In vivo diffusion tensor imaging and tractography of human brain at submillimeter isotropic resolution on a clinical MRI scanner

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Target Audience: Researchers and clinicians interested in high resolution Diffusion Tensor Imaging (DTI) and Tractography.

Purpose: The advantages of high-resolution DTI were clearly demonstrated in a recent imaging study that achieved 0.73 mm³ resolution of a post-mortem human brain at 3 Tesla (1). This present study aims to further demonstrate that white matter (WM) tracts can be more accurately detected in DTI capable of achieving submillimeter isotropic resolution compared to conventional 2 mm³ DTI data. This high-level of resolution, however, is extremely challenging to achieve in vivo and, to our knowledge, sub-millimeter isotropic resolution has yet to be routinely achieved in vivo for the human brain. Here we report a novel technique capable of routinely acquiring high quality and high-SNR human brain DTI data at a submillimeter isotropic resolution of .85mm³. At this spatial resolution, researchers and clinicians are able to identify tracts that are otherwise indiscernible at conventional resolutions, which will allow them to investigate regions of the brain that are currently overlooked (e.g. human brainstem).

Methods: A slab-selected 3D multi-shot interleaved EPI sequence was used to acquire the DTI data. 4x accelerated navigator echoes were employed to measure shot-to-shot phase inconsistencies. This information was subsequently used to minimize the EPI aliasing artifacts via the MUSE algorithm (2), comprised of 5 steps: First, each 3D K-space interleaf and its associated accelerated 2D navigator echo were Fourier transformed along the K_x and K_y directions (i.e., into x-y-k_z space); Second, images free from aliasing artifacts were reconstructed from the accelerated navigator signals via the SENSE algorithm (3); Third, the phase information obtained from the preceding step was spatially smoothed; Fourth, this spatially smoothed phase information and the known coil sensitivity profiles were both incorporated into a mathematic framework in order to calculate the unknown source signals from all the EPI segments in the x-y-K_z plane, producing slab-selected data free of aliasing artifacts with high SNR; Fifth, the slab-selected data from step 4 were Fourier transformed along the K_z direction to produce the 3D image data set. Next, eddy current and motion correction was performed using DTIPrep software and cFA maps were generated using FSL software. To assess the dependence of DTI quality on spatial resolution, a set of lower resolution images (2 mm³) was generated by down sampling the dataset with a cubic resampling algorithm available in the FreeSurfer software package. After eddy/motion correction with DTIPrep (http://www.nitrc.org/projects/ dtiprep/), diffusion tensors were generated with the Diffusion Tool Kit (http://trackvis.org/dtk). Whole-brain deterministic streamline tracking procedure was carried out using TrackVis (http://www.trackvis.org). A maximum curvature was set at 35°/mm as the only tracking criterion, no other threshold or filter was used.

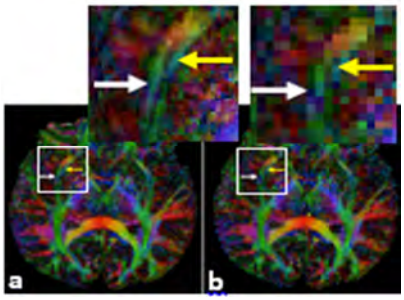

Fig. 1 cFA color maps at **a)** .85 mm³ and **b)** 2 mm³. Grey arrow: external capsule. Yellow arrow: extreme capsule. The boundary is indiscernible at

3D DTI data were acquired from a healthy volunteer on a 3T clinical MRI scanner (GE MR750, Waukesha, WI) equipped with an 8-channel head coil. Scan parameters of the slab-selected 3D 4-shot interleaved EPI pulse sequence were as follows: effective TEs: 59ms (image) and 115 ms (navigator), TR = 3000 ms, partial-Fourier factors along the k_y direction = 70% (for image signals) and 67% (for navigator echoes), slab thickness = 9.4 mm, FOVz = 10.2 mm, number of k_z phase-encoding steps = 12, number of axial slabs = 39, FOV_{xy} = 21.8 cm, matrix size = 256 × 256 × 12 per slab, voxel size = 0.85 × 0.85 × 0.85 mm³, number of diffusion encoding directions = 12, and b = 800 s/mm². The scan time was 32 min for each acquisition and, after acquiring three sets of data (with slab profiles shifted), the total imaging time was 96 min.

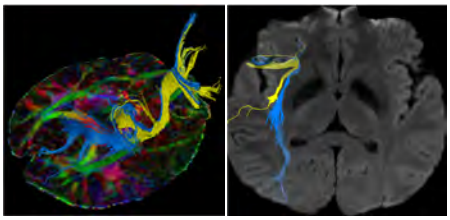

Fig. 2 Multiple depictions of tractography of external (blue) and extreme (yellow) capsules at 0.85 mm³. Unable to acquire at down sampled 2 mm³ DTI data.

Results: Submillimeter isotropic resolution can be reliably achieved at .85 mm³ for human brains in vivo with the integration of 3D 4-shot interleaved EPI and the 3D-MUSE algorithm. In agreement with previously reported post-mortem DTI studies, our results indicate that WM fiber tracts can be more accurately identified at this higher resolution. Further, tracts that are undetectable at conventional 2 mm³ are discernable with the higher spatial resolution achieved in this study. This is illustrated in Figures 1 and 2, which highlight the distinction of the external and extreme capsules at 0.85 mm³ resolution (Fig 1a); a feature that can't be observed at 2mm³ (Fig 1b). Figure 3b, which highlights the Solitary Tract, demonstrates another immediate application of this tool as we were only able to identify specific structures of the brainstem at this submillimeter isotropic resolution.

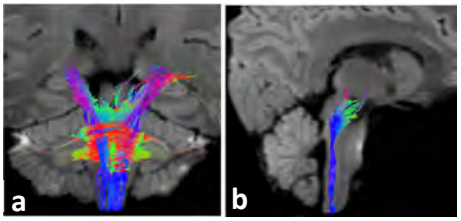

Fig. 3 a) Illustration of brainstem tractography and, specifically, **b)** depiction of Solitary Tract at 0.85 mm³.

Discussion & Conclusion: A major advantage of the 3D-MUSE reconstruction algorithm employed in this study is its capability to achieve high spatial resolution while avoiding the undesirable noise amplification that is present in other reconstruction methods. This yields a favorably higher SNR. Also, the implementation of accelerated navigator echoes results in shorter TE and, as compared with non-accelerated navigator scans, the associated EPI geometric distortions are more similar to that in interleaved EPI based DWI data, making the corrections more reliable. It is also worth noting that in this study we simply used a product RF pulse originally designed for 2D EPI in our 3D DWI scans. As a result, we needed to repeat the scans three times to acquire whole-brain DWI data without significant through-plane signal non-uniformity. Although this approach is obviously not ideal, we were able to demonstrate, as a proof of concept, the feasibility of acquiring DTI data at submillimeter resolution on a clinical scanner in vivo. With further protocol optimization (e.g., improved RF pulse design), the high-resolution DTI should prove highly valuable for neuroscience research.

The figures displayed clearly illustrate the advantages of submillimeter isotropic resolution. The discernable boundaries of the external and extreme capsules is just one example of this tool's abundant translational potential. There has been much debate regarding the extent to which associative fiber bundles (e.g., IFOF, Uncinate Fasciculus, etc.) are entwined with these two structures and we propose that this submillimeter isotropic DTI can be utilized for the demarcation of these individual fiber tracts. Another immediate application that we plan to address is the delineation of WM tracts and structures in the brainstem (Fig 3). It is well established that the brainstem is significantly affected by pathology in a number of neurodegenerative diseases (4). Using Parkinson's disease (PD) as an example, pathology not only exists in this region, but histopathological studies indicate that it precedes the pathology observed in the structures of the basal ganglia that are more commonly associated with PD (this is commonly known as Braak Staging) (4). As such, this is an unexploited area that could yield tremendous insight into the onset and progression of neurodegenerative conditions with the potential to expose reliable preclinical biomarkers. One such example is the Solitary Tract (Fig 3b), which houses the nuclei for cranial nerves VII, IX, and X suggesting that degeneration of this structure could be responsible for ageusia, orthostatic hypotension, and depression, all of which are early symptoms of PD that often precede the hallmark motor symptoms of the disease (5). We plan on employing this tool to identify other key structures of the brainstem, which will then be investigated further in a population of patients with Parkinson's disease.

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