NeuroImage 54 (2011) 2125–2131

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Entropy-based analysis for diffusion anisotropy mapping of healthy and myelopathic spinal cord

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ARTICLE INFO

Article history:
Received 23 March 2010
Revised 24 September 2010
Accepted 6 October 2010
Available online 14 October 2010

Keywords:
Spinal cord
Microstructure
Shannon entropy
Diffusion tensor imaging (DTI)
Fractional anisotropy (FA)

ABSTRACT

The present study utilized diffusion MR imaging and fractional anisotropy (FA) mapping to delineate the microstructure of spinal cord. The concept of Shannon entropy was introduced to analyze the complex microstructure of healthy and injured spinal cords based on FA map. A total of 30 volunteers were recruited in this study with informed consent, including 13 healthy adult subjects (group A, 25 ± 3 years), 12 healthy elderly subjects (group B, 53 ± 7 years) and 5 cervical spondylotic myelopathy (CSM) patients (group C, 53 ± 15 years). Diffusion MRI images of cervical spinal cord were taken using pulsed gradient spin-echo-echo-planar imaging (SE-EPI) sequence with a 3 T MR system. The region of interest was defined to cover the spinal cord in FA maps. The Shannon entropy of FA values of voxels in the cord was calculated as well as the average FA values. The significant differences were determined among three groups using one-way ANOVA and *post-hoc* test. As compared with adult and elderly healthy subjects, the entropy of whole spinal cord was significantly lower in CSM patients (group A: 6.07 ± 0.18; B: 6.01 ± 0.23; C: 5.32 ± 0.44; $p<0.05$). Whereas there were no significant difference in FA values among groups (group A: 0.62 ± 0.08; B: 0.64 ± 0.09; C: 0.64 ± 0.12). In CSM patients, there was a loss of architectural structural complexity in the cervical spinal cord tissue as noted by the lower Shannon entropy value. It indicated the potential application of entropy-based analysis for the diagnosis of the severity of chronic compressive spinal cord injuries, i.e. CSM.

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Introduction

The spinal cord is composed of an inner core gray matter (GM) and an outer layer of white matter (WM) and surrounded by cerebrospinal fluid (CSF). In WM, the majority of the nerve fibers run longitudinally and exit as the spine nerve roots at different segment levels, whereas the GM contains longitudinal as well as collateral connecting fibers which play a role in the communication (Maier, 2007; Mamata et al., 2006). The complex nature of the spinal cord nerve fibers is necessary for it to play an integral role in helping to form the motor and sensory tracts as well as the interconnections between the brain and peripheral nervous system.

Although the conventional magnetic resonance imaging (MRI) is currently the most widely used modality for the evaluation of spinal cord parenchyma, it is limited by its capability to only delineate changes at the macroscopic level (Baron and Young, 2007). Recently, there has been growing interests on diffusion tensor imaging (DTI), which permits the detection of tissue water molecular diffusion at microscopic dimensions (Thurnher and Law, 2009). The diffusion tensor matrix, including eigenvectors and eigenvalues, enable the display of the direction and intensity of the water molecules movements, respectively. Fractional anisotropy (FA) has become the most commonly used parameter for examination of spinal cord tissue architecture. FA is derived from the diffusion tensor matrix to describe the diffusion properties of the voxel, which ranges from 0% (isotropic diffusion) to 100% (diffusion along one orientation only) (Basser and Jones, 2002). FA is attributed to the densely packed axonal membranes in spinal cord, and it is able to reflect the microstructural changes associated with the de- and remyelination process in the neurological diseases or injuries (DeBoy et al., 2007; Giorgio et al., 2010).

In the analysis of the diffusion tensor matrix derived indices, FA was always taken as an average in the region of interest (Mamata et al., 2005; Van Hecke et al., 2008). Yet the average FA values obtained from healthy cervical spinal cord of human beings were spread in a very wide range, the mean value previously reported from 0.43 to 0.75 with a large standard deviation ranging from 0.03 to 0.09 (Rossi et al., 2008; Voss et al., 2007). In addition, FA values varied between the different segments of cervical spinal cord (Mamata et al., 2005; Van Hecke et al., 2008). At each segment of cervical spinal cord, FA values were different between gray and white matter, and they also varied among ventral, lateral and dorsal columns of white matter (Hesseltine et al., 2006). All of these findings suggested the complex nature of spinal cord tissue structure.

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doi:10.1016/j.neuroimage.2010.10.018

Shannon entropy is a basic concept in the information theory, to characterize the chaos or the complexity of the information (Shannon, 1997). Shannon entropy has been used in biomedical research for the analysis in the electromyographic data and functional MRI time series (de Araujo et al., 2003; Xie et al., 2010). Attempts have been made to analyze the diffusion properties of brain tissue architecture in two-dimensional diffusion weighted images (Metwalli et al., 2006; Neuvonen and Salli, 2005). The purpose of the present study was to introduce the concept of Shannon entropy to help illustrate the complexity of healthy and myelopathic spinal cord tissue structure based on diffusion MR imaging derived FA mapping.

Materials and methods

Subjects

A total of 30 volunteers, including 20 males and 10 females ranging from 21 to74 years old, were recruited in this study with informed consent. They were screened to confirm their eligibility. The healthy subjects were those having intact sensory and motor function evaluated by Japanese Orthopaedic Association (JOA) score system (Yonenobu et al., 2001), and negative Hoffman's sign under physical examination. Those who had any neurological signs and symptoms, and the past history of neurological injury, diseases and operations were excluded. The healthy subjects were further divided into two groups: the adult healthy subjects (group A, $n=13$, aged 25 ± 3 years old) and the elderly healthy subjects (group B, $n=12$, aged 53 ± 7 years old). The cervical spondylotic myelopathy (CSM) patients with confirmed diagnosis by orthopaedic specialists, were recruited for comparison (group C, $n=5$, aged 53 ± 15 years old). Written informed consent forms that were approved by the ethics committee were signed by all subjects prior to testing.

MRI scanning

All imaging were taken by 3.0-Tesla MRI scanner (Philips Achieva). The pulse sequence programming was performed prior to scanning to optimize the image quality. During the acquisition process, the subject was placed supine with the SNV head and neck coil enclosing the cervical region, and was instructed not to swallow to minimize the motion artifacts. The subject was then scanned with the anatomical T1-weighted (T1W), T2-weighted (T2W) images and diffusion tensor images (DTI). The standardized procedures in this study were approved by the authors' Institutional Review Board.

Sagittal and axial T1W and T2W images were acquired for each subject. Fast spin echo (FSE) sequence was employed. For sagittal imaging, the imaging parameters were as follows: Field of view (FOV) = 250×250 mm, slice thickness = 3 mm, slice gap = 0.3 mm, fold-over direction = Feet/Head (FH), Number of excitation (NEX) = 2, resolution = $0.92\times1.16\times3.0$ mm^3 (T1W) and $0.78\times1.01\times3.0$ mm^3 (T2W), recon resolution = $0.49\times0.49\times3.0$ mm^3, Time of echo (TE)/Time of Repetition (TR) = 7.2/530 ms (T1W) and 120/3314 ms (T2W). A total of 11 sagittal images covering the whole cervical spinal cord were acquired. For axial imaging, the imaging parameters were as follow: FOV = 80×80 mm, slice thickness = 7 mm, slice gap = 2.2 mm, fold-over direction = anterior/posterior (AP), NEX = 3, resolution = $0.63\times0.68\times7.0$ mm^3 (T1W) and $0.63\times0.67\times7.0$ mm^3 (T2W), recon resolution = $0.56\times0.55\times7.0$ mm^3 (T1W) and $0.63\times0.63\times7.0$ mm^3 (T2W), TE/TR = 8/1000 ms (T1W) and 120/4000 ms (T2W). Cardiac VCG triggering was applied to minimize the pulsation artifact from CSF. A total of 12 transverse images covering the cervical spinal cord from C1 to C7, each of which was placed at the centre of either vertebra or intervertebral disc, were acquired. Diffusion MRI images were acquired using pulsed sequences: spin-echo echo-planar imaging (SE-EPI). Diffusion gradients in 15 directions were applied with b-value = 600 s/mm^2. The imaging parameters were as follow: FOV = 80×80 mm, slice thickness = 7 mm, slice gap = 2.2 mm, fold-over direction = AP, NEX = 3, resolution = $1\times1.26\times7.0$ mm^3, recon resolution = $0.63\times0.64\times7.0$ mm^3, TE/TR = 60 ms/5 heart beats. The image slice planning was the same as the anatomical axial T1W and T2W images, with 12 slices covering the cervical spinal cord from C1 to C7. The duration of diffusion tensor imaging (DTI) averaged 24 minutes per subject with an average heart rate of 60 beats per minute. Spatial saturation with Spectral Presaturation with Inversion Recovery (SPIR) was applied to suppress the fold-over effect. To alleviate EPI distortion problem caused by increased magnetic susceptibility at 3.0-T, the distortion correction method based on the reversed gradient polarity and parallel imaging were employed (Andersson et al., 2003; Chuang et al., 2006; Morgan et al., 2004). Diffusion measurement was performed using DTI Studio software (Version 2.4.01 2003, Johns Hopkins Medical Institute, Johns Hopkins University, Baltimore, MD). Image volume realignment and 3D rigid body registration with different diffusion gradients were conducted by Automated Image Registration (AIR) program, a source code embedded in DTI Studio, in order to reduce the effect of motion artifact. The realigned and co-registered diffusion weighted data sets were double checked for image quality and then used for estimation of diffusion tensors, including three eigenvalues and the corresponding eigenvectors. The fractional anisotropy (FA) maps were derived for quantitative analysis. The region of interest (ROI) was defined to cover the spinal cord (Fig. 1). The FA values were calculated and averaged all selected voxels in the cord for all subjects using Image J (National Institute of Health, USA). The FA maps were also used for Shannon entropy analysis subsequently.

Shannon entropy analysis

In communication theory, Shannon's entropy represented the average or mean amount of information per message (Shannon, 1997). Specifically, the Shannon entropy in this study was calculated as,

$$H(X_i) = -\sum_{x_i \in K} p(x_i)\log p(x_i),$$

where *Xi* was FA values of voxels within the cord. *k* was the set at optimal level—128 in the FA map with 128×128 pixels, which was determined after comparing with other number of bins, including 32, 64 and 256; and *p(xi)* was the probability of that attenuation value being repeated throughout *k*. *p(xi)* was calculated by binning the FA values for each voxel across the set levels of gray scales and a histogram was constructed from which the *p(xi)*'s were derived. The algorithm was to the base 2 casting the measured entropy or information to be expressed in binary digits or bits.

Statistical analysis

The comparisons between FA value and the entropy along the length of cervical spinal cord were performed among the three groups using one-way ANOVA and *post-hoc* test. The level of significance was set at $p<0.05$. All data analyses were performed using SPSS 15.0 analysis software (SPSS Inc, Chicago, IL, USA).

Results

The average value and entropy of FA map changes along the length of cervical spinal cord

There existed the trend showing the decrease in the average value of FA map from the upper to lower cervical spinal cord in adult healthy

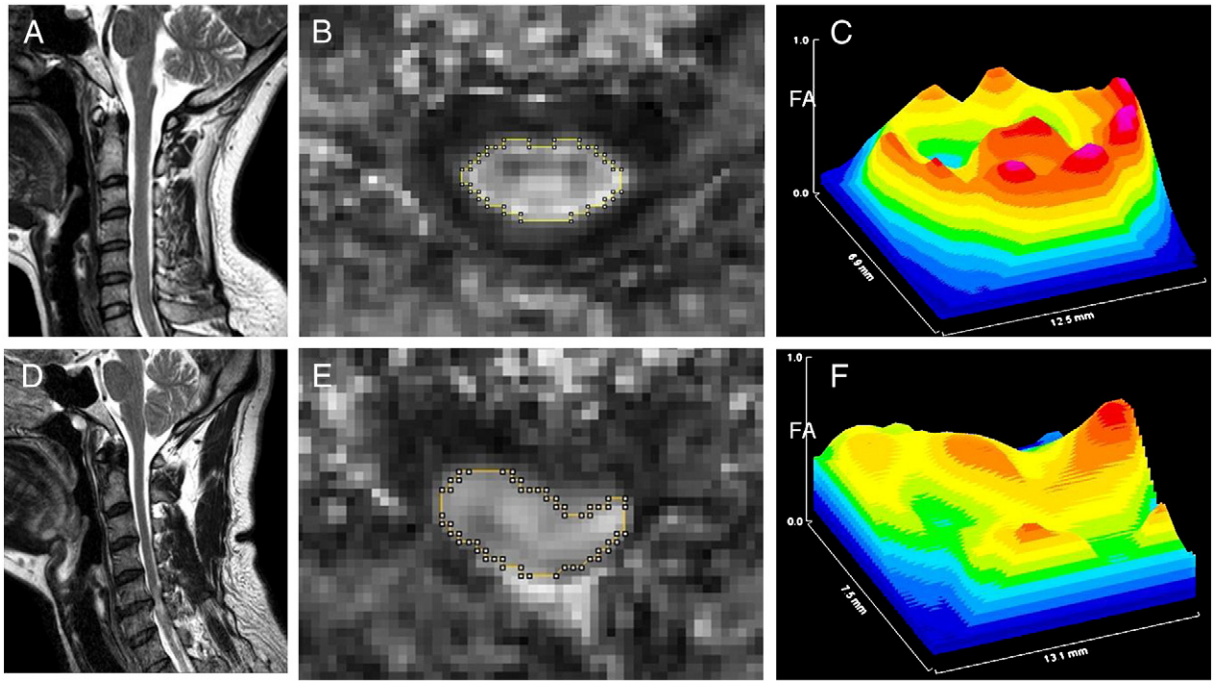


Fig. 1. The representative MR imaging showing the definition of region of interest (ROI) to cover the healthy cord (A, B, C) and myelopathic cord (D, E, F). The axial slice of the cord was taken at vertebral body and intervertebral disc levels. To avoid the partial volume effect, a small elliptic circle was drawn by hand to cover the region of the cord on fractional anisotropy (FA) map (B, E). The three-dimensional surface plot of FA map showed the distribution of FA values of the individual voxels included in the ROI (C, F).

subjects. In the upper cervical regions, it was found that FA values were relatively higher in the upper cervical region (C2–3: 0.66 ± 0.10, C3: 0.65 ± 0.09, and C3–4: 0.65 ± 0.07) than in the lower cervical region (C5–6: 0.59 ± 0.09, C6: 0.57 ± 0.11, and C6–7: 0.51 ± 0.11) ($p<0.05$). Yet there was no significant difference in the Shannon entropy of FA map of spinal cord between the upper (C2–3: 6.12 ± 0.14, C3: 6.11 ± 0.14, and C3–4: 6.09 ± 0.16) and lower cervical regions (C5–6: 6.04 ± 0.23, C6: 6.02 ± 0.15, and C6–7: 5.95 ± 0.28) ($p>0.05$), although the entropy appeared slightly higher in the upper cervical region (Fig. 2).

It was also noted in adult healthy subjects that there was large variation among the individuals in the average values of FA map (0.62 ± 0.08), with the coefficient of variance (CV) in 12.8%; whereas the variation among the individuals in the entropy of FA map was relatively small (6.05 ± 0.17), with the CV in 2.8%.

The age-related changes of the average value and entropy of FA map

As shown in Fig. 2, there was no significant difference in the average value of FA between the elderly and adult healthy subjects. The trend of the decrease in FA from the upper to lower cervical spinal cord in adult healthy subjects remained in the elderly. In the upper cervical regions, it was found that FA values were relatively higher in the upper cervical region (C2–3: 0.69 ± 0.10, C3: 0.68 ± 0.11, and C3–4: 0.63 ± 0.13) than in the lower cervical region (C5–6: 0.62 ± 0.11, C6: 0.61 ± 0.08, and C6–7: 0.57 ± 0.10) ($p<0.05$).

There was also no significant difference in the Shannon entropy of FA map of elderly spinal cord between the upper (C2–3: 6.02 ± 0.24, C3: 6.03 ± 0.19, and C3–4: 5.97 ± 0.34) and lower cervical regions (C5–6: 5.94 ± 0.30, C6: 5.89 ± 0.38, and C6–7: 5.86 ± 0.31) ($p>0.05$). As shown in Fig. 3, the entropy of cervical spinal cord in the elderly appeared to be slightly lower than that in the adult healthy subjects but there was not statistical significance between two groups.

The CSM-related changes of the average value and entropy of FA map

The trend of the decrease in FA from the upper to lower cervical spinal cord in adult and elderly healthy subjects was lost in CSM patients. In CSM patients, there was no significant difference in FA values between the upper cervical region (C2–3: 0.60 ± 0.03, C3: 0.61 ± 0.05, and C3–4: 0.62 ± 0.08) and the lower cervical region (C5–6: 0.62 ± 0.10, C6: 0.63 ± 0.05, and C6–7: 0.57 ± 0.05) ($p>0.05$). The FA values at and above the level of cervical spondylosis and cord compression, i.e. C2, were relatively lower than the other levels (Figs. 2 and 3).

The Shannon entropy of FA map of cervical spinal cord was lower at the level of spinal cord compression in CSM patients, as well as in the upper (C2–3: 5.36 ± 0.07, C3: 5.42 ± 0.61, and C3–4: 5.50 ± 0.61), but also in the lower cervical regions (C5–6: 5.67 ± 0.47, C6: 5.39 ± 0.61, and C6–7: 5.43 ± 0.52) ($p<0.05$ for all) (Figs. 2 and 3).

Taking the cervical spinal cord as a whole, the entropy was significantly lower in CSM patients than in the adult and aged healthy subjects (group A: 6.07 ± 0.18; B: 6.01 ± 0.23; C: 5.32 ± 0.44; $p<0.05$). Whereas there were no significant difference in FA values among groups (group A: 0.62 ± 0.08; B: 0.64 ± 0.09; C: 0.64 ± 0.12).

Discussion

This study presented a novel application of Shannon entropy for the analysis of diffusion anisotropy mapping of spinal cord. This method enabled us to characterize the complexity of tissue architecture in healthy and myelopathic spinal cord. Cervical spondylotic myelopathy is characterized by spinal stenosis i.e. spondylosis and/or disc degeneration, with induced chronic compression on the cord and the subsequent motor and sensory deficit (Baron and Young, 2007). However, the insidious onset of CSM, the variety of clinical signs and symptoms, and lack of objective evaluation tool poses a big challenge to make an early and

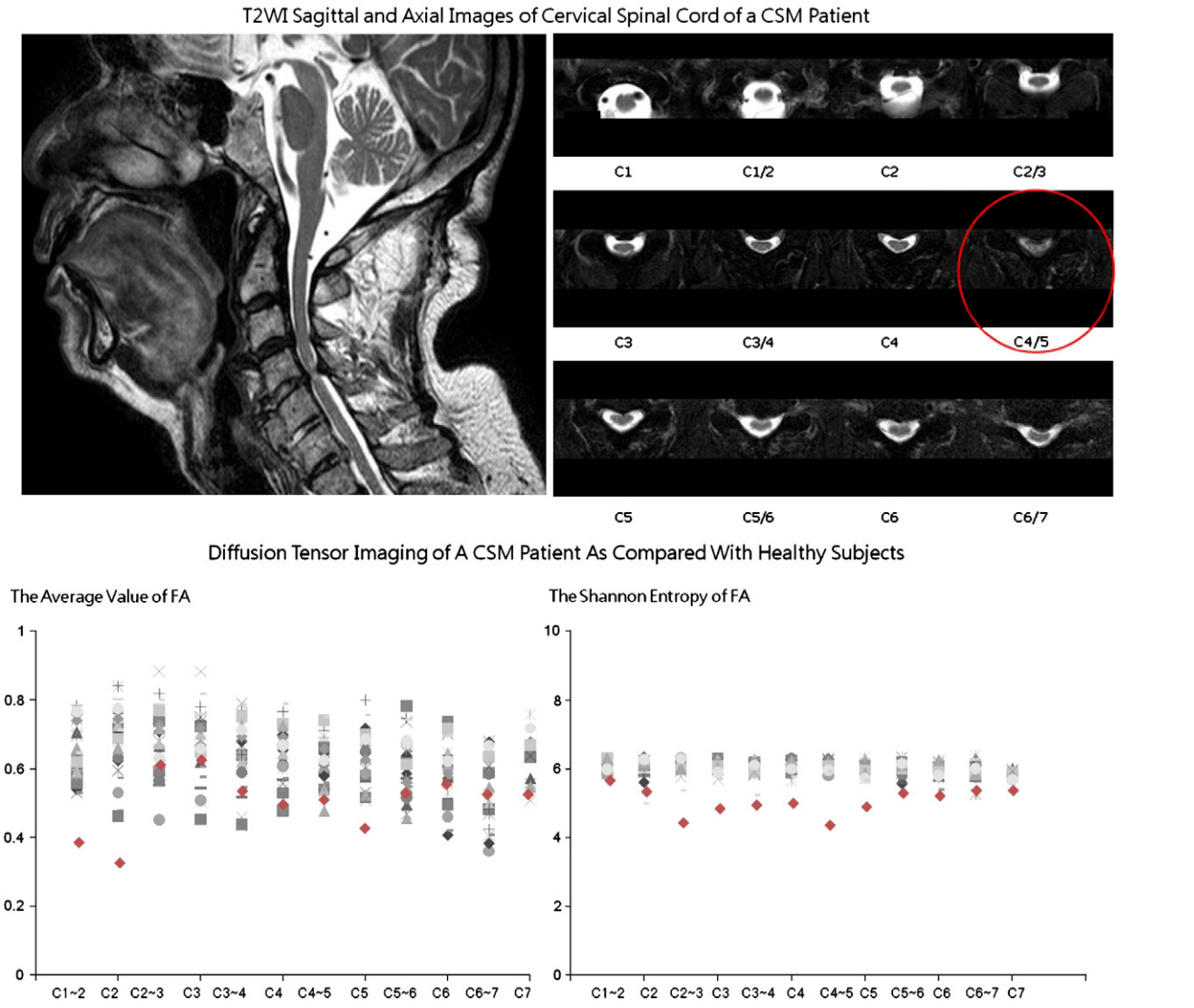


Fig. 2. The sagittal and axial T2-weighted images (T2WI) of a CSM cases showing the cord compression at C4–5 level (red circle). Under diffusion MR imaging, it was revealed that the fraction anisotropy (FA) was only relatively lower at the level of C5 and also C2 (red dots) when comparing with the wide normal range of FA values in healthy subjects (gray dots). Based on the entropy-based analysis, it was noted that the entropy generally decreased along the length of cervical spinal cord, in particular at the stenotic level C4–5 (red dots) in comparison with the narrow normal range of entropy values of healthy subjects (gray dots).

precise diagnosis and prognostication for surgical decompression (Baron and Young, 2007; McCormick et al., 2003). The findings generated from this study suggested that the entropy-based analysis of MR diffusion images would be helpful to separate CSM patients from healthy subjects as an objective evaluation parameter, which was found to be independent of the levels of cervical spine.

Recently, the emerging diffusion tensor images allowed the detection of myelopathic cord with higher sensitivity and specificity in comparison with the conventional anatomic MR images (Facon et al., 2005). Yet as shown in both the previous and present studies, FA values obtained from healthy cervical spinal cord of human beings were spread in a very wide range with large individual variation (Facon et al., 2005; Mamata et al., 2005; Shanmuganathan et al., 2008; Van Hecke et al., 2008; Voss et al., 2007). It was reported that only 54% of all CSM cases showed the decreased FA at the stenotic level in comparison with the normal spinal cord (Mamata et al., 2005). In this study, the introduction of Shannon entropy to analysis of diffusion anisotropy of spinal cord tissue architecture successfully decreased the individual variation from 12.8% for average FA values to 2.8% for the entropy value. In all five CSM patients, the entropy was significantly lower at the stenostic level. It suggested the potential application of Shannon entropy as an objective assessment for level diagnosis in CSM.

The complexity of cervical spinal cord architecture was once studied under MR diffusion images based on the analysis of FA value in ventral, lateral and dorsal columns of white matter and gray matter (Hesseltine et al., 2006). In healthy subjects, the FA value of the dorsal and lateral column of the cord was higher than that of ventral column as well as gray matter (Hesseltine et al., 2006). As compared with healthy subjects, it was found in the five CSM patients in this study that the FA values were lower in the dorsal and lateral column of white matter, yet such change was not present in ventral column of white matter as well as gray matter (see Appendix). Such changes made the FA values in the dorsal and lateral column of white matter closer to the ventral column and also gray matter, which could explain why there was lower

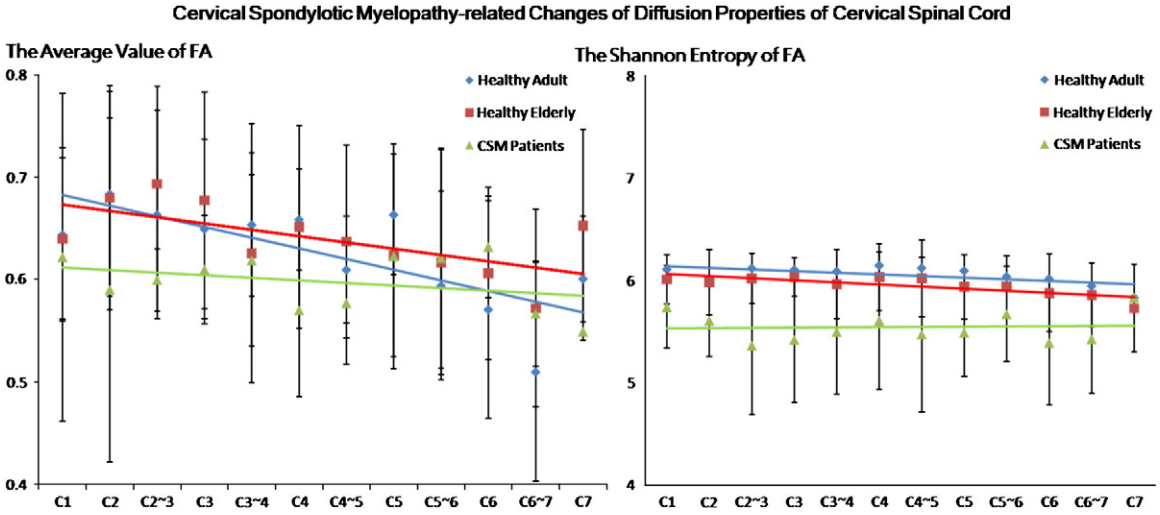


Fig. 3. The data showing the trend of diffusion properties of cervical spine cord along the whole length of cervical spine were analyzed in adult and elderly healthy subjects, and cervical spondylotic myelopathy (CSM) patients, respectively. As shown by the lineal trend line, the FA values decreased along the length of cervical spine in healthy subjects whereas such trend disappeared in CSM patients. Interestingly, the changes of the entropy values along the length of cervical spine were obscure. Yet the entropy value in CSM patients was significantly lower than the healthy subjects.

Shannon entropy of FA map in CSM patients. Such CSM-related diffusion anisotropy changes were not uniform, and the average FA values in the whole cord might not be able to separate the CSM patients from healthy subjects.

The anterograde and retrograde axon degeneration in CSM occurred, which could contribute to the diffusivity changes even at the locations distant from the injury site. The decrease in the entropy value could be found at the levels of cervical regions both above and below the narrowing canal levels. The decreased FA values could be observed at the stenostic level or above. But such FA changes could not be detected in the cord at the levels below it. Although the underlying reasons remain unknown, the changes of Shannon entropy at the adjacent levels of spinal stenosis appear to be more consistent with such anterograde and retrograde axon degenerations of the spinal cord. The extent of Shannon entropy changes might serve as a prognostic factor for surgical outcome of CSM patients.

Diffusion anisotropy of brain decreases with normal aging process (Pfefferbaum and Sullivan, 2003; Pfefferbaum et al., 2000; Zhang et al., 2010). Yet such a trend might not be found in the spinal cord. In this study, it was found that there was no significant difference in both FA and entropy values between the adult and elderly healthy subjects. The findings suggested that the microarchitecture of cervical spinal cord does not change during aging process. Our results were consistent with previous studies which showed a weak correlation between FA values and the age of the subjects (Mamata et al., 2005; Van Hecke et al., 2008).

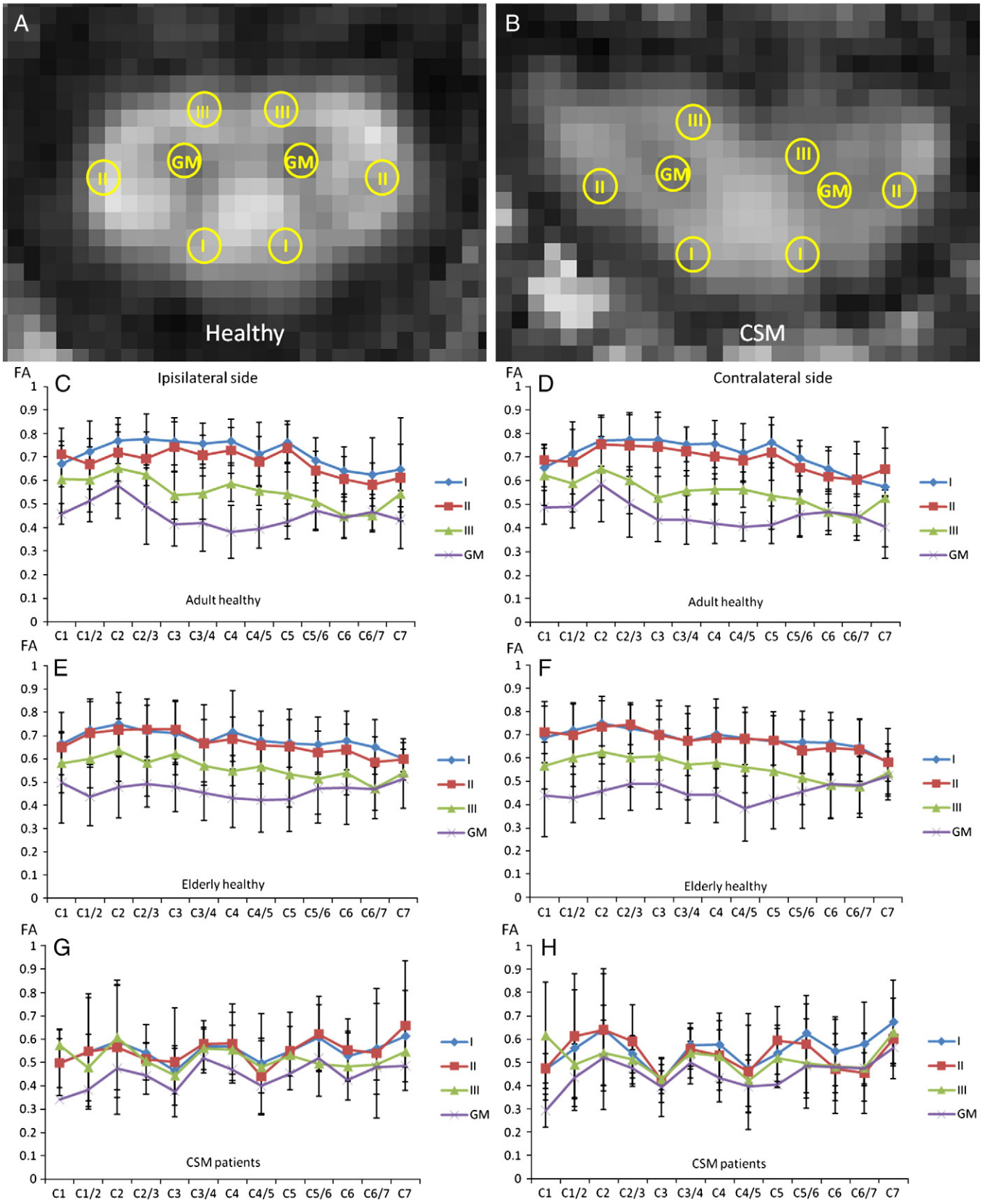
In this study, the axial MR diffusion tensor images of cervical spinal cord were obtained at vertebral body and intervertebral disc levels in healthy subjects and the patients with cervical spondylosis. The image quality of the reconstructed FA maps, as shown in the present study, was remarkably good and permitted the differentiation of white and gray matter. This was one of the strength of the present study over the previous CSM studies based on the sagittal DTI images (Demir et al., 2003; Facon et al., 2005; Mamata et al., 2005). Meanwhile, it should be also known that DTI of spinal cord was comparatively more technically challenging than the technique applied to brain (Maier and Mamata, 2005). Namely, that breathing, swallowing or cerebrospinal fluid (CSF) pulsation caused stronger motion artifacts than in the brain. The high field, 3-Tesla MRI scanner was employed in this study to increase SNR ratio and shorten scan time. In addition, the cardiac gating technique was applied to reduce the motion artifacts. The images were also corrected via a well established co-registration process. The spinal cord runs deep inside the body and it was more difficult to achieve higher signal-to-noise (SNR) ratio in conjunction with better spatial resolution. The compromised spatial resolution of spinal cord caused the partial volume effect, which poses a big challenge for the analysis of diffusion MR images of spinal cord (Maier and Mamata, 2005). The small area of spinal cord contained the limited voxels. The FA value of individual voxel on the boundary of the spinal cord would be affected by partial volume effect due to its small area. Shannon entropy provided the information related to the distribution of FA values of all voxels within ROI, instead of the exact value of a certain voxel, which might be less influenced by partial volume effect.

In summary, Shannon entropy was successfully introduced to distil the information of the complexity of spinal cord tissue architecture based on FA map under diffusion MR imaging. It provided an alternative approach for characterizing diffusion anisotropy of spinal cord. It might be a useful tool for the diagnosis and prognostication of CSM. It was well known that the loss of the tissue architecture complexity would lead to functional impairment (Metwalli et al., 2006; Neuvonen and Salli, 2005; Walsh et al., 2008). The drop in the Shannon entropy of diffusion anisotropy of spinal cord tissue architecture might account for the neurological deficit in CSM patients. Limitations of this study included the small sample group of CSM patients recruited as well as the sensitivity of the Shannon entropy to noise, which suggests the need for the calibration among different DTI scan protocols. Future studies will seek to emphasize the relationship between changes in the Shannon entropy of the myelopathic cord and the sensorimotor performance of CSM patients.

Acknowledgments

The study is supported by the General Research Fund of the University Grant Council of Hong Kong (771608M). The authors would like to thank Dr. Kin-Cheung Mak and Dr. Henry Mak for their assistance in patient recruitment and MRI scanning.

Appendix



Appendix Fig. 1. The four regions of interest were defined in the dorsal (I), lateral (II) and ventral (III) aspects of white matter and also gray matter (GM) in healthy and myelopathic cord along its whole length; FA values were measured for comparison (A, B). For healthy subjects of either adult or elderly, the FA values were higher in the dorsal and lateral aspects of white matter than that in the ventral aspect and also gray matter (C–F). Such region-dependent diffusion pattern was disturbed in CSM with diminished disparities in FA values among the regions of spinal cord (G, H).

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