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Spinal Cord Normalization in Multiple Sclerosis

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Abstract

Background—Spinal cord(SC) pathology is common in multiple sclerosis(MS), and measures of SC-atrophy are increasingly utilized. Normalization reduces biological variation of structural measurements unrelated to disease, but optimal parameters for SC volume(SCV)-normalization remain unclear. Using a variety of normalization factors and clinical measures, we assessed the

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effect of SCV-normalization on detecting group differences and clarifying clinical-radiological correlations in MS.

Methods—3T cervical SC-MRI was performed in 133 MS cases and 11 healthy controls(HC). Clinical assessment included:expanded disability status scale(EDSS), MS functional composite(MSFC), quantitative hip-flexion strength(“strength”), and vibration sensation threshold(“vibration”). SCV between C3-C4 was measured and normalized individually by:subject height, SC-length, and intracranial volume(ICV).

Results—There were group differences in raw-SCV and after normalization by height and length(MS vs. HC; progressive vs. relapsing MS-subtypes, $p<0.05$). There were correlations between clinical measures and raw-SCV(EDSS: $r=-0.20$; MSFC: $r=0.16$; strength: $r=0.35$; vibration: $r=-0.19$). Correlations consistently strengthened with normalization by length(EDSS: $r=-0.43$; MSFC: $r=0.33$; strength: $r=0.38$; vibration: $r=-0.40$) and height(EDSS: $r=-0.26$; MSFC: $r=0.28$; strength: $r=0.22$; vibration: $r=-0.29$), but diminished with normalization by ICV(EDSS: $r=-0.23$; MSFC: $r=-0.10$; strength: $r=0.23$; vibration: $r=-0.35$). In relapsing MS, normalization by length allowed statistical detection of correlations that were not apparent with raw-SCV.

Conclusions—SCV-normalization by length improves the ability to detect group differences, strengthens clinical-radiological correlations, and is particularly relevant in settings of subtle disease-related SC-atrophy in MS. SCV-normalization by length may enhance the clinical utility of measures of SC-atrophy.

Keywords

multiple sclerosis; MRI; spinal cord; atrophy; normalization

Background and Purpose

Spinal cord (SC) pathology is common in multiple sclerosis (MS), and the importance of utilizing SC-based MRI measures in clinical investigation is increasingly recognized.^{1,2} An important unresolved issue is the optimal normalization factor for SC atrophy measures in cross-sectional studies. Normalization reduces the biological variation of structural measurements unrelated to disease effects; in the brain, this is typically accomplished by measuring intracranial volume (ICV).^{3,4} Elimination of variation unrelated to MS maximizes the statistical power to detect group differences, enabling more effective assessment of differences between MS cases and healthy control subjects (HC).

Prior studies have assessed a variety of normalization factors for SC volume (SCV), including ICV,^{5–7} thecal-sac volume,⁸ and SC length (yielding average cross-sectional area).⁹ These studies in relatively small cohorts have resulted in differing conclusions regarding appropriate normalization factors. One compared raw cervical SCV to normalization by thecal-sac and ICV, concluding that raw SCV showed the largest group differences and the strongest correlations with EDSS.¹⁰ Another study found normalization provided only limited improvement over raw SCV, but among the factors assessed (which included ICV, SC length, body surface area, and body-mass index), normalization by length best accentuated group differences and improved clinical-radiological correlations.⁹

The aim of our study was to assess the effect of cervical SC normalization by three different factors (subject height, ICV, and SC length) on the detection of group differences and clarification of clinical-radiological correlations in MS. To expand on existing work, we assessed a relatively large MS cohort (n=133) with adequate representation from both progressive and relapsing MS, enabling a thorough evaluation of normalization effects across the MS spectrum. Furthermore, to better assess clinical-radiological correlations, we utilized a variety of global and system-specific clinical measures, relevant to SC function, including EDSS, vibration sensation threshold, motor strength, and MSFC. We hypothesized that normalization by appropriate factors would result in improved detection of group differences between MS and HC, and among MS subtypes, and would also clarify clinical-radiological correlations.

Methods

Study Participants

This study was approved by the institutional review board; all participants provided informed consent.

The study sample consisted of individuals with clinically-isolated syndrome, relapsing-remitting MS, secondary-progressive MS, primary-progressive MS, and HC (Table 1). To perform comparative analyses between high and low inflammatory MS, patients with clinically-isolated syndrome and relapsing-remitting MS were together categorized as “relapsing” and those with secondary-progressive and primary-progressive MS as “progressive.” MS cases were recruited from the MS clinic by convenience sampling. Diagnosis was confirmed by the treating neurologist, according to 2010 criteria.¹¹ EDSS was determined by a Neurostatus-certified examiner within 30 days of MRI. Hip strength and vibration sensation thresholds were measured within 2 weeks of MRI. Medical records were reviewed to determine disease duration and treatment status. MS cases scanned within 3 months after a clinical relapse were excluded. HC were recruited from the community. Subject heights were self-reported.

Magnetic Resonance Imaging

Cervical SC MRI was performed on all participants using a 3T Philips scanner with body-coil excitation and two-element surface-coil reception. Axial images were acquired using a 3D gradient-echo sequence with multishot echo-planar readout (3 lines-per-shot) with parallel imaging factor of 2 (TR/TE/flip angle=121ms/12.5ms/9°). The scan yielded 30 contiguous 3mm slices between C2 and C6, with nominal in-plane resolution 0.6×0.6mm. An automated, reproducible segmentation protocol delineated SC cross-sectional area between C3 and C4 (Figure 1).¹² These segments were defined based on identification of intervertebral disc spaces, and chosen for analysis as the images were least degraded by motion artifact. Full details of the automated segmentation protocol are provided elsewhere. Briefly, this is a fully automated spinal cord segmentation algorithm that combines deformable registration with topology preserving intensity classification using a topological atlas that is appropriate for the spinal cord, and a statistical atlas that is dynamically adjusted to match its variability. To ensure accuracy of automated segmentation, results in 20

subjects were compared with manual segmentation, yielding a Dice coefficient of 0.92, suggesting high reliability. For inter-rater agreement of manual segmentation, the Dice coefficient was 0.93. Nonetheless, all regions-of-interest generated using automated segmentation were manually inspected, and corrected if necessary. SC length was measured between segments C3 and C4 (number of slices spanning C3-C4 multiplied by slice thickness). Although we chose to calculate SCV over the same anatomic portion of the SC in each subject (C3-C4), an alternative would have been to determine the SCV in a fixed number of slices at a particular landmark. The use of either method would have resulted in equivalent conclusions.

DTI images of the brain were also acquired with 2.2mm isotropic voxels and TE=69 ms; TR=shortest; 70 slices; parallel imaging factor=2.5; 32 diffusion directions (“overplus high” scheme); $b_0 \sim 33 \text{ s/mm}^2$; $b=700 \text{ s/mm}^2$; repetitions=2. These images were used to calculate supratentorial brain and cerebrospinal fluid volumes, as described previously.¹³ For this dataset, DTI-based brain volume segmentation had lower scan-to-scan variability than alternate T1-based methods, including SIENAX and lesion-TOADS.¹⁴ ICV was calculated as the sum of brain and cerebrospinal fluid volume.

Quantitative Clinical Measures

Vibration sensation threshold of the right great toe was quantified using Vibratron II (Physitemp, Huron, NJ). For strength, we averaged two maximal hip flexion efforts at the right hip using a Microfet2 handheld dynamometer. Both devices have been described in detail and validated for use in MS to reliably detect and quantify sensorimotor dysfunction.¹⁵

Statistical Analysis

Statistical calculations were performed using STATA Version 11 (StataCorp, College Station, TX). Multivariable linear regression was used to compare group outcomes adjusted for age. Spearman’s rank method assessed correlations between outcomes and clinical measures. Statistical significance was set at $p < 0.05$, and due to the exploratory nature of this study, there was no adjustment for multiple comparisons.

Proportional normalization was performed by dividing raw SCV by the normalization factor of interest. Residual normalization was performed by including the normalization factor of interest as a covariate in the multivariable regression models. Normalization factors were selected based on existing literature and the identification of moderate correlations between each factor and SCV. Likelihood ratio tests of nested models assessed the value of multiple normalization factors in detecting group differences and improving clinical correlations.

Results

This study included 133 MS cases (4 clinically-isolated syndrome, 74 relapsing-remitting, 36 secondary-progressive, 19 primary-progressive; 78 “relapsing”, 55 “progressive”) and 11 HC. MS cases were predominantly women (65%) and had a mean age of 44 years. Average disease duration was 10 years, and 67% of patients were on disease-modifying therapies (interferon- β : 40%, glatiramer acetate: 30%, natalizumab: 25%, other medications: 5%).

Relapsing cases were younger, had shorter disease durations, and were less disabled than progressive cases (Table 1).

Raw SCVs, without normalization, demonstrated moderate correlations with all normalization factors ($r=0.39$ with subject height, $r=0.55$ with SC length, $r=0.40$ with ICV). In age-adjusted comparisons of MS vs. HC, raw SCV and normalizations by height and length, but not by ICV, were significantly different between MS and HC. SCV normalized by height and length, but not raw SCV or normalization by ICV, showed differences between relapsing and progressive MS (Tables 2a). In age-adjusted group comparisons of primary-progressive MS vs. HC and primary-progressive vs. secondary-progressive MS, normalization by length or height showed differences ($p<0.05$), but raw SCV did not ($p>0.10$).

Age-adjusted group comparisons were performed utilizing both proportional and residual normalization, yielding similar results (Tables 2a and 2b). To facilitate interpretation, the proportional method was used for clinical-radiological correlation analyses (Tables 3a, 3b, 3c and Figures 2a and 2b). Overall, normalization by length consistently increased the strength of the correlations (Table 3a). Normalization by height generally increased, whereas normalization by ICV was erratic, increasing correlations with EDSS and vibration, but decreasing correlations with MSFC and strength. There were no correlations with raw SCV in relapsing MS, but normalization by length suggested correlations with EDSS, strength, and vibration (Table 3b). In progressive MS, raw SCV and normalization by length demonstrated robust correlations, whereas normalization by height and ICV diminished these correlations (Table 3c). Residual normalization (Table 4) by length also yielded increased correlations, but normalization by ICV diminished correlations with MSFC and strength.

Finally, additional normalization to ICV after normalization by length slightly accentuated differences between MS and HC ($p<0.01$ for likelihood-ratio test) and between relapsing and progressive MS ($p<0.01$). On the other hand, in the assessment of clinical-radiological relationships, additional normalization by ICV contributed only to the vibration model ($p<0.01$) but not to the other clinical measures, including EDSS, MSFC, and strength ($p>0.10$).

Discussion

We assessed the effect of cervical SCV normalization by a number of factors on the ability to detect group differences, and to strengthen clinical-radiological correlations using a spectrum of clinical measures, in MS. We found that normalization by SC length – essentially, resulting in a measurement of mean cross-sectional area – was consistently the best strategy to accentuate group differences between MS and HC, and among MS subtypes, and to strengthen clinical-radiological correlations. Normalization appears to be particularly relevant in settings where there is subtle disease-related SC atrophy.

Our findings are in keeping with a recent study that found normalization by length to most robustly accentuate group differences and strengthen clinical-radiological correlations.⁹ As

in this prior study, which also assessed normalization by body-mass index and body surface area, we included a variable related to subject size (specifically, height) as a normalization factor, as the SC is generally longer in taller people. Although height performed relatively well as a normalization factor in our analyses, SC length more consistently accentuated group differences and clinical-radiological correlations. However, in settings where it is difficult or time-consuming to obtain SC length, subject height would nonetheless be a useful normalization factor. Interestingly, in contrast to this prior study that found normalization by length resulted in only a small improvement over raw SCV, we found that normalization by length substantially improved our ability to detect group differences and magnify clinical correlations. This difference may result from the nearly fourfold larger sample size in the current study (133 vs. 34 MS cases). As our study patients did not routinely undergo lumbar MRI, we were unable to normalize by the lumbar-enlargement area, which performed relatively well in another study.⁸ Of note, any comparisons between our results and those from prior studies must be made taking into account methodological differences.

As seen in prior studies, normalization by ICV was generally of limited utility.^{9,10} This observation underscores the importance of utilizing relevant and appropriate factors, since normalization by irrelevant factors such as ICV can paradoxically hinder the ability to detect group differences and clinical-radiological correlations. Interestingly, normalization by ICV consistently increased clinical correlations with vibration, in contrast to all other clinical measures. Furthermore, additional normalization by ICV, after normalization by length, contributed to explaining variance in vibration, but not any of the other clinical measures. These findings suggest that vibration may be uniquely correlated with ICV, such that individuals with larger heads have higher vibration sensation thresholds, perhaps due to the increased length of sensory fibers in the dorsal columns.

Our relatively large sample size allowed more detailed assessment of normalization effects by MS subtype and showed that normalization by SC length and subject height accentuated group differences. Normalization by length most increased the magnitude of clinical-radiological correlations in relapsing MS, where the correlation was not apparent with raw SCV but only emerged with normalization by length (EDSS, strength, vibration). In progressive MS, raw SCV and SCV normalized by length demonstrated robust correlations, whereas normalization by height and ICV actually diminished correlations. This observation expands on a prior study in RR that found a relationship between SCV and EDSS only after normalization by lumbar-enlargement area.⁸ Taken together, these findings suggest that normalization is particularly relevant for identifying subtle differences (which is the case when comparing MS subtypes) and clinical correlations in cases where there is less intrinsic SC damage (especially relapsing MS). This is also a highly pertinent issue in longitudinal studies where subtle changes in SC measurements and their relation to disability progression are important to identify.

In this study, we comprehensively assessed clinical-radiological correlations using a variety of clinical measures, including two quantitative measures that are highly relevant in the SC (motor strength and vibration sensation threshold) as well as two measures of global disability (EDSS and MSFC). Although EDSS is a global measure, it is heavily weighted

towards ambulatory function,¹⁶ while MSFC is a more multidimensional measure of disability, since it includes measures of lower-limb function (25-foot timed walk), upper-limb function (9-hole peg test), and cognition (paced auditory serial addition test).¹⁷ As expected, with both raw and normalized SCV, we consistently observed stronger correlations with strength, vibration, and EDSS in comparison to MSFC, likely a reflection of the specificity of structure-function relationships in the SC. Regardless of the clinical measure, we found that normalization by SC length consistently accentuated the observed correlations, whereas ICV generally diminished correlations. These observations further support the notion that only relevant normalization factors should be applied to identify clinical-radiological correlations.

Prior studies compared the residual and proportional methods of normalization in the brain, with each method harboring different relative strengths and weaknesses.¹⁸ In order to ensure the stability of our observations, we compared normalization using both methods, finding no substantial differences. Therefore, for ease of interpretation, we preferentially utilized the proportional method to assess clinical-radiological correlations.

In keeping with a prior study,⁹ we found that normalization by multiple factors simultaneously (SC length and ICV) diminished the ability to detect clinical correlations. Although there was suggestion of an improvement in the detection of group differences with normalization by both length and ICV, after taking into account the lack of an improvement in detecting clinical correlations, we believe that the use of multiple normalization factors simultaneously are generally not useful.

There are a number of limitations to this study. First, since there was no “gold standard” against which we could compare normalized volumes, we utilized the combination of accentuation of group differences and strengthening of clinical-radiological correlations to indicate an appropriate normalization factor. Taking into account pathological and imaging literature demonstrating group differences and clinical correlations with SCV in MS,^{19–21} this approach seems reasonable. Second, we measured the volume of a limited segment of the cervical SC (C3-C4), as this was the segment with the best image quality. We therefore did not perform the same analyses utilizing the entire cervical SC; however, as demonstrated in a previous study,⁹ it is unlikely that including a larger portion of the cervical SC would have changed our general conclusions. It is worth noting that the portion of the SC we analyzed is typically accessible for volumetric measurement using head coils, and could thus be easily combined with routine imaging of the brain. Finally, subject height was self-reported, making information bias a potential issue. However, self-reported height is generally reported with a systematic tendency towards overestimation. If most study participants overestimated their height to a similar extent, such a bias would not change the magnitude of the group differences or correlations observed.^{22,23}

In conclusion, using a number of normalization factors and clinical measures, normalization of SCV by SC length – essentially, measuring the average cross-sectional area – consistently improves the ability to detect group differences and clinical-radiological correlations in MS. This is particularly important in settings where subtle differences in SC atrophy need to be

detected. If substantiated in larger, prospective studies, these findings have important implications for the use of SC measurements in both clinical practice and trial settings.

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Figure 1.
(a) Axial section of cervical spinal cord on axial images (b) with superimposed region-of-interest encompassing spinal cord cross-sectional area

Figure 2.

Figure 2a. Scatter plots of clinical-MRI correlations (raw C3-C4 spinal cord volume)

Figure 2b. Scatter plots of clinical-MRI correlations (C3-C4 spinal cord volume normalized to spinal cord length by the proportional method (to yield mean cross-sectional area)

Table 1

Clinical characteristics and MRI measures in patient subgroups

	All MS	Relapsing MS	Progressive MS	HC
Subjects, n	133	78	55	11
Age at MRI scan, [years] (SD)	44 (12)	39 (11) **	52 (8)	40 (9)
% Female	65	69	58	71
Disease duration, [years] (SD)	10 (9)	7 (6) **	16 (11)	n/a
Median baseline EDSS (IQR)	3.5 (2–6)	2.5 (1.5–3.5) **	6.0 (4.0–6.5)	n/a
% on disease-modifying treatment	67	83 **	44	n/a
MSFC, Z-score	0.022 (0.68)	0.27 (0.51) **	−0.33 (0.75)	n/a
Vibration sensation threshold, [microns] (SD)	14.6 (22.1)	7.7 (13.2) **	24.8 (28.1)	n/a
Hip flexion strength, [pounds] (SD)	39.8 (18.6)	46.7 (15.5) **	29.3 (18.0)	n/a
Height [m]	1.71 (0.09)	1.70 (0.09)	1.72 (0.09)	1.67 (0.09)
Intracranial volume [mL]	887 (87)	880 (86)	896 (88)	903 (94)
Spinal cord length [mm] (SD)	33.5 (3.1)	33.0 (3.2)	34.1 (3.0)	34.3 (2.6)

*
p < 0.05 in comparison vs. HC**
p < 0.05 vs. progressive MS

Table 2a
Age-adjusted group comparisons of spinal cord volume with normalization by the proportional method

Spinal cord volume (C3-C4)	MS	HC	Mean difference	p-value	Relapsing	Progressive	Mean difference	p-value
Raw [mm ³], (SD)	2576.94 (388.17)	2838.46 (288.76)	-261.51	0.03	2632.95 (392.22)	2497.52 (371.50)	-135.43	0.32
Normalized to subject height [mm ²], (SD)	1.52 (0.20)	1.68 (0.15)	-0.16	0.02	1.56 (0.18)	1.46 (0.21)	-0.097	0.04
Normalized to spinal cord length [mm ²], (SD)	77.0 (9.2)	83.1 (9.2)	-6.1	0.04	79.6 (8.5)	73.3 (8.9)	-6.4	0.008
Normalized to intracranial volume* (x10 ⁻³), (SD)	2.92 (0.43)	3.16 (0.28)	-0.24	0.08	3.00 (0.40)	2.80 (0.44)	-0.20	0.18

* unitless measure

Table 2b

Age-adjusted group comparisons of spinal cord volume with normalization by the residual method

Spinal cord volume (C3-C4)	Mean Difference (MS vs. HC) [mm ³]	p-value	Mean Difference (Progressive vs. Relapsing) [mm ³]	p-value
Raw	-235.96	0.03	-81.01	0.32
Normalized to subject height	-247.32	0.02	-171.11	0.03
Normalized to spinal cord length	-171.19	0.05	-172.47	0.006
Normalized to intracranial volume	-201.04	0.04	-100.22	0.19

* MS = multiple sclerosis, HC = healthy control subjects

Table 3a

Spearman's correlation coefficients using proportional method (all MS cases, n=133)

	Spearman's rank correlation coefficient (p-value)			
	EDSS	MSFC	Hip flexion strength	Vibration sensation threshold
Raw spinal cord volume	−0.20 (0.02)	0.16 (0.06)	0.35 (0.0001)	−0.19 (0.03)
Normalized to height	−0.26 (0.006)	0.28 (0.003)	0.22 (0.02)	−0.29 (0.002)
Normalized to spinal cord length	−0.43 (<0.001)	0.33 (0.0001)	0.38 (<0.001)	−0.40 (<0.001)
Normalized to intracranial volume	−0.23 (0.01)	0.10 (0.24)	0.23 (0.01)	−0.35 (0.0001)

* EDSS = expanded disability status scale, MSFC = multiple sclerosis functional composite.

Table 3b

Correlations between clinical measures and spinal cord volume with normalization by the proportional method (relapsing cases, n=78)

	Spearman's rank correlation coefficient (p-value)			
	EDSS	MSFC	Hip flexion strength	Vibration sensation threshold
Raw spinal cord volume	−0.0082 (0.95)	0.0065 (0.96)	0.28 (0.02)	−0.082 (0.48)
Normalized to height	−0.087 (0.49)	0.089 (0.47)	0.15 (0.23)	−0.09 (0.45)
Normalized to spinal cord length	−0.19 (0.10)	0.13 (0.27)	0.25 (0.04)	−0.25 (0.03)
Normalized to intracranial volume	−0.039 (0.75)	−0.092 (0.43)	0.077 (0.52)	−0.21 (0.07)

* EDSS = expanded disability status scale, MSFC = multiple sclerosis functional composite.

Table 3c

Correlations between clinical measures and spinal cord volume with normalization by the proportional method (progressive cases, n=55)

	Spearman's rank correlation coefficient (p-value)			
	EDSS	MSFC	Hip flexion strength	Vibration sensation threshold
Raw spinal cord volume	−0.38 (0.005)	0.22 (0.10)	0.45 (0.001)	−0.27 (0.05)
Normalized to height	−0.22 (0.15)	0.31 (0.04)	0.21 (0.18)	−0.37 (0.01)
Normalized to spinal cord length	−0.45 (0.0007)	0.29 (0.03)	0.41 (0.004)	−0.30 (0.03)
Normalized to intracranial volume	−0.15 (0.29)	−0.0099 (0.94)	0.28 (0.06)	−0.40 (0.004)

* EDSS = expanded disability status scale, MSFC = multiple sclerosis functional composite.

Table 4

Correlations between clinical measures and spinal cord volume with normalization by the residual method

	Regression coefficient (p-value)			
	EDSS	MSFC	Hip flexion strength	Vibration sensation threshold
Raw spinal cord volume	−0.0012 (0.02)	0.00043 (0.005)	0.018 (<0.001)	−0.011 (0.05)
Normalized to height [mm ^{−3}] (	−0.0016 (0.005)	0.00062 (<0.001)	0.017 (0.001)	−0.019 (0.003)
Normalized to spinal cord length [mm ^{−3}	−0.0029 (<0.001)	0.00073 (<0.001)	0.028 (<0.001)	−0.026 (<0.001)
Normalized to intracranial volume [mm ^{−3}]	−0.0014 (0.01)	0.00036 (0.03)	0.017 (<0.001)	−0.017 (0.002)

* EDSS = expanded disability status scale, MSFC = multiple sclerosis functional composite.