Research article

Analysis of the diffusion tensor imaging parameters of a normal cervical spinal cord in a healthy population

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Background: Diffusion tensor imaging (DTI) shows great advantage in the diagnosis of brain diseases, including cervical spinal cord (CSC) disease. This study aims to obtain the normal values of the DTI parameters for a healthy population and to establish a baseline for CSC disease diagnosis using DTI.

Methods: A total of 36 healthy adults were subjected to magnetic resonance imaging (MRI) for the entire CSC using the Siemens 3.0 T MR System. Sagittal DTI acquisition was carried out with a single-shot spin-echo echo-planar imaging (EPI) sequence along 12 non-collinear directions. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were determined at different cervical levels using a region of interest (ROI) method, following which they were correlated with parameters, like age and sex. Further, diffusion tensor tracking (DTT) was carried out to reconstruct the white matter fiber bundles of the CSC.

Results: The full and complete fiber bundle structure of a normal CSC was confirmed in both the T2-weighted and DTI images. The FA and ADC values were significantly negatively correlated with each other and showed strongly negative and positive correlations with age, respectively, but not with sex. Additionally, there was no significant difference between the FA and the ADC values at different cervical levels.

Conclusion: The DTI technique can act as an important supplement to the conventional MRI technique for CSC observation. Moreover, the FA and ADC values can be used as sensitive parameters in the DTI study on the CSC by taking the effects of age into consideration.

Keywords: Cervical spinal cord, Diffusion tensor imaging, Fractional anisotropy, Apparent diffusion coefficient

Introduction

Magnetic resonance imaging (MRI) has long played an important role in the diagnosis and follow-up of cervical spinal cord (CSC) disease and tumors. However, it is not sensitive to the detection of some clinical cervical lesions using conventional T1- and T2-weighted imaging (T1WI and T2WI, respectively).¹ In general, it has been accepted that a difference between conventional MRI findings and clinical manifestations exists.² Since then, efforts have been made to resolve this issue using newly developed techniques, including diffusion-weighted imaging (DWI)—a functional MRI technique that assesses changes in the random motion of water protons *in vivo*.³

Diffusion tensor imaging (DTI)—an advanced DWI technique—can measure anisotropic water diffusion in at least six directions, and it has been successfully applied to brain disease diagnosis on the basis of physiological parameters that are used to assess the changes in the brain ultrastructure.⁴ However, the application of DTI to the spinal cord is limited owing to spinal stenosis, artifacts of susceptibility, and heart motion or respiratory motion. Initially, the application of DTI to the spinal cord of rats was reported, wherein an implantable coil was used under a high field strength of 4.7–7.0 T.^{5,6} These results indicate that the white and gray matter structures of the spinal cord can be clearly distinguished through DTI images, with the measured parameters showing obvious differences at different cervical levels.

Additionally, preliminary studies on the application of DTI to the CSC,^{7–11} such as for the diagnosis of

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spinal cord injuries or diseases, suggest that the results obtained using DTI are more accurate than those obtained using conventional MRI. Further, the parameters obtained using DTI showed better correlation with the degree of clinical disability than those obtained using conventional MRI. Furthermore, DTI can track and graphically depict fiber bundles by tractography, namely, diffusion tensor tracking (DTT), which has been used to reconstruct the three-dimensional structure of the white matter fiber bundle using the information of the diffusion tensor.^{12–14}

Despite the fact that researchers have attempted to establish normative reference values for CSC (trauma) patients,¹⁵ there is still a lack of normative databases for the DTI metrics of the spinal cord in healthy people. The objective of this study was to establish a baseline for the application of DTI to diagnose CSC diseases by detecting the normal values of the DTI parameters and by analyzing their distribution characteristics, variations, and influencing factors in healthy volunteers. DTT was also carried out to observe the white matter fiber bundles.

Materials and methods

Study subjects

First, 43 healthy volunteers (age range of 18–80 years) without any neurological deficits or clinical symptoms were selected according to the inclusion criteria. Among the enrolled volunteers, those with a history of neurological diseases, those who considered MRI to be a taboo, and those whose T2 images of the CSC showed a high signal were excluded. The final sample comprised 21 healthy male subjects and 15 healthy female subjects with an age range of 18–77 years, and the mean age of the entire sample was 43.6 ± 17.6 years. The sex distribution within different age ranges is also listed in Table 1. Ethics approval for the study was obtained from the ethical committee of the local hospital district, and written informed consent was obtained from each subject.

Table 1 Distribution of sex in different age ranges

Age ranges	Male	Female	Total number
10–19	2	1	3
20–29	4	2	6
30–39	4	4	8
40–49	3	3	6
50–59	3	2	5
60–69	3	2	5
70–79	2	1	3

Conventional MRI and DTI protocol

All images were acquired with a 3.0 T MRI scanner (Siemens Trio, Siemens Medical Solutions, Erlangen, Germany) equipped with a 12-channel head coil and a 4-channel neck coil. For conventional sequences, scanning orientations included a sagittal T1-weighted image (T1WI), an axial T2-weighted image (aT2WI), a coronal T2-weighted image (cT2WI), and a sagittal T2-weighted image (sT2WI). Fast spin-echo (FSE) was used for both the T1-weighted image (T1WI; TR/TE = 735 ms/11 ms) and the T2-weighted image (T2WI; TR/TE = 3,130 ms/91 ms), with a field of view (FOV) of 300 mm for sagittal scanning (slice/gap = 3.0/0.3 mm) and 160 mm for axial scanning (slice/gap = 3.6/0.4 mm) at C1–C7 levels, with an image matrix of 448×314 . Further, the 3D structure of the T2WI was acquired using the 3D-SPACE sequence (TR/TE = 3,000 ms/502 ms, FOV = 250×250 mm, 128 continuous slices with a slice thickness of 1.0 mm, matrix size = 256×256) across the entire head.

DTI acquisition was carried out using single-shot fast spin-echo echo-planar imaging (EPI) on the basis of T2-3D scanning (TR/TE = 5,500 ms/93 ms, FOV = 240×240 mm, 38 continuous slices with a slice thickness of 3.5 mm, matrix size = 128×128). Twelve diffusion gradient directions (DGDs) were realized with a *b*-value of 1000 s/mm^2 and a non-diffusion weighted image volume (null image, *b*-value = 0 s/mm^2 ; number of excitation (NEX) = 1). The scanning time for DTI acquisition was around 91 s along the craniocaudal axis. Further, all the subjects were asked to use foam pillows placed inside the coil to avoid swallowing or moving during image acquisition to minimize artifacts generation.

Data and image processing

All the obtained images were transferred to the workstation of Siemens Syngo MR B15 (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) after data collection and were analyzed offline by two experienced neuroradiologists who were blinded to the patients' clinical data. The final value of all the DTI parameters was expressed as the average value of the two measurements. The FA and ADC values, in the CSC at the C1–C7 levels, were measured using a region of interest (ROI) technique with Neuro3D software ((Siemens Medical Solutions USA, Inc.) under a sagittal T2 anatomic sequence. Briefly, the ROI (diameter = 7 mm) was manually drawn in the middle regions of each segment of the cervical vertebra. Then, the FA and ADC values were automatically calculated for each ROI. The DTT images were acquired with a fiber assignment

by continuous tracking (FACT) fiber-tracking algorithm using the provided software. The seed points were placed on color-encoded sagittal FA maps. An FA threshold value of 0.18 and an angulation threshold with a turning angle of 35° were established in fiber tractography, whereas the derived fibers with a length of less than 20 mm were automatically discarded. The primary T2-3D and DTT images were compared for the observation of fiber tracts and integrity.

Statistical analysis

Data were expressed in terms of mean ± standard deviation (SD). Statistical analysis was performed using standard SPSS 21.0 software (IBM Corp., Armonk, NY, USA). The relationship between the FA value and the ADC value or their respective values and ages was analyzed by Pearson correlation analysis, and the correlation coefficient *R* and the *P* values were calculated accordingly. The effect of sex on the FA and ADC values was analyzed by a *t*-test within two independent samples. The difference between the FA value and the ADC value at different CSC levels was analyzed by one-way analysis of variance (ANOVA). If the difference was significant, Bonferroni method was used for multiple comparisons among multiple groups. *P* < 0.05 was considered statistically significant.

Results

FA and ADC maps of CSC

DTI manifestations were exhibited by FA and ADC maps of CSC and DTT images of fiber bundles of healthy volunteer. No distortion was observed in the sagittal color FA map (Fig. 1A), as well as basal

T2WI map (Fig. 1B). And, with the combination of FA or ADC map and T2WI, FA and ADC values were measured at different cervical levels, as presented in Figure 1C. Cerebrospinal fluid and spinal cord appeared hyperintense (white) and isointensity (gray) respectively on the ADC map, while spinal cord was indicated by homogeneous blue on FA map (Fig. 2).

DTT images of fiber bundles

Typically, water molecules within the spinal cord prefer a craniocaudal diffusion direction along white matter fibers; therefore, this direction is often coded in blue color.¹⁶ As shown in Figure 3, the craniocaudal direction of fiber bundles with a string-like shape showed the successful reconstruction of DTT images for a normal CSC, whereas the T2WI images also showed a full and complete structure of the normal CSC after 3D reconstruction. Moreover, the color FA maps showed lateral, frontal, and posterior funicles, which also indicated that the fiber bundle could be rotated at any angle in the DTT images.

Measurements of the entire cord at different cervical levels

The mean FA and ADC values of the entire cord at different cervical levels were listed in Table 2, and the correlation between the two variations was analyzed by Pearson’s correlation analysis, as illustrated in Figure 4A. The obtained results showed a significantly negative correlation between the FA and the ADC values (*r* = −0.559, *P* < 0.001). The overall differences between the cervical levels were also tested with one-way ANOVA, and no significant difference was observed for the FA (*F* = 1.718, *P* = 0.117) and ADC

Figure 1 Measurement of the FA and ADC values at different cervical levels (C1–C7) using the ROI method. Sagittal color FA or MR T2WI map of the CSC in a representative healthy volunteer indicated the homogeneous signal intensity of the CSC, with the C1–C7 levels labeled by different colors; this result is in good agreement with the automatically calculated FA and ADC values. (Colour online)

Figure 2 FA and ADC maps of the CSC in the same patient as shown in Fig. 1. ADC maps showed a gray normal spinal cord (yellow arrow) and a white cerebrospinal fluid (red arrow), whereas the FA map showed the normal spinal cord (yellow arrow) in blue color. (Colour online)

Figure 3 Color DTI map of a 22-year-old adult male showing a smooth and full fiber bundle. No abnormality was detected in the sagittal T2WI map, as well as in the lateral, frontal, and posterior funicles. (Colour online)

values ($F = 1.790$, $P = 0.102$). The effect of sex on the change in the FA and ADC values was also compared using the t -test, with results showing no significant difference between the FA and the ADC values of the female and male subjects ($P > 0.05$; Table 3).

In order to examine the effects of age, the scatter diagram between the age and the FA or ADC values

was analyzed using Pearson's correlation analysis. As shown in Figures 4B and C, correlation between the age and the FA or ADC values was significantly negative ($r = -0.801$; $P < 0.001$) or positive ($r = 0.426$; $P < 0.010$), respectively. Therefore, the FA and ADC values of the entire CSC were not related to the sex, but showed a significant correlation with age.

Table 2 Whole cord FA and ADC values at different cervical levels

Cervical level	FA value	ADC value ($\times 10^{-3} \text{ mm}^2/\text{s}$)
C1	0.687 ± 0.069	1.137 ± 0.237
C2	0.721 ± 0.071	1.072 ± 0.178
C3	0.692 ± 0.068	1.119 ± 0.203
C4	0.700 ± 0.059	1.091 ± 0.207
C5	0.695 ± 0.067	1.104 ± 0.186
C6	0.678 ± 0.056	1.205 ± 0.217
C7	0.684 ± 0.058	1.164 ± 0.193

Discussion

The objective of this study is to obtain normal values of the DTI parameters with possible variations for

reference, as well as to establish a baseline for the study of the CSC disease. The specific procedure involves the use of 3.0 T magnetic resonance DTI technology for CSC detection in 36 cases of healthy subjects in order to study the characteristics of the DTI parameters. Our results showed that (1) DTI manifestations in the FA and ADC images exhibited obvious characteristics, implying the application of DTI for distinguishing cerebrospinal fluid and a normal CSC structure; (2) fiber tractography clearly indicated the craniocaudal direction of the white matter fiber bundle structure with 3D imaging, as well as allowed for an arbitrary rotation angle with the observation of the fiber bundle; (3) the FA and ADC values showed significantly

Figure 4 Analysis of the correlation between the FA and ADC values, as well as between the FA and ADC values with age. The mean FA and ADC values of 36 adults were subjected to correlation analysis, with results showing negative correlation between the FA and ADC values (A; $r = -0.559$, $P < 0.001$), whereas they showed negative (B; $r = -0.801$, $P < 0.001$) and positive (C; $r = 0.426$, $P = 0.010$) correlation with the volunteer's age, respectively.

Table 3 Whole cord FA and ADC values ($\times 10^{-3} \text{ mm}^2/\text{s}$) from male and female

DTI parameters	Sex		Homoscedasticity (Levene test)	t value	P
	Male	Female			
FA value	0.702 ± 0.055	0.685 ± 0.051	$P = 0.675$	0.906	0.371
ADC value	1.120 ± 0.157	1.139 ± 0.151	$P = 0.805$	0.362	0.720

negative correlation with each other, and these values of the entire CSC showed a significant negative and positive correlation with age, respectively; however, these values were not related to the sex; and (4) there was no significant difference between the FA and ADC values at different levels along the entire CSC.

Gradually, DTI has developed into a clinical imaging diagnostic tool for various white matter structures in spite of its primary application in fundamental research.^{5,17} Magnetic resonance (MR) diffusion weighted imaging can detect the movement of water molecules in tissues. When the water molecules are displaced, the signal obtained from MR diffusion weighted scanning is attenuated. Owing to the characteristics of the central nervous system, the structure of the white matter in the central nervous system is likely to promote the diffusion of water molecules in the direction parallel, and not perpendicular, to the fiber.¹⁸ Diffusion limitation of fiber orientation is more derived from the cell membrane than the attribution of the myelin sheath.¹⁹ Thus, it is possible to deduce the orientation of the axon fibers as well as to delineate their anatomical boundaries on the basis of the direction-related diffusion characteristics using the DTI technology. Although the lower cervical cord is easily affected by the partial volume owing to reduced spatial resolution, the advantages gained from the application of the 3.0 T magnetic resonance scanner can overcome the abovementioned adverse effects. It has been shown that the 3.0 T scanner can generate images with a relatively high resolution and high signal-to-noise ratio (SNR).^{20,21} The high field strength can not only improve the accuracy of the DTI parameters but also improve the contrast of the gray matter region, in order to enhance the accuracy and efficiency of the tracing process.²² It has been indicated that there is almost no difference between the FA and ADC values in the axial and sagittal positions.²³ Thus, the sagittal DTI parameters were only used here.

It is more difficult to detect the spinal cord than the brain using DTI. It is also a challenge to detect a small volume and physiological movement, as well as the structure of the vertebral body, in the spinal cord, using DTI. However, owing to the longitudinal arrangement of all the fiber bundles, the structure of the spinal cord was significantly simpler than that of the brain tissue. The application of the DTI technology to the diagnosis of the spinal cord (mainly the CSC) disease is only a matter of recent years. To date, only a few studies have assessed the normal DTI parameters of the entire CSC. Clinical sample numbers and the size of the DTI acquisition parameters, such as the area of

the ROI or the direction of dispersion, both have an effect on the variation in the FA value.²⁴ From the summary of these reports, it was found that the average FA value for a majority of cases is 0.6–0.7, with a standard deviation of 0.06–0.07.^{25–27} In this study, the average FA values at C1–C7 levels of the CSC were measured to be 0.678–0.721, with a standard deviation of 0.056–0.071, indicating a higher average FA value with small variations than that obtained in previous studies, owing to a relatively large sample size and a wide range of age. The distribution of the FA and ADC values at different levels in the CSC has been reported, indicating that the FA value gradually decreases and the ADC value gradually increases.^{2,8,28,29} Therefore, it was speculated that cervical enlargement could contribute toward increased gray matter within the lower part of the CSC²⁷ or that the FA value of the brachial plexus decreased in the direction of the root and outside of the lower cervical cord.³⁰ Indeed, there is also report showing no difference in the distribution of the FA and the ADC values at different CSC levels.²⁵ In our study, the trend in the FA values was not obvious in the case of the cervical cord, where the highest and the lowest values appeared at the C2 and C6 levels, respectively; however, the difference in the FA values was not statistically significant at different levels. The possible reason for this insignificant difference could be attributed to the fact that a *b*-value of 1000 s/mm² resulted in a low SNR (Signal to Noise Ratio) in the lower level of the CSC, which in turn led to the overestimation of the FA value. Similarly, although the difference in the ADC values was also not obvious, the ADC and FA values showed a significant negative correlation with each other. Further analysis showed that the average value of the ADC was 1.072–1.205, with a standard deviation of 0.178–0.237. Further, a greater variation in the ADC values than that in the FA values indicated that the FA value was more reliable. Studies have also reported the FA values within all the cables in the white matter structure; the results of these studies indicated that the anterior index was significantly lower than that of the posterior and lateral cords, while no significant difference was found in posterior and lateral index.^{31–33} These results indicate the difference between the diameter or the density of axons and the spacing of the cables.³⁴

Body and imaging studies have also shown that spinal cord is associated with age-related degenerative changes, such as the loss of neurons, increased astrocytes, and a decrease in the spinal cord volume.^{35–37} Existing reports on the relationship between the FA or the ADC values and age are often limited to some specific

CSC levels. Mamata *et al.* found that the FA value was negatively correlated with age at the C3–C4 levels in the normal spinal cord, whereas the ADC value showed positive correlation in a group of patients with cervical spondylosis.²⁸ Agosta *et al.* showed that the FA value was negatively correlated with age in a study on the upper cervical spine.³⁸ There are also individual reports showing that the DTI parameters are independent of age.¹⁰ This study showed that there was a significant correlation between the DTI parameters and age, whereas the FA values were significantly negatively correlated with age, and the ADC values showed significantly positive correlation. The result further confirmed that the FA value was sensitive to age-related structural changes in the spinal cord. At the same time, the results of this study further encourage researchers to conduct a study on spinal cord lesions using DTI, where attention should be paid to the establishment of an age-matched control group. Besides, our results also showed that the FA and ADC values were not related to the sex; this result was in good agreement with that obtained from previous studies.

Currently, it is still difficult to obtain adequate spatial resolution and produce each fiber bundle in the white matter, particularly in the lower thoracic segment, primarily owing to the activity of the heart, respiratory system, and cerebrospinal fluid. The occurrence of these artifacts can be reduced by the use of faster imaging techniques such as parallel imaging and single echo imaging, with the use of cardiac pulse gating. The scanning time is considerably reduced by single-shot echo planar imaging by around 91 seconds; however, some subjects still cannot meet the requirements of a DTI scan. Scanning time is a special limitation for patients with acute spinal cord injury, wherein it is rather difficult for them to tolerate a relatively long scan time because of pain and other reasons. In addition, the SNR is not homogeneous in the CSC, with a decreasing tendency alongside lower position.³⁰ However, a low SNR could lead to overestimated anisotropy values, particularly for low anisotropic tissues, such as gray matter structures.³⁹ Although the use of a 3.0 T magnetic resonance scanner can improve the SNR,²¹ it has not been used for general application in most of medical institutions of China due to high cost. Moreover, the use of internal fixation to maintain stability during spinal surgery can produce a large number of artifacts, seriously impeding the postoperative application of DTI in the CSC. Indeed, it is necessary to develop standardized software to deal with tensor images, making it feasible to use the DTI technology in clinical routine.

In conclusion, the FA and ADC values obtained from the MRI observation for the CSC can be used for quantitative analysis, whereas the structure of the white matter fiber bundle was directly shown by using the tracer technique. This study revealed a significantly enhanced role of MRI in the diagnosis of CSC diseases, as well as its potential for evaluating some subtle variations within the CSC ultrastructure. Moreover, the DTI study for CSC analysis among healthy people provided a baseline for the subsequent studies on CSC disease diagnosis. Nevertheless, the FA and the ADC values showed strongly negative and positive correlation with age, respectively, but not with the sex or the cervical levels, indicating the role of age as a confounding factor. Thus, it is critical to establish age-matched control groups for further DTI studies on the CSC.

Disclaimer statements

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Conflict of interest None.

Ethics approval None.

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