assessed between three investigators (ZL, OY and MP), who independently measured cord area once at each level in each of the 10 subjects.

2.6. Associations between cord area measures at different levels and brain volumes

To determine if OP, P2, P2.5 cord area measures were more closely linked with cord area measure at the conventional C2/3 level than brain tissue volumes, brain tissue volumes were obtained using the new segment tool in SPM8 after white matter lesion filling (Chard et al., 2010). Brain parenchymal (the sum of white and grey matter; BPV) and intracranial (the sum of white matter, grey matter and cerebrospinal fluid; ICV) volumes were estimated.

2.7. Statistics

Statistics were undertaken using SPSS (version 21, IBM). With the reliability data, coefficients of variation (CV; calculated as the square root of the mean intra-subject measurement variation divided by the mean cross-sectional area in all subjects) and intraclass correlation coefficients (ICC; calculated using restricted estimate of maximum likelihood variance components) were computed. To determine if the area measurements at the level of the OP, P2 and P2.5 were more closely related to those at C2/3 or

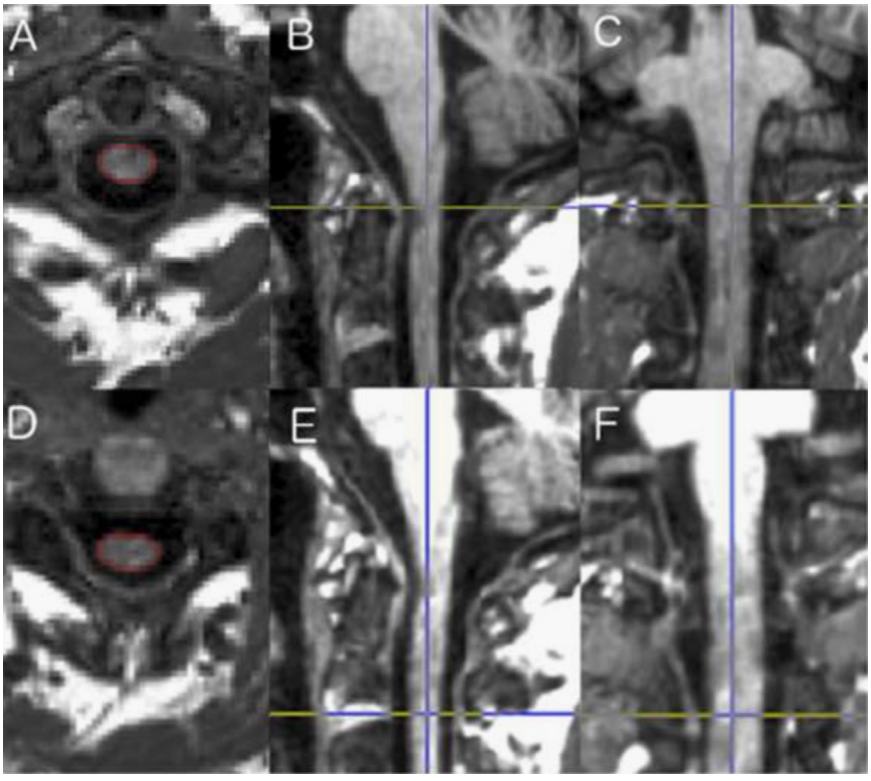

Fig. 1 Example of reconstructed cord images in a person with MS. A and D show an axial slice extracted using the P2.5 and C2/3 landmarks, with the cord outlined. B and C show reconstructed sagittal and coronal views using P2.5 landmark; E and F show these for the C2/3 landmark in a same person.

Table 1 Reproducibility figures for each of the 4 cord levels measured in five slices (1a) and one slice (1b) by one investigator on three occasions (intra-rater reproducibility), and in five slices by three investigators (inter-rater reproducibility).

1a

Cord level	Coefficient of variation		Intraclass correlation coefficient	
	5 slices, 1 rater	5 slices, 3 raters	5 slices, 1 rater	5 slices, 3 raters
C2/3	1.3%	2.3%	0.99	0.97
OP	8.8%	14.6%	0.65	0.24
P2	4.2%	3.7%	0.93	0.95
P2.5	2.3%	1.5%	0.95	0.99

1b

Cord level	Coefficient of variation		Intraclass correlation coefficient	
	1 slice, 1 rater	1 slice, 3 raters	1 slice, 1 rater	1 slice, 3 rater
C2/3	3.2%	4.0%	0.94	0.89
OP	8.1%	19.7%	0.59	0.07
P2	3.9%	11.4%	0.94	0.64
P2.5	1.9%	6.0%	0.97	0.79

OP=odontoid peg; P2 and P2.5=caudally 2 cm and 2.5 cm below the inferior margin of pons.

Table 2 Brain and spinal cord MRI measures (mean $\pm$ standard deviation).

Group	Cord cross sectional area (mm^2)				Tissue volume (ml)	
	C2/3	OP	P2	P2.5	ICV	BPV
Control	74.8 $\pm$ 8.9	96.6 $\pm$ 12.3	95.6 $\pm$ 15.8	83.7 $\pm$ 10.9	1430 $\pm$ 139	1188 $\pm$ 101
RRMS	67.1 $\pm$ 10.8	83.2 $\pm$ 23.1	90.3 $\pm$ 15.2	79.3 $\pm$ 13.1	1399 $\pm$ 137	1144 $\pm$ 117
SPMS	59.5 $\pm$ 13.3	76.2 $\pm$ 14.0	74.2 $\pm$ 18.9	70.4 $\pm$ 10.4	1386 $\pm$ 136	1074 $\pm$ 104
PPMS	63.7 $\pm$ 5.9	79.2 $\pm$ 12.1	90.2 $\pm$ 19.4	76.3 $\pm$ 12.1	1411 $\pm$ 139	1141 $\pm$ 111

OP=odontoid peg; P2 and P2.5=caudally 2 cm and 2.5 cm below the inferior margin of pons; BPV=brain parenchymal volume; ICV=intracranial volume; RRMS=relapsing remitting multiple sclerosis; SPMS=secondary progressive MS; PPMS=primary progressive MS.

Table 3 Pearson correlations and associated *P*-values between cord area (based on five slices in 3a and one slice in 3b) and cranial volume measures in 37 people with multiple sclerosis and 13 healthy controls.

Measure	C2/3	OP	P2	P2.5	BPV
3a					
OP	0.741, $<$0.001				
P2	0.731, $<$0.001	0.737, $<$0.001			
P2.5	0.811, $<$0.001	0.801, $<$0.001	0.939, $<$0.001		
BPV	0.408, 0.003	0.427, 0.002	0.431, 0.002	0.502, $<$0.001	
ICV	0.318, 0.024	0.286, 0.044	0.366, 0.009	0.408, 0.003	0.951, $<$0.001
3b					
OP	0.775, $<$0.001				
P2	0.741, $<$0.001	0.793, $<$0.001			
P2.5	0.840, $<$0.001	0.846, $<$0.001	0.921, $<$0.001		
BPV	0.415, 0.003	0.457, 0.002	0.434, 0.002	0.474, $<$0.001	
ICV	0.326, 0.024	0.321, 0.044	0.362, 0.009	0.378, 0.003	0.951, $<$0.001

Note: OP=odontoid peg; P2 and P2.5=cross-sectional cord area caudally from 2 cm and 2.5 cm below the inferior margin of pons; BPV=Brain parenchymal volume; ICV=Intracranial volume.

brain tissue volumes, Pearson correlations were calculated, and linear regression modeling with the area measure of interest as the dependent variable, and BPV and C2/3 mean area as predictor variables. Associations between EDSS, TWT and HPT *z*-scores, and spinal cord areas were assessed using Spearman correlations.

3. Results

Of the 10 subjects included in the reliability study, at C2/3 20 of the 150 cord contours were manually edited (14 of these in a single subject with marked kyphosis), for OP, P2 and P2.5 none required editing. The measure at P2.5 and C2/3 was more reproducible than that at other levels, in terms of higher ICC and lower CV (Table 1). Table 2 shows the measurement results of the interest levels of spinal cord and brain of all subjects. Table 3 shows the Pearson correlations between the cord area and brain volume measures.

In the regression models using the five slice cord area data, only C2/3 reached significance predicting OP area (partial Eta=0.47, $P<0.001$, model $R^2=0.57$) and P2 area (partial Eta=0.45, $P<0.001$, $R^2=0.56$). For P2.5 area both C2/3 (partial Eta=0.59, $P<0.001$) and BPV (partial Eta=0.10, $P=0.024$)) were significant (total model $R^2=0.69$). Repeating these analyses using cord area determined with a single slice did not materially differ, except for P2.5 where BPV was no longer a significant factor.

Table 4 shows the Spearman correlations between cord area measures, HPT and TWT *z*-scores. In the combined control and MS groups, and MS group alone, significant correlations of spinal cord measures with 9HPT and TWT *z*-scores were observed, except for 9HPT *z*-scores with cord area at P2 in the MS group, where it was of borderline significance. Correlations with EDSS were only significant in the combined control and MS group (C2/3 $r_s=-0.30$, $P=0.032$; OP $r_s=-0.40$, $P=0.004$; P2 $r_s=-0.29$, $P=0.043$, and P2.5 $r_s=-0.34$, $P=0.015$).

Table 4 Correlation between MSFC and MRI parameters from five cord slices (4a) and one cord slice (4b).

	MS and control group				MS group			
	TWT		9HPT		TWT		9HPT	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
4a								
P2	0.46	0.001	0.31	0.029	0.46	0.004	0.34	0.041
P2.5	0.44	0.002	0.30	0.037	0.47	0.004	0.33	0.049
OP	0.51	<0.001	0.41	0.003	0.51	0.001	0.38	0.020
C2/3	0.46	0.001	0.40	0.004	0.44	0.006	0.38	0.021
4b								
P2	0.44	0.001	0.28	0.045	0.46	0.004	0.32	0.053
P2.5	0.44	0.001	0.33	0.018	0.48	0.003	0.39	0.018
OP	0.50	<0.001	0.38	0.006	0.52	0.001	0.39	0.018
C2/3	0.44	0.001	0.38	0.006	0.42	0.010	0.36	0.029

4. Discussion

In people with MS, cervical cord area is usually measured using dedicated spinal cord volumetric imaging at the C2/3 level. In this study we investigated the possibility of using volumetric brain MRI scans for cervical cord area measurements, and whether or not measures from short segments at levels higher than C2/3 were reliable and still representative of cord area at C2/3. We found that reliability measures at P2.5 and C2/3 were comparable with a previous study using volumetric brain images to measure cord area over a 1.5 cm cord segment (Freund et al., 2010) (in which CVs of 1.6–1.7% were found, compared with 1.5–2.3% for P2.5 over a 0.5 cm segment and 1.9–5.2% or a single 1 mm slice, and 1.3–3.2% and 3.2–6.0% respectively for C2/3 in the present work). ICC at these levels were also high, ranging between 0.94 and 0.99), indicating that nearly all measurement variabilities were due to inter-subject differences rather than measurement errors. These figures are similar to those previously obtained in the medulla oblongata by Liptak et al. (intra-rater ICC 0.97) (Liptak et al., 2008). Compared with cord area measures over 0.5 cm segments, measurement reproducibility in 1 mm segments was similar when a single rater undertook the analysis, but noticeably lowers when three raters analyzed the MRI data.

Comparing the average cord area measure at C2/3 obtained with the method used in this study with the literature values, they were similar (for example, 68.6 ± 12.3 mm^2 for RRMS patients in a study by Kearney et al. and 67.1 ± 10.8 in the present work) (Kearney et al., 2014a). Also consistent with the previous literature, cord area measures at C2/3 correlated with measures of limb function impairment (TWT, HPT and, to a lesser degree, EDSS) (for example Horsfield et al. 2010), and similar correlation were seen at all the cord levels assessed and with area measures over 5 mm or 1 mm of the cord.

For cord areas measures using the OP landmark, both inter-rater and intra-rater reproducibilities were substantially worse than those at other levels. There are two likely explanations for this. First, it is difficult to precisely locate the top of the OP on *T*1-weighted volumetric scans, and this will limit reliability. Second, the cord can move substantially relative to this bony landmark, with head flexion or extension (Reid 1996), and we found that OP level could be higher than P2 or lower than P2.5, or somewhere between them.

Correlation analyses showed that for all the area measures above C2/3 there was a strong association with cord area at C2/3 and a much more modest one with brain parenchymal volume. Regression analyses confirmed this, demonstrating that for P2 and OP measures, only C2/3 area was a significant predictor, and for P2.5 C2/3 predicted much more variation than BPV (partial Eta for C2/3 0.59 and BPV 0.10). Together this suggests that short-segment high cervical cord measures are much more representative of cord area at C2/3 than brain volume.

The method proposed in this work was not designed as a replacement for volumetric analysis of dedicated cord imaging, with measures based on high-resolution cervical images achieving intra-rater CVs of 0.002% over a 1.5 cm cord sample (Kearney et al., 2014b). Instead, it was developed with the application to previously collected MRI data in mind, or in circumstance where it may not be possible to obtain separate cervical cord scans due to time and cost constraints. Future work could look at optimising brain imaging to improve cervical cord coverage without compromising brain atrophy measures.

For example, while we did not see reduced cord signal intensity towards the edge of the imaging field of view on the scans used in this study, this may be more noticeable on brain scans acquired using different machines or with different techniques. Similarly, in this study subject positioning did not take account of the cord, and we found that we had to edit cord contours most in a person with a marked kyphosis. As such, when acquiring brain scans with the possibility of undertaking cord area measures in mind, it may be worthwhile trying to ensure that neck flexion is minimised as far as possible, and the neck immobilised (Kearney et al., 2013). There may also be further scope to improve the cord area measurement technique for use in high cervical spine and medulla oblongata.

In conclusion, we have shown that it is possible to extract from brain images short segment (5 mm or 1 mm) cross-sectional cord area measurements above the conventional C2/3 level that are comparable, in terms of both reproducibility and correlations with disability, with established techniques for measuring cord cross-sectional area in clinical studies. This may be of particular interest in longitudinal studies or treatment trials where cord area may not have been included as an original outcome measure but would be of interest now.

Conflicts of interest

Professor Miller has received honoraria through payments to his employer, UCL Institute of Neurology, for Advisory Committee and/or Consultancy advice in multiple sclerosis studies from Biogen Idec, GlaxoSmithKline, Novartis, Merck, Chugai, Mitsubishi Pharma Europe and Bayer Schering Pharma. He also received compensation through payments to his employer for performing central MRI analysis of multiple sclerosis trials from GlaxoSmithKline, Biogen Idec, Novartis and Merck. The NMR Research Unit at UCL Institute of Neurology is supported by the UK MS Society and UCL-UCLH Biomedical Research Centre. Dr Chard has received honoraria through his employer from Bayer, Teva and the Serono Symposia International Foundation for faculty-led education work, Teva for advisory board work, and holds stock in GlaxoSmithKline. Dr Yaldizli received honoraria for lectures from Teva and Bayer Schering exclusively used for funding of research or educational courses at University Hospital Basel. The other authors report no conflicts of interest.

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References

Bonati U, Fisniku LK, Altmann DR, Yiannakas MC, Furby J, Thompson AJ, et al. Cervical cord and brain grey matter atrophy independently associate with long-term MS disability. J Neurol Neurosurg Psychiatry 2011;82:471–2.

Chard DT, Jackson JS, Miller DH, Wheeler-Kingshott CAM. Reducing the impact of white matter lesions on automated measures of brain gray and white matter volumes. J Magn Reson Imaging 2010;32:223–8.

Cohen AB, Neema M, Arora A, Dell'Oglio E, Benedict RHB, Tauhid S, et al. The relationships among MRI-defined spinal cord involvement, brain involvement, and disability in multiple sclerosis. J Neuroimaging 2012;22:122–8.

Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999;122(5):871–82.

Fischer JS, Jak A, Knicker J, Rudick RA. MSFC Manual and Forms: Guidebook.National Multiple Sclerosis Society; 1–44. (pdf).

Freund PA, Dalton C, Wheeler-Kingshott CA, Glensman J, Bradbury D, Thompson AJ, et al. Method for simultaneous voxel-based morphometry of the brain and cervical spinal cord area measurements using 3D-MDEFT. J Magn Reson Imaging 2010;32:1242–7.

Gilman S, Newman SW. Anatomy of the brain stem: medulla, pons, and midbrain. In: Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology, 9th edition. Philadelphia, Davis, 1996, p. 91.

Horsfield MA, Sala S, Neema M, Absinta M, Bakshi A, Sormani MP, et al. Rapid semi-automatic segmentation of the spinal cord from magnetic resonance images: application in multiple sclerosis. NeuroImage 2010;50:446–55.

Kearney H, Miszkiel KA, Yiannakas MC, Ciccarelli O, Miller DH. A pilot MRI study of white and grey matter involvement by multiple sclerosis spinal cord lesions. Mult Scler Relat Disord 2013;2:103–8.

Kearney H, Rocca M, Valsasina P, Balk L, Sastre-Garriga J, Reinhardt J, et al. Magnetic resonance imaging correlates of physical disability in relapse onset multiple sclerosis of long disease duration. Mult Scler 2014a;20:72–80.

Kearney H, Yiannakas MC, Abdel-Aziz K, Wheeler-Kingshott CAM, Altmann DR, Ciccarelli O, et al. Improved MRI quantification of spinal cord atrophy in multiple sclerosis. J Magn Reson Imaging 2014;39:617–23.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–52.

Liptak Z, Berger AM, Sampat MP, Charil A, Felsovalyi O, Healy BC, et al. Medulla oblongata volume: a biomarker of spinal cord damage and disability in multiple sclerosis. AJNR Am J Neuroradiol 2008;29:1465–70.

Losseff NA, Webb SL, O'Riordan JI, Page R, Wang L, Barker GJ, et al. Spinal cord atrophy and disability in multiple sclerosis. A new reproducible and sensitive MRI method with potential to monitor disease progression. Brain 1996;119:701–8.

Lukas C, Sombekke MH, Bellenberg B, Hahn HK, Popescu V, Bendfeldt K, et al. Relevance of spinal cord abnormalities to clinical disability in multiple sclerosis: MR imaging findings in a large cohort of patients. Radiology 2013;269:542–52.

Reid JD. Effects of flexion–extension movements of the head and spine upon the spinal cord and nerve roots. J Neurol Neurosurg Psychiatry 1996;23:214–21.