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Cross-validation of serial optical coherence scanning and diffusion tensor imaging: A study on neural fiber maps in human medulla oblongata

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ABSTRACT

We established a strategy to perform cross-validation of serial optical coherence scanner imaging (SOCS) and diffusion tensor imaging (DTI) on a postmortem human medulla. Following DTI, the sample was serially scanned by SOCS, which integrates a vibratome slicer and a multi-contrast optical coherence tomography rig for large-scale three-dimensional imaging at microscopic resolution. The DTI dataset was registered to the SOCS space. An average correlation coefficient of 0.9 was found between the co-registered fiber maps constructed by fractional anisotropy and retardance contrasts. Pixelwise comparison of fiber orientations demonstrated good agreement between the DTI and SOCS measures. Details of the comparison were studied in regions exhibiting a variety of fiber organizations. DTI estimated the preferential orientation of small fiber tracts; however, it didn't capture their complex patterns as SOCS did. In terms of resolution and imaging depth, SOCS and DTI complement each other, and open new avenues for cross-modality investigations of the brain.

Introduction

Diffusion magnetic resonance imaging (dMRI) has revolutionized our understanding of structural connections in humans. The technique provides a unique solution to noninvasively visualize white matter fiber bundles over macroscopic distances in the living brain. dMRI captures the anisotropic diffusion of water molecules in the brain which run preferentially along the direction parallel to the axonal axes, and can be used to infer fiber organization and orientation. Recent technical developments have improved the spatial resolution to sub-millimeter scale and enabled high angular resolution imaging which describes the human brain with unprecedented details. dMRI has been proven to be valuable in clinical neuroscience (Fields, 2008; Thomason and Thompson, 2011), with studies showing that an array of disorders may have corresponding connectional components, including Alzheimer's disease (Kitamura et al., 2013; Wang et al., 2007), schizophrenia (Miyata et al., 2007; Rosenberger et al., 2012; Schmitt et al., 2011; Voineskos et al., 2010), autism spectrum disorders (Nair et al., 2013; Pollonini et al., 2010), major depression (Maller et al., 2010; Tham et al., 2010), and dyslexia (Koyama et al., 2013; Pugh et al., 2000; Vandermosten et al., 2012).

While there have been a number of neuroscientific and clinical applications of dMRI, the systematic validation of the dMRI technique for evaluating microstructural properties and connectivity in the human brain remains incomplete. Although light microscopy is able to visualize single axons, axonal tracking is extremely labor intensive, and cannot realistically be carried out for multiple fascicles traversing many centimeters of brain tissue through the white matter. Traditional validations by histology are divided into two realms: 1) neural tract tracers have been injected into local regions, and compared with selected tracks by dMRI tractography (Caminiti et al., 2013; Harsan et al., 2013; Seehaus et al., 2013); and 2) quantitative information have been derived by digital signal processing of myelin stained images and compared with dMRI orientation (Budde et al., 2011; Choe et al., 2012; Hansen et al., 2011; Leergaard et al., 2010). Those studies are predominantly performed on 2D slices. Early three-dimensional (3D) histological validation has proven to be difficult and has resulted in a relatively low correlation with dMRI tracks (Dauguet et al., 2007). Using multi-step registrations, Jbabdi et al. (2013) reported both agreements and dissociations between neural tracing trajectories and dMRI tractography on the organizations of ventral prefrontal fibers in macaque monkey. Polarized light imaging (Axer et al., 2011) has

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recently been proposed as an alternative technique for imaging fiber orientation, as it provides 3D orientation information with an isotropic voxel size of approximately 100 μm. However, the technique requires tissue slicing before the imaging, which makes inter-slice tracking of fiber bundles difficult and is prone to registration errors due to distortions intrinsic to cutting and mounting of large tissue sections.

The development of optical coherence tomography (OCT) (Huang et al., 1991) has shown promise for depicting fiber tracts in the central and peripheral nervous system (Arous et al., 2011; Leahy et al., 2013; Wang et al., 2011) and creating high-resolution brain images that have been correlated with histology (Assayag et al., 2013; Magnain et al., 2014). OCT is a depth-resolved imaging technique that generates cross-sectional images and 3D reconstruction of tissue microstructures. By integrating a tissue slicer with multi-contrast OCT, serial optical coherence scanner (SOCS) provides insight into large-scale brain imaging with microscopic resolution (Wang et al., 2014). SOCS enables a comprehensive 3D reconstruction of the brain and supports quantitative assessments of fiber architecture and orientation with intrinsic optical contrasts. Reflectivity is the conventional OCT contrast that measures the intensity of back-scattered light, and is sensitive to the variations of refractive index in tissue. On the other hand, polarization sensitive OCT (de Boer et al., 1997) utilizes an optical property called birefringence that originates from structural anisotropy. The birefringent tissues such as muscle, tendon and nerve have an optic axis on a plane orthogonal to the direction of light propagation. Because refractive indices for light polarized parallel and perpendicular to the optic axis are different (the difference is defined as birefringence), the polarization state of light traveling in such a tissue changes due to a delay between the orthogonal polarization components. The delay, known as retardance, is equivalent to the birefringence multiplied by the distance light travels, and it can be represented by phase as one wavelength corresponds to 360°. Brain imaging with SOCS showed that the reflectivity contrast portrays the morphology, and the polarization contrasts primarily probe myelinated nerve fibers in the white matter: the retardance delineates the architecture of nerve fibers, and the optic axis orientation quantifies the in-plane fiber orientations (Wang et al., 2011). In addition to the sectioning capability with multiple optical contrasts, the high acquisition speed of SOCS makes it appealing for macroscopic brain imaging in humans and non-human primates.

In this paper, we present cross-validation of SOCS and diffusion tensor imaging (DTI), which is a dMRI technique, on a postmortem human medulla sample. We establish a strategy that allows registration between 3D datasets of DTI and SOCS at high resolution. The white matter structures in the medulla are correlated on co-registered images. The fiber orientation maps produced by these modalities are compared. This study shows the potential for a cross-modality investigation of structural connectivity in normal and diseased brain.

Materials and methods

Tissue

Tissue sample was taken from the right hemisphere of a 60 year old male initially fixed in 10% buffered formalin beginning 14 hours postmortem for 2 months, and then subsequently stored in 4% periodate–lysine–paraformaldehyde (PLP) prior to and during data collection. Brain tissue was obtained from the Neuropathology Department at the Massachusetts General Hospital and is considered to be cognitively normal. A block of tissue, with an approximate size of 11 × 15 × 30 mm^3, containing the medulla oblongata was removed from the right brainstem which fit within a 28 mm inner diameter (ID) plastic cylinder. MRI human brain tissue experiments were approved by an Institutional Review Board at Massachusetts General Hospital. After the acquisition of DTI data at Massachusetts General Hospital, the sample was transferred to University of Minnesota for optical imaging.

DTI data acquisition

DTI data was acquired using a Bruker BioSpec Avance system (4.7 T/40 magnet, 12 cm bore, 40 G/cm gradients) at a 300 μm isotropic spatial resolution. The acquisition employed a 3D spin-echo sequence (TR/TE = 320/28, $\delta = 7$ ms, $\Delta = 10.4$ ms, matrix size = 256 × 96 × 96). The scan included diffusion-weighted images acquired with a b-value of 4032 s/mm^2 and 20 non-collinear diffusion-encoding directions, and two images acquired with a b-value of 0 s/mm^2. Total scan time was 18 h.

Radio frequency coil

A custom-built transmit/receive solenoid coil was designed to minimize the distance between the blocked sample in the plastic cylinder container and the surrounding coil, with an inner diameter of 30 mm and active length of 70 mm resulting in 5 turns of the copper coil element.

DTI post-processing

Diffusion tensor estimation and tractography was performed using the Diffusion Toolkit (Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital). The Fiber Assignment by Continuous Tracking (FACT) algorithm (Mori et al., 1999) was used with a maximum bending angle of 35°. The tensor maps were used to estimate the apparent diffusion coefficient, fractional anisotropy (FA), and fiber orientations.

SOCS imaging

SOCS integrates a multi-contrast OCT and a Vibratome tissue slicer (Wang et al., 2014). The multi-contrast OCT is a spectral-domain polarization-maintaining-fiber (PMF) based technique (Wang et al., 2010) that is capable of making intensity, phase and polarization sensitive measurements. The light source is a super-luminescence diode (central wavelength: 840 nm; bandwidth: 50 nm) yielding an axial (z-axis) resolution of 5.5 μm in tissue. A scan lens (focal length: ~36 mm) providing an estimated lateral (x/y-axis) resolution of ~15 μm is employed in the sample arm for consistent imaging quality over a large area. The acquisition speed for a depth profile (A-line) is set to 25 kHz. This is determined by a line scan camera recording interference related spectral oscillations on the orthogonal PMF channels. Inverse Fourier transform of the spectra in k (wave number) space yields the complex depth profiles in the form of $A_{1,2}(z)exp\{i\Phi_{1,2}(z)\}$, where the subscripts represent the polarization channels. The reflectivity $R(z)$, phase retardance $\delta(z)$ and relative axis orientation $\theta'(z)$ along depth z are extracted from the magnitudes and phases of the complex depth profiles as $R(z) \propto A_1(z)^2 + A_2(z)^2$, $\delta(z) = \arctan(A_1(z)/A_2(z))$, and $\theta'(z) = (\phi_1(z) - \phi_2(z))/2$, respectively. Construction and operation details of the imaging system can be found in Wang et al., 2010.

The medulla sample was cropped into a 2 × 1 × 0.7 cm^3 block (in xyz) and mounted on a vibratome slicer (Leica Microsystems, Bannockburn, IL) positioned under the scanner. One volumetric scan (optical section) contained 300 cross-sectional frames with 1000 A-lines in each frame. Each scan covered a 3D volume of 7 × 7 × 1.78 mm^3 and produced images with a voxel size of 7 × 23 × 3.47 μm^3. Eight scans were performed to cover the entire sample surface (2 cm × 1 cm). The scan head was repositioned between the adjacent sections, which had a 15% overlap to aid post-processing. One of these scans was also used for calibrating the axis orientation contrast, since a retarder with a known axis was placed next to and imaged together with the medulla sample. After imaging the superficial region, a 150 μm thick tissue slice was removed from the top surface, allowing for deeper regions to be exposed to light. The physical slice thickness was less than the useful imaging