In vivo structural template of human brainstem nuclei based on multi-contrast MRI at 7 Tesla

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Target Audience: Researchers interested in *in vivo* structural delineation of human brainstem nuclei

Introduction: Despite spectacular advances in neuroimaging of the human cerebral gray matter (GM), *in vivo* visualization of human brainstem nuclei (Bn) is more challenging. A major obstacle to the precise localization of these small regions *in vivo* is the limited sensitivity and contrast between Bn and adjacent white matter (WM) using standard neuroimaging methods, such as relaxivity-based MRI and clinical scanners.

Purpose: To investigate the feasibility of identifying *in vivo* human Bn by the use of: 1) cutting-edge technology (7 Tesla scanner, 32-channel receive coil-array), which pushed the current limits of MRI sensitivity; 2) a novel high-resolution (1.1 mm isotropic) multi-contrast (diffusion fractional anisotropy (FA) and T_2-weighted) EPI approach, which provided exquisite complementary contrasts for Bn anatomy with precisely matched geometric distortions and resolution (see Figure 1).

Methods: Twelve subjects (6m/6f, age 28 ± 1) underwent 7 Tesla MRI under IRB approval. We adopted a common single-shot 2D EPI readout for 1.1 mm isotropic diffusion-tensor (DTI), T_2w and T_2*w sagittal images, with matrix size/GRAPPA factor/nominal echo-spacing = 180 × 240/3/0.82 ms. This yielded multi-contrast anatomical images with exactly matched resolution and geometric distortions. We also acquired a T_1w 1 mm isotropic multi-echo MPRAGE image [1]. Additional MRI parameters for each MRI contrast were: – *DTI:* spin-echo EPI, 61 slices, unipolar method, TE/TR = 60.8 ms/5.6 s, partial Fourier: 6/8, 60 diffusion directions (b-value ~ 1000 s/mm^2), 7 interspersed "b0" images (non-diffusion weighted, b-value ~ 0 s/mm^2, which were used as T_2w MRI), 4 repetitions, acquisition time/repetition 6'43"; – *T_2*w MRI:* gradient-echo EPI, N. slices/TE/TR/FA/N. repetitions/SMS factor = 123/32 ms/2.5 s/75°/28/3. On a single-subject basis, multi-contrast (FA maps, computed from DTI, and T_2w) images were automatically segmented by k-means clustering using minimal manual input. Labels of several Bn were mapped to MNI space through high dimensional non-linear transformations, and a probabilistic template for these structures was created using the transformed labels (highest probability = 100 % overlap across subjects).

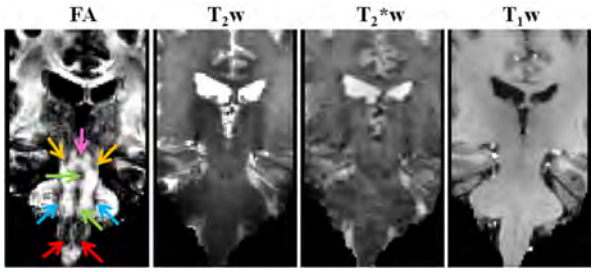

Figure 1 *The diffusion FA map displays exquisite GM-WM contrast in the brainstem, which provides complementary information to relaxivity-based (T_2-, T_2*-, and T_1-weighted - T_2w, T_2*w, and T_1w) MRI. Shown is an example 7 Tesla data-set, in native 1.1 mm isotropic EPI space, coronal view. On the FA map the locations of several Bn are indicated: periaqueductal gray (pink arrow), mesencephalic tegmental nuclei (orange arrows), raphe nuclei (green arrows), pontine nuclei (blue arrows) and inferior olivary nuclei (red arrows).*

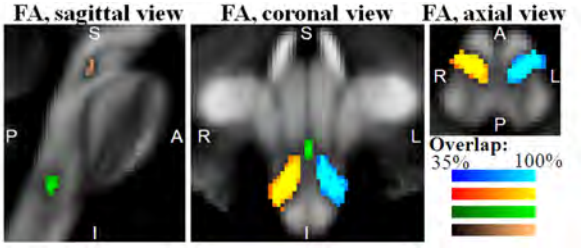

Figure 2 *Probabilistic labels in MNI space of left (blue to cyan) and right (red to yellow) inferior olivary nuclei, raphe magnus (dark to light green), and median raphe (dark to light brown). Labels of Bn are overlaid on the group average FA map (n = 12). Bn appeared as regions of hypointensity compared to WM in FA maps. Very good spatial agreement of labels across subjects was observed indicating the feasibility of delineating a probabilistic label of these Bn.*

Results and Discussion: Through combined examination of 1.1 mm isotropic multi-contrast (FA and T_2w) anatomical images, we automatically generated *in vivo* probabilistic brainstem labels of subcortical hubs of the ascending arousal (median and dorsal raphe, raphe magnus), autonomic (periaqueductal gray) and motor (inferior olivary nuclei, substantia nigra pars compacta and pars reticulata, two subregions of the red nucleus and, in the diencephalon, two subregions of the subthalamic nucleus) systems, see Figures 2–4. A high degree of spatial overlap was observed across subjects in all identified Bn.

Conclusion: These labels constitute a first step in the development of an *in vivo* neuroimaging template of Bn in standard space to facilitate future clinical and research investigations of human brainstem function and pathology. Future work will focus on identifying additional Bn and on *ex vivo* histology validation with myelin and iron stains to elucidate the tissue properties underlying the observed MRI contrasts.

References: [1] van der Kouwe et al., Neuroimage, 40:559-69, 2008. [2] Olszewski and Baxter (1982) Cytoarchitecture of the human brain stem (Karger, Basel). [3] Paxinos and Huang (1995) Atlas of the human brainstem (Academic Press, San Diego). **Support:** NIH-NIBIB P41EB015896

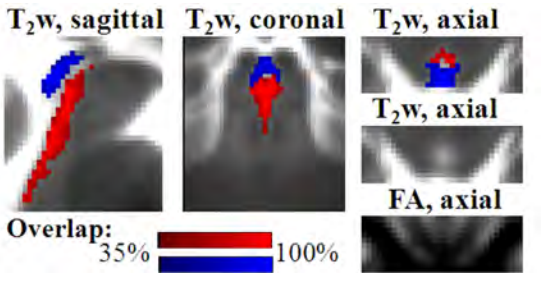

Figure 3 *Probabilistic labels in MNI space of dorsal raphe (red) and periaqueductal gray (blue). The periaqueductal gray displayed similar T_2w signal to the dorsal raphe (see for example in the group average T_2w MRI, axial view, the hypointense ring around the cerebral aqueduct) but lower diffusion FA than the dorsal raphe (see the group average FA, axial view), likely due to a lower content of oriented microstructures. Interestingly, there are major cytological differences [2] between these two nuclei, including the neuronal size and density, which might underlie the observed MRI contrast.*

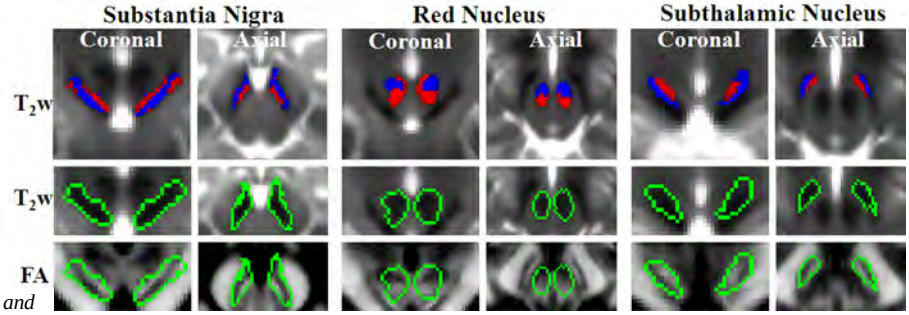

Figure 4 *Probabilistic labels in MNI space of two identified subregions (subregion 1/2 = blue/red colorbars as in Figure 3) of substantia nigra, red nucleus, and subthalamic nucleus overlaid on the group average T_2w image (n = 12) (top row panels); for each nucleus, contour plot (green) surrounding both subregions overlaid on the T_2w signal (zoomed view, middle row panels) and on the FA maps (zoomed view, bottom row panels). For each nucleus, subregion 1 displayed similar T_2w signal to subregion 2, but lower diffusion FA values than subregion 2. The two subregions of substantia nigra corresponded anatomically to substantia nigra pars reticulata and pars compacta [3].*