Validation of in vivo structural template of human brainstem nuclei by fMRI at 7 Tesla

Marta Bianciardi[1], Nicola Toschi[1,2], Cornelius Eichner[1], Kawin Setsompop[1], Jonathan R. Polimeni[1], Bruce R. Rosen[1], and Lawrence L. Wald[1]
[1]*Department of Radiology, A.A. Martinos Center for Biomedical Imaging, MGH and Harvard Medical School, Boston, MA, United States,* [2]*Medical Physics Section, Department of Biomedicine and Prevention, Faculty of Medicine, University of Rome "Tor Vergata", Rome, Italy*

Target Audience: Researchers interested in *in vivo* structural and functional investigation of human brainstem nuclei

Introduction: *In vivo* structural and functional neuroimaging of human brainstem nuclei (Bn) is challenging because of limited sensitivity and contrast to noise ratio. Recently, we have developed an *in vivo* structural template of human brainstem nuclei (Bn) of the ascending arousal, autonomic and motor systems by semi-automatic segmentation of high-resolution and distortion-matched multi-contrast EPI at 7 Tesla [1]. Validation of this template, consisting of 18 probabilistic labels of Bn in standard MNI space (see Figure 1 for a list of Bn labels), is a key step towards its use in future clinical and research studies of human brainstem function and pathology.

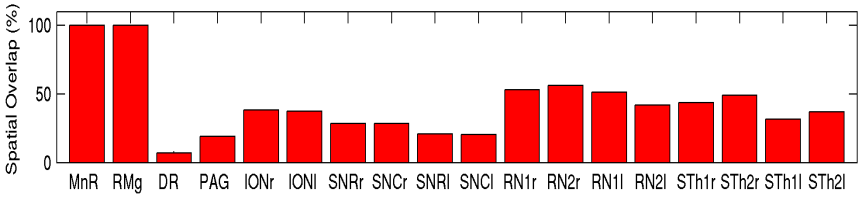
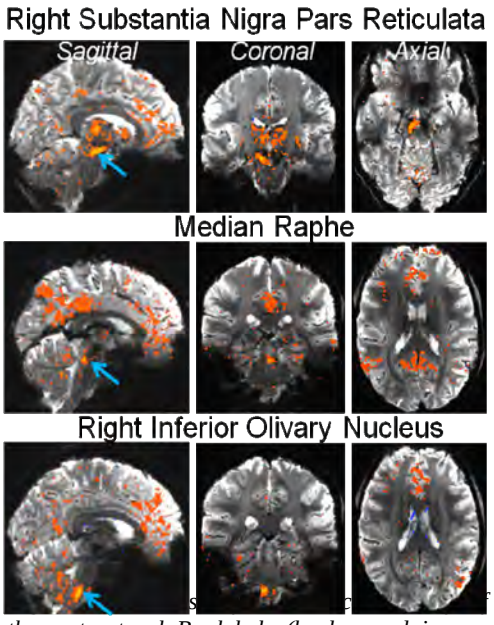


Figure 1 *Spatial overlap between structural Bn labels [1] and matched functional IC maps. The following Bn labels were considered: median raphe (MnR), raphe magnus (RMg), dorsal raphe (DR), periqueductal gray (PAG), left/right (l/r) inferior olivary nuclei (ION), l/r substantia nigra pars reticulata (SNR) and compacta (SNC), l/r subregion 1/2 of red nucleus (RN1, RN2) and of subthalamic nucleus (STh1, STh2).*

Purpose: To validate our structural template of Bn [1] by investigating the presence of: 1) functional parcels in the brainstem spatially overlapping with structural Bn labels; 2) plausible functional connectivity patterns of the identified Bn with subcortical and cortical regions.

Methods: Twelve subjects (6m/6f, age 28 ± 1) underwent 7 Tesla fMRI under IRB approval. 1.1 mm isotropic gradient-echo EPIs were acquired with parameters: matrix size/GRAPPA factor/nominal echo-spacing/N. slices/TE/TR/FA/SMS factor/acquisition time = 180 × 240/3/0.82 ms/123/32 ms/2.5 s/75°/3/9'. We also acquired a 1 mm isotropic multi-echo MPRAGE image [2]. Slice timing, motion correction, coregistration to MNI space, 1.5 mm spatial smoothing and physiological noise correction (high pass filtering at 0.01Hz and removal of the mean time-course in a CSF mask) was applied to fMRI data. To functionally parcellate the brainstem we: considered brainstem voxels only, by using a box bounding the brainstem, and masking the surrounding CSF and other brain regions (e.g. the cerebellum); concatenated the brainstem fMRI data across subjects over time; and performed group-based [3] independent component analysis (ICA) using FSL-MELODIC and 400 components. We then identified the 18 IC maps that provided the best spatial correlation with the 18 structural Bn probabilistic labels (thresholded at 35 % probability), and for each identified IC map we computed its spatial overlap (%) with the matched structural Bn label as the number of common voxels divided by the number of voxels in the structural Bn label. To investigate the functional connectivity of structural Bn labels with the rest of the brain, we performed single-subject seed-based correlation analysis for each label using the average time-course across voxels of each Bn label as regressors, followed by group analysis of single-subject regression coefficients (random-effects model, $p < 0.001$).



three structural Bn labels (background image: average fMRI across time-points for an example data-set; the blue arrows indicate the Bn label locations). Notably, the substantia nigra pars reticulata displayed significant functional connectivity with the basal ganglia and the thalamus, as expected from previous work [4]; the median raphe with the default mode network, which is involved in arousal mechanisms [5]; and the inferior olivary nucleus with the cerebellum [6].

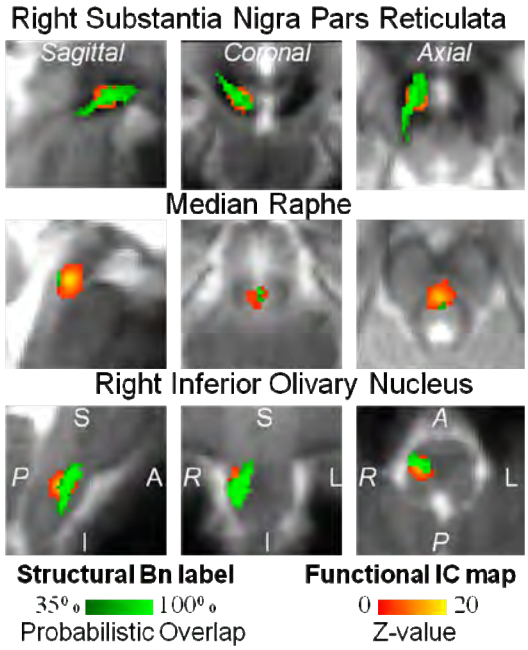


Figure 2 *The structural labels of three Bn [1] and the matched functional IC maps displayed good spatial overlap (background image: average fMRI across time-points and subjects).*

Results: For each Bn label, the spatial overlap between functional ICA-based parcels and structural Bn probabilistic labels is shown in Figure 1. For the right substantia nigra pars reticulata, median raphe and right inferior olivary nucleus, the structural Bn label and the matched IC functional map are shown in Figure 2. The functional connectivity of the same nuclei is shown in Figure 3.

Discussion and Conclusions: For each Bn label, we identified a spatially matched functional parcel in the brainstem by ICA of high spatial resolution fMRI at 7 Tesla. The spatial overlap was good (on average (s.e.) across labels the overlap was 42 % (7 %)), suggesting the presence of multiple functional ICs within each structural label. Our results also showed that structural Bn labels were functionally connected to specific brain regions as expected from previous work. In summary, this work provides a preliminary validation of the recently developed *in vivo* structural template of Bn [1].

References: [1] Bianciardi et al., *submitted*. [2] van der Kouwe et al., *Neuroimage*, 40:559-69, 2008. [3] Calhoun et al., *Hum Brain Mapp*, 14:140-51, 2001. [4] Yetnikoff et al., *Neuroscience*, 282 :23-48, 2014. [5] Horovitz et al., *PNAS*, 106 :11376-81, 2009. [6] Armstrong et al., *J Neuropathol Exp Neurol*, 58 :1-11, 1999. **Support:** NIH-NIBIB P41EB015896.