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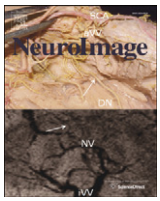

Orientation entropy analysis of diffusion tensor in healthy and myelopathic spinal cord

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ABSTRACT

The majority of nerve fibers in the spinal cord run longitudinally, playing an important role in connecting the brain to the peripheral nerves. There is a growing interest in applying diffusion tensor imaging (DTI) to the evaluation of spinal cord microarchitecture. The current study sought to compare the organization of longitudinal nerve fibers between healthy and myelopathic spinal cords using entropy-based analysis of principal eigenvector mapping. A total of 22 subjects were recruited, including 14 healthy subjects, seven cervical myelopathy (CM) patients with single-level compression, and one patient suffering from multi-level compression. Diffusion tensor magnetic resonance (MR) images of the cervical spinal cord were obtained using a pulsed gradient, spin-echo echo-planar imaging (SE-EPI) sequence with a 3T MR system. Regions of interest (ROIs) were drawn manually to cover the spinal cord, and Shannon entropy was calculated in principal eigenvector maps. The results revealed no significant differences in orientation entropy values along the whole length of cervical spinal cord in healthy subjects (C2–3: 0.73 ± 0.05; C3–4: 0.71 ± 0.07; C4–5: 0.72 ± 0.048; C5–6: 0.71 ± 0.07; C6–7: 0.72 ± 0.07). In contrast, orientation entropy values in myelopathic cord were significantly higher at the compression site (0.91 ± 0.03), and the adjacent levels (above: 0.85 ± 0.03; below: 0.83 ± 0.05). This study provides a novel approach to analyze the orientation information in diffusion MR images of healthy and diseased spinal cord. These results indicate that orientation entropy can be applied to determine the contribution of each compression level to the overall disorganization of principal nerve tracts of myelopathic spinal cord in cases with multi-level compression.

Introduction

Magnetic resonance imaging (MRI) is currently the most widely used imaging technique for evaluating spinal cord parenchyma. However, conventional MRI, such as T1 and T2 weighted imaging, is limited to providing macroscopic information, including gross deformity and hemorrhage (Baron and Young, 2007a). Diffusion tensor imaging (DTI) was recently developed to enable the detection of tissue microarchitecture at the microscopic level based on a rank-two diffusion tensor model (Thurnher and Law, 2009). Commonly used parameters for delineation of spinal cord tissue microarchitecture include fractional anisotropy (FA), apparent diffusion coefficient (ADC) and mean diffusivity (MD). All of these parameters are derived from eigenvalues to evaluate the scalar properties of water molecule diffusion (Hagmann et al., 2006). Eigenvectors and eigenvalues derived from the diffusion tensor matrix respectively reflect the direction and strength of the movement of water molecules (Hagmann et al., 2006). The principal eigenvector indicates the dominant diffusion orientation of water molecules, which, in theory, is paralleled by the nerve bundles (Lin et al., 2001; Maier, 2007). The disturbance in the orientation of water molecule movement thus reflects the disorganization of nerve bundles. Although fiber tractography (FT) techniques have been developed for visualization of nerve bundles based on both eigenvalues and eigenvectors (Thurnher and Law, 2009), a mathematical approach for quantifying the severity of the disturbance in the orientation of water molecule movement is currently lacking.

Directional entropy has been proposed as a measure of the distribution of the dominant orientation of diffusion in the assessment of microstructural properties in the brain (Neuvonen and Salli, 2005). In our study, we want to introduce this entropy-based principal eigenvector analysis into the cervical spinal cord for evaluating microstructural changes after cervical myelopathy. It was postulated that such a method would be much more useful in the spinal cord than in the brain for detecting orientation changes, due to the orientational uniformity of spinal cord nerve tracts. In the present study, we measured orientation entropy as an index of disorder in orientation distribution, allowing us to examine a feature of cervical myelopathy (CM) after aligning single compression levels as the center. In addition, multiple level compression of the cervical spinal cord is common in CM. This poses a challenge for clinical diagnosis in determining the pathogenic level that should be targeted for surgical

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decompression to provide maximum benefit to patients with the fewest complications. We used feature extraction data in cases of confirmed CM to estimate the probabilities for pathogenic level along the multiple level compression cervical spinal cord in one case. These findings might help to guide treatment strategies for surgical decompression.

Materials and methods

Subjects

A total of 22 volunteers, including 11 males and 11 females ranging from 30 to 84 years of age, were recruited in this study with informed consent. All volunteers were screened to confirm their eligibility. The inclusion criteria of healthy subjects were intact sensory and motor function evaluated by the Japanese Orthopaedic Association (JOA) score system (Yonenobu et al., 2001), and negative Hoffman's sign under physical examination. Exclusion criteria included the presence neurological signs and symptoms, or a past history of neurological injury, diseases and operations. CM patients were recruited with confirmed diagnosis by senior spine surgeons with seven single level compression patients (four males, three females, aged 64 ± 20 years) and one multiple level compression patient (female, 58 years old). The healthy subjects were recruited as a control group ($n = 14$, aged 46 ± 16 years).

MR data acquisition

The procedures and protocols in this study were approved by the authors' Institutional Review Board (UW 04-104 T/246). All images were acquired with a 3.0T MR scanner (Achieva, Philips, Netherlands) with pulse sequence programming performed prior to scanning to optimize the image quality. During the acquisition process, the subject was placed supine using a SENSE neuro-vascular (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 for anatomical T1-weighted (T1W) images, T2-weighted (T2W) images and DTI.

Sagittal and axial T1W and T2W images were acquired for each subject using a fast spin-echo (FSE) sequence. 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 = $0.92 \times 1.16 \times 3.0$ mm^3 (T1W) and $0.78 \times 1.01 \times 3.0$ mm^3 (T2W), recon resolution = $0.49 \times 0.49 \times 3.0$ mm^3, and echo time (TE)/repetition time (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 follows: FOV = 80×80 mm, slice thickness = 7 mm, slice gap = 2.2 mm, fold-over direction = anterior/posterior (AP), NEX = 3, resolution = $0.63 \times 0.68 \times 7.0$ mm^3 (T1W) and $0.63 \times 0.67 \times 7.0$ mm^3 (T2W), recon resolution = $0.56 \times 0.56 \times 7.0$ mm^3 (T1W) and $0.63 \times 0.63 \times 7.0$ mm^3 (T2W), and TE/TR = 8/1000 ms (T1W) and 120/4000 ms (T2W). Cardiac vectorcardiogram (VCG) triggering was applied to minimize the pulsation artifact from cerebrospinal fluid. Image acquisition began right after the rise of the wave of QRS complex. A total of 12 transverse images covering the cervical spinal cord from C1 to C7 were acquired, each of which was placed at the center of either a vertebra or an intervertebral disk. The pulse sequence used was single-shot spin-echo echo-planar imaging (SE-EPI). Diffusion encoding was performed in 15 non-collinear and non-coplanar diffusion directions with b-value = 600 s/mm^2. The imaging parameters were as follows: FOV = 80×80 mm, image matrix, 128×128, slice thickness = 7 mm, slice gap = 2.2 mm, fold-over direction = AP, NEX = 3, resolution = $1 \times 1.26 \times 7.0$ mm^3, recon resolution = $0.63 \times 0.63 \times 7.0$ mm^3, and TE/TR = 60 ms/5 heartbeats. The image slice planning was the same as in the anatomical axial T1W and T2W images, with 12 slices covering the cervical spinal cord from C1 to C7. The average duration of DTI was 24 min 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 problems caused by increased magnetic susceptibility at 3.0-T, the distortion correction method based on reversed gradient polarity and parallel imaging was employed (Andersson et al., 2003; Chuang et al., 2006; Morgan et al., 2004).

Data analysis for DTI and FT

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 using the Automated Image Registration (AIR) program (a source code embedded in DTI Studio software) to reduce the effect of motion artifact. The realigned and co-registered diffusion weighted data sets were double checked for image quality, then used for estimation of diffusion tensors, including three eigenvalues and the corresponding eigenvectors. The region of interest (ROI) was defined by B0 images to cover the spinal cord (Fig. 1) using Image J software (National Institute of Health, USA). For color coding of the eigenvector map in DTI Studio, each voxel is composed of three orthogonal direction components in an image reference frame: (r, g, b) – (ν_x, ν_y, ν_z), where r, g, and b represent red, green, and blue components of the voxel color, and (ν_x, ν_y, ν_z) is the normalized principal eigenvector, which points towards the coronal, axial and sagittal directions respectively (Jiang et al., 2006). The calculation of orientation entropy and least squares method (LSM) was performed using MATLAB (MathWorks, Natick, MA, USA).

Orientation entropy analysis

The eigenvector is a voxel-based measurement derived from the diffusion tensor so that the principal eigenvector only corresponds to the average fiber orientation within the voxel, and orthograde and retrograde directions of axonal tracts are not distinguished (Jiang et al., 2006). An angle resolution of 5° was used here, which was determined after comparison with other bin angles, including 3, 10, and 15°. Thus, the whole space was segmented as $K = (360°/5°) \times (90°/5°) = 1{,}296$ angle bands. The spatial direction pointed by the eigenvector in each voxel can be indicated by a pair of angles (θ, φ):

$$\text{Elevation angle } \theta = \sin^{-1}\left(\frac{\nu_z}{\sqrt{\nu_x^2 + \nu_y^2 + \nu_z^2}}\right)$$

$$\text{Azimuth angle } \varphi = \cos^{-1}\left(\frac{\nu_y}{\sqrt{\nu_x^2 + \nu_y^2}}\right).$$

The orientation entropy was defined in our study by

$$H = -\sum_{i=1}^{K} \frac{p(i)\ log_2[p(i)]}{log_2 N}$$

where $p(i)$ was the probability density that the eigenvector direction fell into the ith angle band, $\log_2 N$ was used to normalize the orientation entropy value to range from 0 (one orientation only) to 1 (all the orientations) where N was the number of the voxels covered. Orientation entropy does not identify the dominant orientation. Rather, it serves as an indicator of orientation spread or the scattering of eigenvector mapping (Neuvonen and Salli, 2005).