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Ultra-high resolution diffusion tensor imaging of the microscopic pathways of the medial temporal lobe ☆

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ABSTRACT

Diseases involving the medial temporal lobes (MTL) such as Alzheimer's disease and mesial temporal sclerosis pose an ongoing diagnostic challenge because of the difficulty in identifying conclusive imaging features, particularly in pre-clinical states. Abnormal neuronal connectivity may be present in the circuitry of the MTL, but current techniques cannot reliably detect those abnormalities. Diffusion tensor imaging (DTI) has shown promise in defining putative abnormalities in connectivity, but DTI studies of the MTL performed to date have shown neither dramatic nor consistent differences across patient populations. Conventional DTI methodology provides an inadequate depiction of the complex microanatomy present in the medial temporal lobe because of a typically employed low isotropic resolution of 2.0–2.5 mm, a low signal-to-noise ratio (SNR), and echo-planar imaging (EPI) geometric distortions that are exacerbated by the inhomogeneous magnetic environment at the skull base. In this study, we pushed the resolving power of DTI to near-mm isotropic voxel size to achieve a detailed depiction of mesial temporal microstructure at 3 T. High image fidelity and SNR at this resolution are achieved through several mechanisms: (1) acquiring multiple repetitions of the minimum field of view required for hippocampal coverage to boost SNR; (2) utilizing a single-refocused diffusion preparation to enhance SNR further; (3) performing a phase correction to reduce Rician noise; (4) minimizing distortion and maintaining left–right distortion symmetry with axial-plane parallel imaging; and (5) retaining anatomical and quantitative accuracy through the use of motion correction coupled with a higher-order eddy-current correction scheme. We combined this high-resolution methodology with a detailed segmentation of the MTL to identify tracks in all subjects that may represent the major pathways of the MTL, including the perforant pathway. Tractography performed on a subset of the data identified similar tracks, although they were lesser in number. This detailed analysis of MTL substructure may have applications to clinical populations.

Introduction

The intricate circuitry of the medial temporal lobe (MTL) subserves mnemonic function in humans and non-human primates (Aggleton and Brown, 1999). Pathology of the MTL results in the memory complaints that form the hallmark of Alzheimer's disease (AD) (Giannakopoulos et al., 2009; Gómez-Isla et al., 1997; Mirra et al., 1991; Trojanowski and Lee, 2002). In particular, neurofibrillary pathology starts at the entorhinal cortex (ERC), the gateway of input and output between the hippocampus and the remainder of the neocortex (Braak and Braak, 1991). Cell loss in the ERC is marked in AD, particularly at early stages, and tangle-driven neurofibrillary pathology correlates well with memory complaints (Gómez-Isla et al., 1996; Hyman et al., 1984; Van Hoesen et al., 1991). This cell loss necessarily affects the perforant pathway, the main fiber tract connecting the ERC to the hippocampus proper (Suzuki and Amaral, 1994; Witter et al., 1989). Evaluation of the perforant pathway with diffusion tensor imaging (DTI) may provide insights into pre-clinical disease in the elderly, but identification of this tract has been elusive, with relatively few *in vivo* studies to date that only partially or indirectly image this pathway (Kalus et al., 2006; Yassa et al., 2010). Epilepsy often is clinically suspected to originate in the MTLs, but traditional methods of structural MRI often fail to identify an abnormality that is later proven surgically. Similar to AD, there have been only a few epilepsy DTI studies that have attempted to address medial temporal microstructure and micropathology (Salmenpera et al., 2006).

Abbreviations: MTL, medial temporal lobe; AD, Alzheimer's disease; DWI, diffusion weighted image; DTI, diffusion tensor imaging; EPI, echo-planar imaging; FA, fractional anisotropy; MD, mean diffusivity; isoDWI, isotropic diffusion weighted image, b = 0 image: b = 0 s/mm^2 (no diffusion weighting) image; GRAPPA, generalized auto-calibrating partially parallel acquisition; ERC, entorhinal cortex; PRC, perirhinal cortex; PHC, parahippocampal cortex; CA, cornu ammonis; DG, dentate gyrus; CA3DG, cornu ammonis 3 and dentate gyrus; Subic, subiculum; SRLMHS, stratum radiatum lacunosum moleculare and hippocampal sulcus; HS, hippocampal sulcus.

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Isotropic high-resolution *in vivo* DTI studies of the MTL are absent in the literature. High-resolution acquisitions are needed to tease apart the anatomically distinct subregions of the MTL, but almost all *in vivo* DTI studies are done at 2.0–2.5 mm isotropic resolution, including most studies done in AD and epilepsy (Zeineh et al., 2010). Of the few studies investigating the perforant pathway, one study utilized highly anisotropic voxel sizes to demonstrate changes in a fractional anisotropy (FA) based metric along the expected course of this pathway with aging (Yassa et al., 2010). Possibly because tractography algorithms require isotropic voxels to avoid significant bias (Jones and Leemans, 2011), Yassa et al. performed an anatomically based measurement rather than streamline-based tractography. An *ex vivo* study at 200 μm resolution of the hippocampus demonstrated stages of the perforant pathway, but required stopping points in tractography, possibly because of crossing-fibers (Augustinack et al., 2010).

In this study, we attempted to overcome a major obstacle of inadequate resolution and SNR by acquiring images at 1.4 mm isotropic resolution over several repetitions. Note, this is only 34%/17% of the voxel volume compared to a 2.0 mm/2.5 mm isotropic study, respectively, with a similar expected drop in signal-to-noise ratio (SNR). To achieve images with symmetric and minimal distortion, we have imaged in the axial plane using our in-house built *g*eneralized *a*uto-calibrating *p*artially *p*arallel *ac*quisition (GRAPPA) DTI sequence with a tailored reconstruction (Bammer, 2003; Griswold et al., 2002; Qu et al., 2005; S. Holdsworth et al., 2009; Skare et al., 2007). While eddy currents are typically addressed with twice-refocused preparations (Reese et al., 2003), this incurs a significant SNR penalty, which is prohibitive at this resolution. Instead, we performed an image-based higher-order eddy-current correction to align precisely the higher SNR single-refocused acquisition. Our final dataset was sinc-interpolated to 0.7 mm isotropic voxel size.

To identify the tracts present in this high-resolution data set, all of our datasets were processed with deterministic tractography using the traditional (second-order) diffusion tensor model based on Gaussian diffusion because this is the most established and well-tested method in the literature (Basser et al., 1994). A significant problem in the field of tractography is that tracts are, at best, only synthetic representations of reality. At worst, they are fabrications and do not represent underlying structure. We visually compared tracts from all subjects with their expected trajectories. Additionally, we compared tractography results from subsets of each subject's data, i.e. only part of all the signal averages, to assess the sensitivity to noise as well as reproducibility of results with shorter acquisitions.

Methods

High-resolution diffusion tensor imaging

Acquisition

Six right-handed subjects provided written informed consent in accordance with Stanford's Institutional Review Board and Health Insurance Portability and Accountability Act compliance. Each subject was imaged on a GE 750HDx 3.0 T magnet using an 8-channel receive head coil and body transmit (GE Healthcare, Waukesha, WI). A 2nd order high-order shim sequence achieved a uniformity of approximately 20 Hz r.m.s. across the shimmed region of approximately 20 cm in size. Structural sequences included a localizer sequence and a direct coronal T_2-weighted FSE (TE 102 ms, TR ~ 7500 ms, 2 mm skip 0, FOV 180–200 mm, 384 × 256, flow compensation in the slice direction, ETL 15, bandwidth 64 kHz). In most subjects, a 3D sagittal T_2-weighted CUBE FSE (320 × 320, FOV 240, 1.2 mm thick) and a 3D Ax T_1-weighted BRAVO SPGR (1 mm isotropic) were also acquired at the end of the exam, as subject tolerance permitted.

The DTI acquisition was prescribed off the coronal T_2-weighted FSE and utilized the following parameters: axial plane echo-planar imaging (EPI), GRAPPA acceleration of 2 (Skare et al., 2007), number of signal acquisitions/shots 2, b-value 1500 s/mm^2, TR 3150 ms, TE 69 ms with a partial k-space acquisition (with 24 overscans, i.e. partial Fourier factor of 68.8%), single-refocused diffusion preparation, 70 diffusion-encoding directions, 10 b = 0 mm/s^2 images, anterior–posterior phase-encode direction, chemical fat saturation, acquisition matrix 128 × 128, reconstruction matrix 256 × 256, 18 cm FOV, slice thickness/gap = 1.4 mm/0 mm, 27 slices, and acquisition resolution of 1.4 mm isotropic. Acquisition time was 8.5 min, and seven repetitions were performed in each subject. GRAPPA estimation and calibration were performed on all 10 b = 0 images within each repetition (Skare et al., 2007), and the best GRAPPA weight set was applied to all other acquired volumes within each repetition (S.J. Holdsworth et al., 2009). In order to benefit from complex averaging (i.e. reduced Rician noise), each individual DW image (each shot) was phase-corrected with the low-resolution image phase using a triangular-window (Pipe et al., 2002), modified for partial Fourier data, before averaging with the next shot. The disadvantage of complex averaging is that incomplete phase correction due to brain motion can result in destructive interferences in the final diffusion data (Skare et al., 2009). In this study, a triangular-window radius of 0.5 (percent of maximum k-space radius) was found to be an appropriate trade-off between reduced Rician noise and phase cancellations on complex-averaged diffusion data. The axial plane was utilized so that only single physical gradient coils were used for EPI readout and phase-encoding—this minimized ghosting artifacts due to anisotropic gradient delays (Reeder et al., 1999). Because the longitudinal extent of the hippocampus is oriented obliquely and the scans were acquired in the axial plane, the hippocampal tail fell outside the imaging field of view in most subjects. The reconstructed data was zero-filled in plane to achieve a voxel size of 0.7 × 0.7 × 1.4 mm. The ten b = 0 images were averaged into a single b = 0 image for each repetition. The final isotropic voxel size of 0.7 mm occurs at the end of data pre-processing (see the 'Diffusion-weighted image pre-processing' section).

One subject had a hypointensity representing either an old small calcification or microhemorrhage in the high right frontal lobe. Since this subject had no neurologic complaints and reported that this lesion was known and remote, this data was included in this study.

Diffusion-weighted image pre-processing (Fig. 1, online Supplementary material Fig. S1 and Table S1)

Because we acquired the DTI data using a single-refocused diffusion preparation, images had higher SNR compared to twice-refocused preparations. The downside of single-refocusing is that each individual diffusion weighted image (DWI) has significant zero, first, and second-order eddy-current artifacts along the phase-encode (anterior–posterior) direction (Andersson and Skare, 2002; Haselgrove and Moore, 1996; Jezzard et al., 1998; Rohde et al., 2004; Xu, 2011). Without correction of these eddy-current artifacts, the combination of each DWI (each distorted in different patterns along the phase encode axis) would result in a final FA image that is blurred and inadequate for the determination of hippocampal microstructure. Here we developed and implemented a variant of the Rohde algorithm (Rohde et al., 2004) for correcting eddy currents. Our method uses slice-wise eddy-current correction to the 2nd order followed by 3-D motion correction. To preserve the ability to rotate the b-matrix, the repetitions were not averaged together. An example of axial and sagittal plane cine loops from one subject, before and after the correction procedure, is shown in Movie #1.

Each repetition (R) consisted of a single b = 0 mm/s^2 image and 70 (D) directional diffusion-weighted images (annotated as $DWI_{R,D}$). For the purposes of the steps below, an isotropic diffusion weighted image ($isoDWI_R$) refers to the average of all 70 DWIs within one repetition:

$$isoDWI_R = \frac{1}{70}\sum_{D=1}^{70} DWI_{R,D} \quad (1)$$