A multi-resolution anatomical atlas of the human brainstem based on diffusion tensor imaging at 11.7T

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Purpose: The brainstem is implicated in the pathogenesis of neurological diseases such as Parkinson's disease and multiple sclerosis. Three-dimensional visualization and detailed delineation of brainstem anatomy are therefore important to enhance accurate prognosis of brainstem pathology. Current anatomical atlases of the brainstem are mostly based on 2D histological techniques. Compared to conventional relaxometry-based MR contrasts, diffusion tensor MR imaging (DTI) can provide superior contrasts to delineate brainstem anatomy[1], but existing postmortem DTI studies of the brainstem are limited to 2D acquisitions with through-plane resolutions of 0.5-0.6 mm, which is still too coarse to resolve microstructural details. In this study, we present a novel 3D atlas of the human brainstem based on ultra-high resolution (125-255 μm) DTI using fast acquisition techniques at 11.7T. The DTI data reveal unprecedented level of anatomical details in the brainstem, resolving microscopic features that were previously observable only with histological sectioning. We also demonstrate mapping of the high-resolution postmortem DTI data to an in vivo brain atlas to develop a multi-resolution 3D anatomical atlas of the brainstem in the MNI stereotaxic space.

Methods: The postmortem brainstem from an adult subject was immersion-fixed with 10% formalin. MR imaging was performed on an 11.7T spectrometer, using an 8-channel volume coil. DTI data were acquired using a 12-segment diffusion weighted (DW)-EPI sequence (TE/TR=27/500 ms, 1 signal average, partial Fourier factor of 1.4), with 30 diffusion directions (b~4000s/mm^2) and 2 non-diffusion weighted (b0) images at a resolution of 255 x 255 x 255 μm^3 and scan time of 13.5 h. T2-weighted MRI was performed using a 3D RARE sequence with TE/TR=31/2000 ms, rarefactor of 4, and 4 signal averages. The brainstem was then further dissected to excise the medulla oblongata and the spinomedullary junction to fit 30- and 20-mm birdcage coils for higher spatial resolution DTI. The medulla was imaged at a resolution of 170 x 170 x 170 μm^3 using a DW-MSE sequence (TE/TR=34/400 ms, 2 averages, 2 b0 images and 6 diffusion directions, b~2800 s/mm^2). DTI of the spinomedullary junction was performed at a resolution of 125 x 125 x 125 μm^3, using a DW-GRASE sequence[2] with navigator phase correction (TE/TR=32/800 ms, 4 averages, 2 b0 images and 16 diffusion directions, b~2100 s/mm^2). For each dataset, tensor reconstruction was done using the Log-linear fitting in DtiStudio, and maps of the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were computed. Direction-encoded color (DEC) maps were generated from the primary eigenvector and FA images. Red was assigned to the medial-lateral axis, green to dorsal-ventral, and blue to the superior-inferior axis. For tractography, an FA threshold of 0.3 and inner product threshold of 0.8 were used. To construct a multi-resolution anatomical atlas of the brainstem in the MNI coordinate space, the ex vivo tensor data were registered to an existing in vivo whole-brain atlas[3], using landmark-based nonlinear diffeomorphic mapping[4].

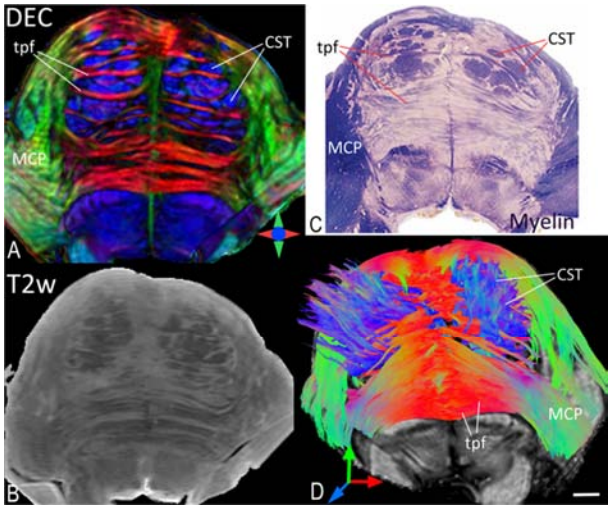

Fig.1: Anatomical details in the brainstem resolved by DTI at 255μm resolution. A-B) Comparison of DEC and T2w contrasts in an axial pons section. C) Myelin-stained section. D) Tractography results show 3D reconstruction of interleaving fibers of the corticospinal tract (CST, blue) and transverse pontine fibers (tpf, red). Scale bar=2mm.

Results & Discussion: **Fig. 1** shows neuroanatomical details in the brainstem resolved with DTI at 255 μm resolution. At the level of the pons, the corticospinal tract (CST) splits into multiple fiber bundles that descend through interdigitating transverse pontine fibers. The DEC maps provided striking contrasts to delineate the craniocaudally-oriented fiber bundles of the CST (blue) and the interleaved mediolaterally-oriented transverse pontine fibers (red), based on their distinct structural orientations (**Fig. 1A**). In comparison, the T2-w image showed limited contrasts to identify major pathways. The level of structural detail resolved by the high-resolution DEC contrasts in our study was anatomically comparable to delineation with myelin-stained histology in the brainstem (**Fig. 1C**). Tractography results from the tensor data enabled 3D reconstruction of the interleaving fascicles of the CST and transverse pontine fibers (**Fig. 1D**), which has not been previously possible. The pontine fibers were traced coursing dorsolaterally and merging with the contralateral middle cerebellar peduncle (MCP). In addition to reconstruction of white matter pathways, ADC maps in our study provided strong grey-white matter contrasts to resolve major grey matter nuclei. For the range of b-values used, ADC in the medullary grey matter (0.57±0.024 μm^2/ms) was significantly ($p<0.005$) higher than that of white matter (0.39±0.019 μm^2/ms). **Fig. 2** shows conspicuous delineation of the inferior olivary nuclei (IO) in the ADC contrasts, which appear relatively homogeneous in T2-w images. The ADC contrasts allowed successful reconstruction and visualization of subnuclei of the inferior olivary complex (**Fig. 2B**). DEC contrasts in the medulla at 170 μm resolution revealed microscopic structural details, including fine olivocerebellar fibers (ocf) that were resolved as red fascicles traversing mediolaterally through the predominantly longitudinal (blue) medial lemniscus fibers (white arrowheads, DEC map in **Fig. 2A**). At the spinomedullary level, DTI at 125 μm enabled 3D visualization of the pyramidal decussation (PyD). Crossing fiber bundles of the left and right pyramidal tracts could be clearly resolved, and three dimensionally reconstructed (not shown). These findings will be important to examine the topographic organization of the decussating Py fibers, which is not possible with axial histology. To register the high-resolution anatomical images of the brainstem to the standard MNI stereotaxic coordinate space, the ex vivo tensor data were nonlinearly mapped to an in vivo brain atlas. **Fig. 3** shows the degree of registration accuracy with representative sagittal sections through the in vivo atlas (2.2 mm resolution) and the registered ex vivo atlas (255 μm resolution) in MNI coordinates.

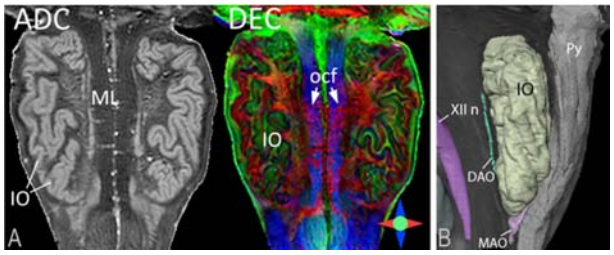

Fig. 2: A) DTI contrasts in the medulla at 170 μm resolution. White arrows show fine decussating olivocerebellar fibers (ocf, red) resolved in DEC contrasts. B) 3D reconstruction of inferior olivary nuclei (IO).

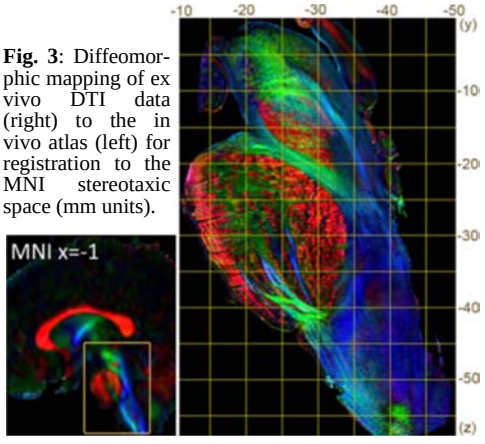

Fig. 3: Diffeomorphic mapping of ex vivo DTI data (right) to the in vivo atlas (left) for registration to the MNI stereotaxic space (mm units).

Conclusion: The results of our study allowed delineation of brainstem anatomy at microscopic levels. The 3D atlas provides high-resolution visualization of brainstem neuroanatomy and reconstructed structures, and in addition, will also significantly benefit the interpretation of relatively low resolution clinical DTI contrasts.

References: [**1**] Naidich *et al*, Springer 2009 [**2**] Aggarwal *et al, Mag Res Med* 64, 2010 [**3**] Mori *et al*, Elsevier 2005 [**4**] Miller *et al, Ann Rev Bio Eng* 4, 2002.

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