Imaging gray matter in human brainstem in vivo by high spatial resolution Diffusion Tensor Imaging at 7 Tesla

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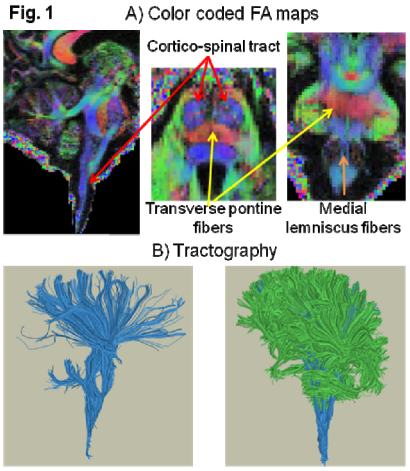
Target Audience: Researchers interested in in-vivo structural segmentation of brainstem gray matter.

Introduction: The human brainstem plays an important role in the regulation of cardiac and respiratory functions, sleep, consciousness, pain control, as well as in the transfer of sensory-motor information between the spinal cord and the brain. In the brainstem, gray matter (GM) is organized in clusters of small nuclei positioned between large white matter (WM) fiber bundles, and displays poor contrast to noise ratio (CNR) in standard in-vivo brain MRI techniques (Fig. 2 A,C,D). Hence, our current knowledge about GM organization within the brainstem derives mostly from ex-vivo studies [1], and there is an unmet need from in-vivo tools able to identify GM structures in the brainstem.

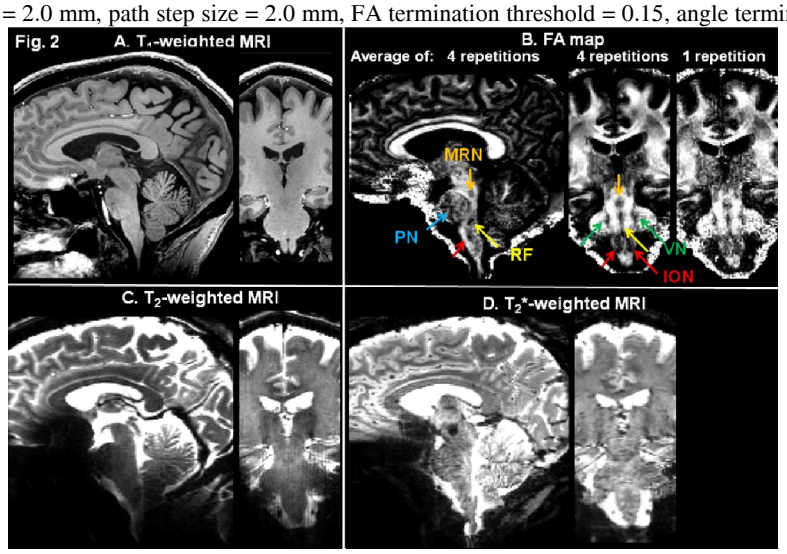
Purpose: To investigate in-vivo brainstem GM organization using high (1.1 mm isotropic) spatial resolution diffusion tensor imaging (DTI) at 7 Tesla.

Fig. 1



Methods: Three subjects (2m/1f, age 28 ± 2) participated in this IRB-approved study. Diffusion-weighted (DW) EPI was performed at 7 Tesla using 32 receive-only coil elements, monopolar diffusion weighting gradients and the following parameters: echo time (TE) = 60.8 ms, repetition time (TR) = 5.6 s, 61 slices, sagittal slice orientation, 1.1 mm isotropic resolution, GRAPPA factor = 3, nominal echo-spacing = 0.82 ms, partial Fourier= 6/8, 60 diffusion directions (b ~ 1000 s/mm^2), 7 interspersed T_2-weighted (non-diffusion weighted, b0) images, 4 repetitions, acquisition time/repetition = 6'. A distortion matched T_2*-weighted EPI dataset was also acquired (TE = 32 ms, TR = 2.5 s, flip angle (FA) = 75°, N. repetitions = 7, same echo spacing/GRAPPA factor/slice orientation/voxel-size used for DTI). T1-weighted 1 mm isotropic multi-echo MPRAGE was also performed (TR = 2.51 s; 4 echoes with TEs =[1.6 3.5 5.3 7.2] ms; inversion time =1.5 s; FA = 7°; FOV = 256×256×176 mm^3, 256×256×176 matrix; bandwidth = 651 Hz/pixel; GRAPPA factor = 2). For each subject, four estimates of fractional anisotropy (FA) maps were obtained by concatenating an increasing number (1 to 4) of repetitions before eddy current correction and tensor estimation (FSL software). Whole-brain deterministic streamline tractography was run (DTIquery software) on the tensor field estimated using 4 repetitions (space between seed points = 2.0 mm, path step size = 2.0 mm, FA termination threshold = 0.15, angle termination threshold = 45 degree, minimum/maximum pathway length = 5.0/300.0 mm, 4th order Runge Kutta integration scheme), and direction-encoded color maps were generated from the primary eigenvector and FA values (red: medial-lateral axis; green: dorsal-ventral axis; blue: superior-inferior axis). FA maps estimated using 4 repetitions were then used to manually draw two GM regions of interest (ROI) (median raphe nucleus (MRN) and right inferior olivary nucleus (rION)), which were supplied as prior information to a clustering algorithm (distance function: normalized squared Euclidean distance, method: kmean clustering)) for ROI refinement. Resulting ROIs (average volume ± s.e. across subjects: MRN 114 ± 9 mm^3, rION 187 ± 25 mm^3) were then inflated by 2 voxels and masked out with the respective original ROIs to obtain two "neighborhood" ROIs which were assumed to contain mostly WM (WM_1 and WM_2 surrounding MRN and rION, respectively). FA values were then extracted for each subject in each ROI. GM-WM FA contrast was computed as the difference between mean FA (estimated based on an increasing number of concatenated repetitions) in each GM ROI and mean FA in its neighboring WM ROI.

Fig. 2



Results & Discussion: High spatial resolution DTI enabled the delineation of large (cortico-spinal tract) and fine (transverse pontine and medial lemniscus fibers) fiber bundles in the brainstem (see Fig. 1A), also visible in high-definition tractography (see Fig. 1B for an example). DTI invariant maps (see FA map, Fig. 2B) demonstrated high GM-WM contrast (up to ~100%) in the brainstem. In the FA map (estimated using 4 repetitions), major clusters of brainstem nuclei were visible including the MRN, the pontine nuclei (PN), the reticular formation (RF), the vestibular nuclei (VN), and the ION (Fig. 2B). This was not the case in T_1-, T_2-, or T_2^*-weighted MRI images (Fig. 2A,C,D). The same nuclei were also visible on FA maps estimated using 1 repetition (6'), although with lower CNR (see Fig. 2B, and Fig. 3 * $p < 0.05$). Using 3 and (in most cases) 2 repetitions yielded an FA contrast similar to the one obtained using 4 repetitions (Fig. 3). Average FA values were above 0.3 in MRN and below 0.2 in rION (Fig. 4) and varied considerably across WM ROIs. These results and our preliminary findings on automated GM-WM segmentation in the brainstem from multi-parametric DTI maps (results not shown) indicate the usefulness of employing multiple intensity constraints and prior spatial information.

Conclusion: High resolution DTI is a promising tool to delineate gray matter structure in the brainstem in-vivo on a subject-by-subject basis. We envisage the employment of this tool to guide the design and interpretation of fMRI-based studies of the brainstem, to provide seed location for fMRI connectivity studies and probabilistic tractography, and to develop an in-vivo atlas of gray matter in the brainstem.

Fig. 3 GM-WM Fractional Anisotropy contrast

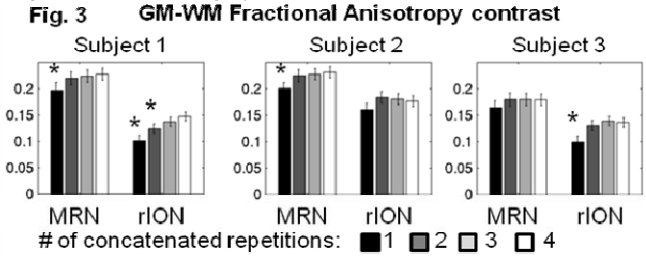
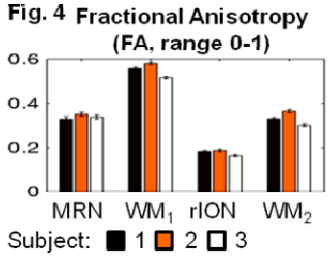


Fig. 4 Fractional Anisotropy (FA, range 0-1)



References: [1] Aggarwal et al, Neuroimage, 74:117:27, 2013.