IN VIVO ASSESSMENT OF SPINAL CORD INTEGRITY USING MAGNETIC RESONANCE DIFFUSION TENSOR IMAGING

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INTRODUCTION

Spinal cord injury (SCI) induces motor (paralysis) and sensory deficits due to the disruption of specific ascending and descending spinal pathways. These deficits evolve in time as a reorganization of the central nervous system occurs, both at local and supraspinal sites. Such functional compensation may involve various anatomical, physiological and neurochemical mechanisms that are currently under investigation [1].

Magnetic resonance imaging (MRI) provides the ability to specifically observe white matter axons by measuring properties of water diffusion within tissues [2]. Diffusion tensor imaging (DTI) is based on the parametric modeling of such diffusion properties and allows for the mapping of principal diffusion directions, (Figure 1). DTI therefore allows for a non-invasive localization of white matter axons, and provides quantitative tools for assessing their integrity [3]. Although widely applied to the brain, DTI is challenging at the spinal level because of the small size of the cord and physiological motions (respiration, cardiac). Also, when using echo planar imaging (EPI) for rapid acquisition, data are very sensitive to magnetic field inhomogeneities. Since such inhomogeneities are commonly found nearby inter-vertebral disks, non-linear distortions – also known as susceptibility artifacts – appear in echo planar-based MR images and compromise anatomical accuracy (Figure 2).

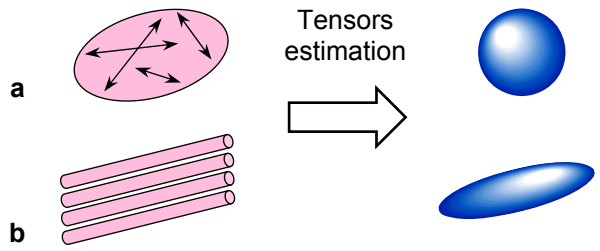

Figure 1. Principle of DTI. On the left are represented two kinds of tissues wherein water molecules are in constant displacement due to Brownian motion. Depending on the fibrous properties of these tissues, the diffusion could be either isotropic (**a**) or anisotropic (**b**), yielding different tensor profiles.

In previous studies, we developed a methodology for imaging the spinal cord of cats at high spatial and angular resolution that was feasible using a clinical MRI system [4]. In the present study, we applied the method in healthy and injured spinal cord of cats as well as in one healthy human. Objectives of the present study were: (i) to reduce image distortions despite a small voxel size, (ii) to compute consistent tensors map regarding the low signal-to-noise ratio, (iii) to assess the integrity of white matter tracts at the site of experimental spinal cord lesions and (iv) to validate the acquisition method in one healthy human.

METHODS

Cat preparation

Five cats were used for this study. Three cats were intact and two cats had complete SCI. Lesions were performed under general anaesthesia (isoflurane 1-2%) preceded by adequate pre-medications. After bilateral laminectomy at T13, a micro-knife was used

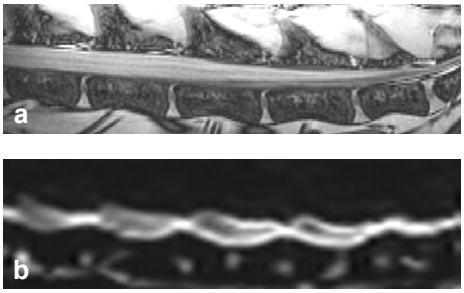

Figure 2. Illustration of susceptibility artifacts around inter-vertebral disks. **a:** T1-weighted distortion-free anatomical image showing sagittal slice of a cat lumbar spinal cord (top-right is dorsal-caudal), **b:** T2-weighted EPI with phase encoding antero-posterior.

for a complete transection of the cord. The gap between the rostral and caudal parts of the cord was filled with a hemostatic agent to prevent axonal re-growth and hemorrhage. The experimental protocols (human and animal) were approved by the relevant Ethics Committees at the University of Montreal.

MRI acquisition

Acquisitions were carried out on a Siemens Trio system (3T; version VA25) using a receive-only spine coil. RF transmission was performed using the body coil integrated into the magnet bore. Cats were positioned feet-first supine. They were anaesthetized (isoflurane 2%) and breathed freely. Field of view for image acquisition covered the thoraco-lumbar region. Diffusion-weighted data were acquired using following parameters: single-shot spin echo EPI, coronal orientation, TR/TE = 9500/109 ms, flip angle = 90°, 128×128 matrix, voxel size = 1.1 mm^3, b = 800 s/mm^2. Gradients for diffusion weighting have been applied in 55 directions using a polyhedron scheme (Figure 3). Acquisition was repeated five times to increase the SNR, yielding total acquisition duration of about 45 minutes. Parallel imaging technique was used to limit susceptibility artifacts [5]. In human, parameters were: single-shot spin echo EPI, axial orientation, TR/TE = 12900/103 ms, flip angle = 90°, 128×128 matrix, voxel size = 2 mm^3, b = 800 s/mm^2, 60 directions. Acquisition duration was about 15 minutes.

Data analysis

After having reconstructed magnitude images, DICOM data were averaged respectively to their diffusion-weighting directions. Datasets were corrected for residual distortions using the framework proposed in [6]. This step consisted of a non-linear registration of diffusion-weighted volumes on a distortion-free volume (T2-weighted Turbo Spin Echo, turbo factor = 13). Tensor estimation and tractography procedures were performed using MedINRIA [7]. Instead of performing the regression in the classical Euclidean space, tensors were computed into the log-Euclidean space which presents the same properties as the affine-invariant family but is computationally faster. A Riemannian framework was used assuming Rician noise. This approach presented some advantages, notably an efficient tensor regularization which is mandatory in datasets with low SNR.

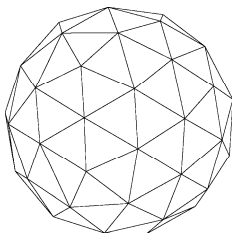

Figure 3. Polyhedron scheme used as directions for diffusion weighted gradients. It represents 55 spatially homogeneous samples on a sphere.

Fractional anisotropy (FA) is a quantitative measure of water diffusion anisotropy, which is computed from the tensor characteristics [2]. In this study, FA was quantified within spinal cord white matter of five cats, from T12 to L3. Then, FA was averaged along each vertebral segment. An analysis of variance (ANOVA) was conducted by comparing FA values between every vertebral segment. This was done to test for FA homogeneity along the cord.

RESULTS

On the image quality

The methodology developed in this study aimed at imaging the cord at relatively high spatial resolution (up to 1.1 mm^3). To avoid aliasing and to image a large portion of the cord, the field of view was large which implied having a long acquisition time for recording all lines of k-space. In the EPI technique, phase error induced by magnetic field inhomogeneities accumulates in successive lines of the acquired Fourier transform. That phase error leads to local image distortion when images are reconstructed using the inverse Fourier transform. Here, the strategy was to decrease acquisition time for limiting image distortions.

A first approach was to use a relatively high frequency-encoding bandwidth of 1200 Hz/pixel, enabling an echo-spacing of about 1 ms. A short echo spacing enabled faster acquisition of each frequency line. However, since the SNR is inversely proportional to the bandwidth, a compromise was found to get sufficient SNR. A complementary approach was to use parallel imaging. This technique uses the sensitivity profiles of different coil elements which acquire signal in several channels simultaneously, thus filling the k-space in an interleaved fashion [5]. We found that a four times accelerated acquisition gave the best results in terms of image distortion [8]. The SNR was 30.37 dB on the b_0 image, which was sufficient for computing consistent tensors.

Fractional anisotropy quantification in healthy and complete SCI cats

Results showed that FA was homogeneous in every healthy cat, and was significantly reduced at the site of lesions (Figure 3). The reduction of anisotropy was interpreted as loss of neural tissue. Since DTI measurements were made on chronic injured cats, we

expected Wallerian degeneration to have occurred rostral and caudal to the lesion since both descending and ascending tracts are severed. Wallerian degeneration is characterized by necrosis of axons which are separated from their cell body [9]. Such loss of myelinated axons might have had an impact on water diffusion, as observed in [10]. However, rostral and caudal to the injured site FA values were similar to that in healthy cats without significant change. For tractography, FA threshold was adjusted to 0.25 for all cats. The local decrease of FA within lesions produced robust fiber bundle disruption (Figure 4). This disruption was observed in both SCI cats. On the contrary, fiber bundles were continuous along the cord from T12 to L4 in the three healthy cats.

Tractography in the human spinal cord

A particularly novel aspect of this work is the application of the methodology in a healthy human subject. The acquisition strategy used for reducing susceptibility artifacts has not proven sufficient to obtain distortion-free image In Figure 5a, one can observe significant curvature of the cervical cord along the antero-posterior direction. In some regions, distortions were larger than 30 voxels. This justified the second step of the methodology for reducing residual distortions using a non-linear co-registration algorithm. Constraining the algorithm for image warping in only one direction – the phase encoding direction – we were able to robustly correct for these distortions (Figure 5b). After this preprocessing step, estimation of tensors and generation of FA color-map gave consistent results, *i.e.*, principal directions were oriented along the rostro-caudal axis (Figure 5c). Then, extrapolating tensors to a standard tractography procedure, fiber bundles were consistent and well registered to the distortion-free T1-weighted anatomical volume (Figure 5d).

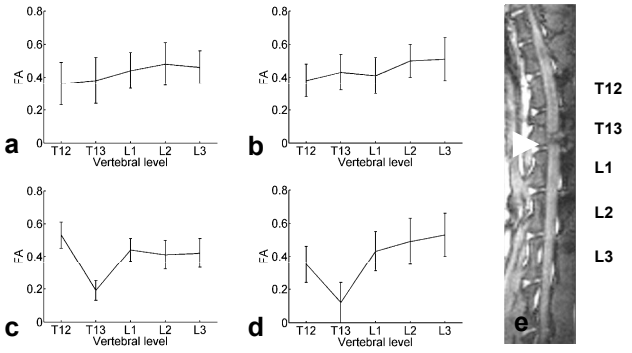

Figure 3. Quantification of fractional anisotropy along the spinal cord white matter of two healthy cats (**a,b**) and two cats with complete spinal cord lesion at level T13 (**c,d**). The lesion is indicated by an arrow in a sagittal view of a T1-weighted anatomical MRI (**e**).

DISCUSSION

What DTI can do

Diffusion tensor imaging allows for the non-invasive quantification of white matter integrity following spinal cord injury [8]. In the present study, we developed a method for imaging the spinal cord at high spatial resolution, and we applied this method for the first time in one healthy human. Gradients for diffusion weighting have been applied in a great number of directions following a polyhedron scheme. This limited any bias in estimating principal diffusion directions [11]. Regarding susceptibility artifacts, we demonstrated a hybrid method consisting in accelerating the acquisition for reducing phase errors, as well as co-registering diffusion-weighted volumes with a distortion-free volume. In a previously published study, we showed that high resolution DTI of the spinal cord enables for the identification of specific spinal pathways [12]. Using this method in healthy cats, we were able to detect dorsal and ventral columns as well as lateral tracts. The identification and quantification of white matter integrity in spinal cord sub-divisions opens the door to longitudinal studies aiming at correlating spinal cord integrity with functional deficits.

Limitations of the diffusion tensor

DTI successfully showed the gross anatomy of spinal pathways. Also, it allowed detection of spinal cord lesions via loss of fractional anisotropy. However, there is a well recognized limitation associated with the tensor. In various part of the central nervous system, white matter pathways might cross or graze each other, yielding two or more principal diffusion directions within one voxel. In such cases, the first tensor's eigenvector results from a linear combination of major diffusion directions within that voxel. Thus, one cannot confidently rely on the tensor for inferring

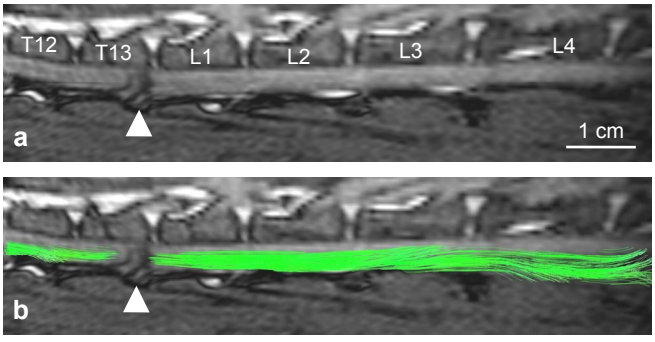

Figure 4. **a:** Sagittal view of a T1-weighted anatomical MRI of a cat spinal cord with complete spinal cord injury (white arrow). **b:** Same image with an overlay of fiber bundles reconstructed from DTI tractography. It shows a clear disruption at the exact lesion location.

on white matter architecture. To overcome this issue, model free approaches have been proposed to measure the microscopic diffusion without constraining its representation. These methods are known as q-ball imaging and have already demonstrated benefits for imaging the brain [13].

Perspectives

Although the proposed method enabled for a significant reduction of susceptibility artifact using single-shot EPI, other types of pulse sequences have been recently developed and could potentially be adapted to spinal cord DTI [14]. Also, the limitation of DTI discussed previously provides an incentive to use model-free approaches to represent the diffusion process in the healthy and injured spinal cord for two reasons. First, white matter architecture at the spinal level includes multiple sites of crossing fibers. Second, the plasticity following injury might induce a reorganization of white matter pathways [1]. Such subtle reorganization or redirection of pathways, involving a limited number of axons, might be invisible to DTI. We hope that such studies will advance diffusion MRI as a possible clinical tool for characterizing spinal cord integrity in various pathologies including multiple sclerosis, amyotrophic lateral sclerosis and spinal cord trauma.

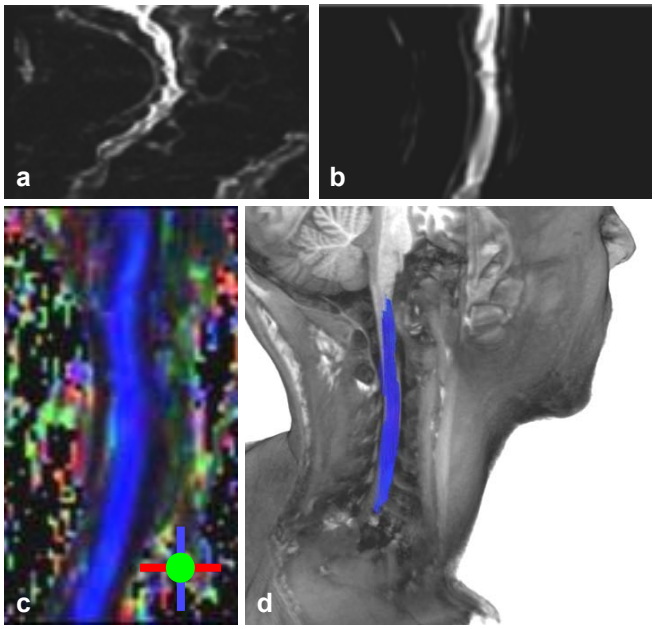

Figure 5. **a:** Sagittal view of a raw EPI T2-weighted human cervical spinal cord at b = 0 s/mm^2. **b:** Same image corrected from susceptibility artifacts using non-linear registration method. **c:** FA color-map computed from all dMRI dataset. Color code corresponds to principal diffusion directions. **d:** 3-D reconstructed anatomical MRI with an overlay of fiber tracts.

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