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Correlation between spinal cord diffusion tensor imaging and postural response latencies in persons with multiple sclerosis: A pilot study

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Abstract

Purpose—Longer latency of postural response in multiple sclerosis (MS) may be linked to imbalance and increased likelihood of falls. It may be caused by the compromised microstructural integrity in the spinal cord, as evidenced by slowed somatosensory conduction in the spinal cord. Thus, the purpose of this study is to investigate the correlation between latency of postural responses and microstructural integrity of the cervical spinal cord, the region particularly related to the disease severity in MS, using diffusion tensor imaging (DTI) metrics.

Methods—Seventeen persons with MS with mild-to-moderate disease severity were enrolled in this study. Postural response latencies of each patient were measured using electromyography of the tibialis anterior muscle (TA) and gastrocnemius muscle (GN) in response to surface perturbations. Cervical spinal cord DTI images were obtained from each patient. DTI mean, radial, axial diffusivity, and fractional anisotropy (FA) were measured between segments C4 and C6. Correlations of DTI metrics with postural response latencies, expanded disability status scale (EDSS) scores, and 25-foot walk (T25FW) were assessed using the Spearman's rank correlation coefficient at $\alpha=0.05$.

Results—Lower FA was significantly correlated with longer latencies measured on right TA in response to forward postural perturbations ($r=-0.51$, $p=0.04$). DTI metrics showed no significant

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correlations with EDSS scores ($r=-0.06-0.09$, $p=0.73-0.95$) or T25FW ($r=-0.1-0.14$, $p=0.6-0.94$). DTI metrics showed no significant differences between subjects with and without spinal cord lesions ($p=0.2-0.7$).

Conclusions—Our results showed a significant correlation between lower FA in the cervical spinal cord and longer latencies measured on right TA in response to forward postural perturbations in persons with MS, suggesting that impaired cervical spinal cord microstructure assessed by DTI may be associated with the delayed postural responses.

Keywords

Multiple sclerosis; Diffusion tensor imaging; Postural response; Spinal cord; Microstructure

Introduction

Multiple sclerosis (MS) is characterized by demyelination, axonal loss, gliosis, and inflammation [1–3], and MRI has been instrumental in diagnosis of the disease. For example, affected tissues can be identified by T2-weighted MRI or fluid attenuation inversion recovery (FLAIR) [4, 5]. However, the relationship between hyperintense lesion measures and physical dysfunction and/or disability in MS has been inconsistent. Some studies reported a correlation between MRI lesions and MS disability assessed by the expanded disability status scale (EDSS) [6, 7], while other studies have failed to find any significant correlations [8–11]. These different findings may result from a lack of specificity of structural MRI to detect the tissue changes or could result from a lack of specificity in the location of MRI abnormalities and MS-related dysfunction and/or disability [8, 9]. Moreover, MS disease progression may be accompanied by subtle microstructural changes that are undetectable using conventional structural MRI.

Diffusion tensor imaging (DTI) offers quantitative measures of white-matter microstructural integrity based on the directional diffusivity and the degree of anisotropic diffusion [12]. DTI measures have been used to characterize microstructural abnormalities in MS [13–26], demonstrating that microstructural abnormalities occur not only within the structural MRI lesions but also in the normal appearing white matter. Furthermore, DTI measures in regions associated with the major sensory and motor pathways have shown correlations with disability, ambulation, strength and balance in persons with MS [13, 15, 17, 19, 21, 26–32]. These findings suggest that regional DTI measures may provide a more relevant structural assessment for functional abnormality in MS, such as impaired balance issues.

Impaired balance is a common symptom in MS and a major contributing factor to falls of persons with MS. Impaired balance can be evaluated by measuring responses to postural perturbations [33]. Compared with normal controls, persons with MS exhibit longer latencies in response to surface perturbations [34, 35]. The delayed response indicates a longer time required to restore balance following the postural perturbation and may increase a likelihood of falling. The delayed postural response has been associated with balance dysfunction of persons with MS during their standing and walking [35]. In addition, persons with MS who have history of falls show longer postural response latencies compared with those with no history of falls [36]. These findings suggest that postural response latencies

may provide information about imbalance and falls in persons with MS, which can be complementary to the standard clinical assessment. The physiological causes of delayed postural response in MS are unknown. Longer postural response latencies in persons with MS have been correlated with the slowed spinal somatosensory conduction but not with supra-spinal somatosensory conduction [34]. This suggests that delayed postural response in persons with MS may arise from slowed spinal somatosensory conduction, likely associated with impaired spinal cord microstructure [34]. However, association between spinal cord microstructure and delayed postural responses has not been previously investigated in persons with MS.

Therefore, the purpose of this study was to investigate the correlation between cervical spinal cord DTI metrics and postural response latencies observed in persons with MS. The correlation may help elucidate the physiological basis underlying the delayed postural response, which is closely associated with impaired balance and falls in persons with MS.

Methods

Subjects

This study was approved by the Institutional Review Board of the University of Kansas Medical Center and informed consents were obtained from all subjects. Seventeen subjects (10 females and 7 males; 47 ± 7 years old, mean $\pm$ SD) diagnosed with relapsing remitting MS were studied. The demographic and clinical characteristics of subjects are summarized in Table 1. The mean disease duration of subjects was 11.13 ± 7.15 years, and mean EDSS score 2.38 ± 1.11 , indicating the mild-to-moderate disease severity. Subjects were able to walk 25 feet without the use of a walking aid with the mean timed 25-foot walk of 5.08 ± 1.46 s. Exclusion criteria were: additional neurological or orthopedic co-morbidities with the potential to alter balance or gait mechanics, female subjects who were pregnant, breastfeeding, or within 3 months post-partum at the time of data collection, persons with vestibular issues, diabetes, or a pre-existing condition which could make exercising difficult, inability to walk a distance of 25 feet without the assistance of a mobility aide, or if they were currently prescribed symptom-specific medication therapies that affect their walking speed, i.e., Fampridine.

Postural Response Latency Measurements

Postural response latency was characterized by the onset times of leg muscle activation in response to postural perturbations [34, 35]. Wireless surface electromyography (EMG) sensors (Trigno Lab, Delsys Inc., Boston, MA) were placed bi-laterally on the tibialis anterior muscle (TA) and medial gastrocnemius muscle (GN) of subjects standing on a Rehabilitation Treadmill (Woodway USA, Waukesha, WI). Figure 1 demonstrates the experimental set up for postural response latency measurements [35]. The stimulus was a translation of the treadmill surface of 6 cm at a rate of 15 cm/s. The delay was computed as the time between the onset of the surface translation and the first detectable increase in bilateral EMG signals from either the TA (response to forward translation) or GN (response to backward translation). Subjects performed forward and backward translations repeated

three times. Postural response latencies for each muscle group were averaged across three repeated trials.

MR Imaging

Cervical spinal cord MRI was performed on a 3T MR system (Skyra, Siemens AG, Erlangen, Germany) using a body transmit coil and a posterior-neck surface receive coil. All subjects underwent an identical MRI scan protocol, including T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE), T2-weighted fast spin echo sequence and single-shot echo planar imaging (EPI)-based diffusion-weighted imaging (DWI) sequence. Parameters for the T1-weighted 3D MPRAGE sequence were: echo time (TE)=3 ms, repetition time (TR)=2300 ms, inversion time=900 ms, flip angle=9°, bandwidth=235 Hz/pixel, field of view (FOV)=320×320 mm², matrix size=320×320, slice thickness=1 mm, 15 coronal slices, and number of excitations (NEX)=1. Parameters for the T2-weighted FSE sequence were: TE=104 ms, TR=3150 ms, flip angle=120°, bandwidth=260 Hz/pixel, echo train length=19, FOV=240×240 mm², matrix size=384×384, slice thickness=3 mm, 15 sagittal slices, and NEX=3. Parameters for the EPI-based DWI sequence were: b=0 s/mm² and 500 s/mm² along 20 non-collinear directions, TE=59 ms, TR=6300 ms, bandwidth=1370 Hz/pixel, FOV=145×142 mm², matrix size=96×94, slice thickness=3 mm, voxel size=1.51×1.51×3 mm³, 20 transverse slices, and the number of repeated scans=3.

MRI Data Analysis

T2 cervical spinal cord lesions were identified between segments C1 and C7 on the T2-weighted sagittal scans for each subject. DWI images acquired from the second and third repeated scans were spatially aligned to those of the first scan through a six-parameter rigid-body transformation using SPM (<http://www.fil.ion.ucl.ac.uk/spm/>). The three sets of spatially aligned DWI images were averaged to increase the SNR. The DWI images were then fitted with diffusion tensor for each voxel, generating parametric maps of DTI metrics, including mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and FA (Fig. 2B) [12]. In light of a reported involvement of low cervical spine somatosensory conduction in the postural response [34], regions-of-interest (ROIs) were selected on the low cervical segments C4-C6 (Fig. 2). ROIs were placed semi-automatically on spinal cord tissues with hyperintense signals on the trace-weighted DWI images using Jim 5.0 software (Xinapse Systems, Aldwinckle, UK). ROIs included only normal appearing spinal cord tissue, excluding axial sections with T2 cervical spinal cord lesions to remove any potential influence of the lesions on the DTI metrics. The mean values of DTI metrics within the ROI were computed for each subject. The ROI drawing was performed by a single rater and was repeated once by the same rater to assess intra-rater variability.

Statistical Analysis

The intraclass-correlation coefficients were used to assess intra-rater variability of each ROI-based DTI measure. The intraclass-correlation coefficients were computed using SPSS (IBM Corp., Armonk, NY, USA). Postural response latencies were compared between the left and right sides and between forward and backward motion stimulus. DTI metrics were correlated with postural response latencies, EDSS scores, and timed 25-foot walk (T25FW),

respectively, using the Spearman's rank correlation coefficient at $\alpha=0.05$. DTI metrics were compared between the subjects with and without cervical spinal cord lesions using Wilcoxon rank-sum test at $\alpha=0.05$.

Results

Postural response latencies showed no significant differences between the left and right sides ($p=0.85$) (Table 2). Postural response latencies showed no significant differences between forward and backward perturbations ($p=0.58$).

The intraclass-correlation coefficients of DTI metrics ranged from 0.97 to 0.99, indicating high intra-rater reliability of the ROI-based DTI measures. Values of DTI metrics indicated a high degree of anisotropic diffusion along white-matter tracts, corresponding to higher values of AD compared with RD, and high values of FA (Table 2, Fig. 2B).

Lower FA was significantly correlated with longer latencies measured on the right TA in response to forward postural perturbations ($r=-0.51$, $p=0.04$) (Table 3, Fig. 3). Other moderate but non-significant correlations were also observed between DTI metrics and postural response latencies. Higher MD ($r=0.41$, $p=0.1$), RD ($r=0.42$, $p=0.1$) and lower FA ($r=-0.42$, $p=0.1$) showed trending correlations with longer latencies measured on the right GN in response to backward postural perturbations. Higher RD ($r=0.47$, $p=0.06$) and lower FA ($r=-0.42$, $p=0.1$) showed trending correlations with longer latencies measured on the right and left TA in response to forward postural correlations.

DTI metrics showed no significant correlations with EDSS scores ($r=-0.06-0.09$, $p=0.73-0.95$) and T25FW ($r=-0.1-0.14$, $p=0.6-0.94$). No significant differences were observed in DTI metrics between the subjects with ($n=4$) and without ($n=13$) T2 cervical spinal cord lesions ($p=0.2-0.7$).

Discussion

Our study demonstrates that lower FA in cervical spinal cord was significantly correlated with longer latencies measured on the right TA in response to forward postural perturbations in persons with MS. Lower FA indicates a low degree of anisotropic diffusion, likely associated with impaired cervical spinal cord white-matter microstructure, e.g., demyelination and axonal loss [2, 37, 38], which may contribute to the previously observed slowed spinal somatosensory conduction and postural response latencies in persons with MS [34].

Previous studies have shown an association of cervical spinal cord DTI metrics with measures of global disability, as well as measures of lower and upper extremity sensory and motor functions in persons with MS, including vibration threshold, 9-hole peg test, strength, and T25FW [13–15, 17–19, 21, 39]. Our findings suggest that cervical spinal cord DTI metrics can also be associated with postural response latencies. Measures of response to a surface translational perturbation may be informative of the tendency to fall by mimicking hazards of natural environments, such as a slip and trip [33]. Measures of postural response may also help better understand the mechanisms of balance restoration. Delayed responses

along with a large magnitude of postural response have been observed in persons with MS with mild-to-moderate disease severity [34]. A large magnitude of response may compensate for delayed reaction, which suggests that weakness may not be associated with slowed postural response. Because imbalance in persons with MS is multi-factorial and involves complex interactions of physiological systems, postural response latencies may provide more information about the balance control in addition to standard clinical assessments. This study found a link between cervical spinal cord structure and delayed postural response latencies. The findings may help elucidate the physiology of the delayed postural response and may further help develop imaging assessment for the targeted treatment of persons with MS with impaired balance.

Although some previous studies have found significant correlations of cervical spinal cord DTI metrics with EDSS and T25FW [13–15, 18, 39], our study along with a recent study [29] did not observe their significant correlations. These inconsistent findings may result from a relatively low b-value of 500 s/mm² used in our study. However, the same b-value has been used in other studies [21, 29, 39], one of which observed a significant correlation between cervical spinal cord DTI metrics and EDSS [39]. Other causes for the inconsistent findings may be the different study designs and the small sample size of our study. In our study, persons with MS had mild-to-moderate disease severity with EDSS of 1–4.5 and T25FW of 2.99–8.55 s, whereas persons with MS in other studies had a broader range of disability, for example, EDSS of 1.5–6.5 or 1–8 [13, 14, 18, 39] and T25FW of 3.3–300 s [13]. Given the relatively narrow range of disability of persons with MS in our study, it is possible that the differences in disability were too small to observe a significant correlation of cervical spinal cord DTI measures and measures of global disability and ambulation. Persons with mild-to-moderate disease severity in MS may only show mild to moderate changes in cervical spinal cord DTI metrics compared with those in healthy controls, whereas more disabled individuals would show a larger change in the DTI metrics [13, 14, 39]. Therefore, future studies including a large cohort of subjects with a greater range of disability are needed to investigate these correlations.

Impaired cervical spinal cord microstructure associated with delayed postural response latencies in persons with MS may result from demyelination and axonal loss. These alternations of microstructure are associated with higher RD and lower FA of DTI metrics [2, 37, 38]. Our study observed that both lower FA and higher RD showed moderate correlations with delayed postural response latencies, but only the correlation between FA and latencies measured on the right TA in response to forward postural perturbations was significant. This may be associated with the higher sensitivity of FA to detect MS pathology-related changes in tissue compared to directional diffusivity measures [14, 16, 19, 22, 30, 31]. Furthermore, applicability of our results may be limited by several factors. Spinal cord DTI is subject to motion artifacts [40, 41] and is also subject to distortion by using EPI-based DWI sequences [42]. Nonetheless, a commonly used single-shot EPI DWI sequence was applied for spinal cord DTI in our study to achieve high SNR efficiency and short scan time. Moreover, similar to other studies [14, 16, 19, 21, 22, 29, 30], our study employed a ROI analysis to reduce effects of image distortion. The ROI-based DTI measures showed high intra-rater reliability. However, precise segmentation of gray and white matter was not achievable due to the low image resolution. The inclusion of both gray and white matter in

the ROI may reduce the specificity of DTI metrics to detect microstructural abnormalities [21].

In this study, the mean values of DTI metrics measured at the C4-C6 level are consistent with the previously reported DTI measures on the C1-C5, C2-C3 or C3-C4 level of persons with MS [21, 22, 29]. However, our measured values show larger differences compared with other previously reported DTI measures [14, 16–19]. The mean FA value was 0.59 in our study, whereas the FA values were lower (~ 0.39 – 0.46) in other studies [14, 18, 19]. Those differences may be a result of different b-values used for DWI. The b-values used in previous DTI studies on spinal cord range from 500 to 1000 s/mm² [14, 16–19, 21, 29, 39]. The use of a higher b-value results in increased diffusion weighting and increased sensitivity to diffusion. However, it also results in a decreased SNR due to increased signal attenuation and longer TE. Considering the SNR, we chose the b-value as 500 s/mm² in this study.

Consistent with a previous study [22], DTI metrics did not differ between subjects with and without T2 hyperintense cervical spinal cord lesions in this study. Spinal cord damage in persons with MS may not be fully revealed by T2-weighted MRI. Disruption of an axon in a lesion along the path of the nerve tract may cause degeneration of the axon throughout its entire course, thus leading to atrophy and loss of function. Since the spinal cord contains all the pathways for sensory and motor functions below the neck, axonal loss in the brain can also cause downstream atrophy and loss of function in the spinal cord. As expected, previous histopathological findings have shown that axonal loss and demyelination have been observed outside of T2 lesions [2, 43, 44]. Additionally, abnormal spinal cord DTI measures have been observed in both T2 lesions and the normal appearing spinal cord [16, 17, 22, 25]. These findings suggest that spinal cord DTI measures may be able to detect microstructural damage outside of T2 lesions and that these abnormalities of spinal cord DTI measures may be independent of the T2 lesions. It is also possible that the number of subjects with T2 spinal cord lesions, i.e., 4 out of 17 patients in the cervical spinal cord and 2 out of those 4 patients at the C4-C6 level, was too small to detect the difference in DTI metrics between patients with and without spinal cord lesions. Comparison of DTI measures inside and outside the lesions would require a larger sample size [21].

With a small sample size, the statistical power of this study is limited, and no correction of p-value was applied for multiple comparisons. Nonetheless, to investigate whether the reported significant correlation was a false positive finding, we have also reported other moderate but non-significant correlations. Higher MD, RD, and lower FA showed trending correlations with longer latencies measured on the right GN in response to backward postural perturbations. Higher RD and lower FA showed trending correlations with longer latencies measured on the right and left TA in response to forward postural correlations. Therefore, these moderate but non-significant correlations showed the same trend for the changes in DTI metrics associated with the delayed postural responses. Moreover, the stronger correlations appear to occur in the postural response latencies measured on the right GN and TA compared with those measured on the left GN and TA. The effect of asymmetry in postural response latencies and its relationship with DTI metrics needs to be investigated in future studies with a large sample size.

In conclusion, we measured a significant correlation between lower FA in cervical spinal cord and longer latencies measured on the right TA in response to forward perturbations in persons with MS. Our results suggest that impaired cervical spinal cord microstructure assessed by DTI may be associated with delayed postural response, which is closely associated with imbalance and falls in persons with MS.

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Figure 1. Illustration of experimental set up for postural perturbation.
The surface is translating forward resulting in a backward shift to the center of mass and activation of the tibialis anterior muscles.

Figure 2. Illustrations of DTI metrics measured in the spinal cord.

A. Directional color-coded FA overlaid on the anatomical T2-weighted images. **B.** 2-D cross-sectional maps of DTI metrics: MD, RD, AD (grayscale) and FA (color-coded) corresponding to the locations shown in **A**.

Figure 3. Illustration of the correlation between FA and postural response latencies.
The correlation, evaluated by Spearman's rank correlation coefficient, between FA and latencies measured on the right TA in response to forward postural perturbations of 17 persons with MS.

Table 1.

Demographics and clinical information of 17 patients with relapsing-remitting multiple sclerosis

Characteristic	Values
Age (years)	47±7
Sex (females/males)	10/7
Disease duration (years)	11.13±7.15
EDSS	2.38±1.11
T25FW (s)	5.08±1.46

Note: Values are given as mean±SD.

Abbreviations: EDSS=expanded disability status scale; T25FW=timed 25-foot walk.

Table 2.

Postural response latencies and DTI metrics measured in 17 subjects with multiple sclerosis

Measurements	Values
Postural response latencies (ms)	
Right GN	129.16±26.98
Left GN	121.99±18.11
Right TA	124.21±28.02
Left TA	133.27±34.70
DTI metrics	
MD ($\times 10^{-3}$ mm ² /s)	1.07±0.07
RD ($\times 10^{-3}$ mm ² /s)	0.67±0.07
AD ($\times 10^{-3}$ mm ² /s)	1.87±0.08
FA	0.59±0.04

Note: Values are given as mean±SD.

Abbreviations: GN=gastrocnemius muscle; TA=tibialis anterior muscle; MD=mean diffusivity; RD=radial diffusivity; AD=axial diffusivity; FA=fractional anisotropy.

Table 3.

Correlations (r) of DTI metrics with postural response latencies, EDSS, and T25FW evaluated using Spearman's rank correlation coefficients

	Backward perturbation				Forward perturbation				EDSS		T25FW	
	Right GN		Left GN		Right TA		Left TA		r	p	r	p
	r	p	r	p	r	p	r	p				
MD	0.41	0.10	-0.01	0.99	0.30	0.25	0.18	0.49	-0.02	0.95	0.02	0.94
RD	0.42	0.10	0.19	0.47	0.47	0.06	0.35	0.17	-0.04	0.89	-0.10	0.70
AD	0.30	0.24	-0.19	0.46	-0.05	0.85	-0.12	0.65	-0.06	0.82	0.05	0.86
FA	-0.42	0.10	-0.27	0.30	-0.51	0.04 [*]	-0.42	0.10	0.09	0.73	0.14	0.60

Note:

(^{*}) indicates $p < 0.05$.

Abbreviations: GN=gastrocnemius muscle; TA=tibialis anterior muscle; EDSS=expanded disability status scale; T25FW=timed 25-foot walk; MD=mean diffusivity; RD=radial diffusivity; AD=axial diffusivity; FA=fractional anisotropy.