Imaging the human brainstem at 7 Tesla using multi-modal echo-planar imaging

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Target audience: Clinicians/researchers interested in imaging of the human brainstem.

Purpose: The human brainstem is a very important but notoriously difficult structure to study with MRI. Its close vicinity to large arteries and ventricles as well as its propensity to spatial distortions caused by the oral cavity place high demands on image acquisition as well as data analysis methods. Furthermore, the small average size of brainstem nuclei necessitates higher accuracy in the spatial coregistration of functional and structural MRI scans than in studies of the cortex. Hence, the biggest error in fMRI analyses of the brainstem is frequently caused by an imperfect coregistration of the distorted functional images and the undistorted structural image. B_0 field maps are a way to mitigate this error but differences in voxel size and image contrasts between functional and structural scans still limit accuracy.

Here, we present an entirely EPI-based approach to multi-modal imaging of the human brainstem at 7 T that allows for the acquisition of distortion matched T_2*-weighted functional (BOLD), T_1-weighted structural as well as diffusion-weighted (DTI) images at a resolution of 1.2 mm isotropic. Due to the matched voxel size and distortion, BOLD and DTI images can be directly normalized to MNI or any other space by applying transformation parameters estimated from the T_1-weighted EPI image (**Fig. 1**). Applying our recently developed mICA approach (masked independent component analysis, [1]), we study resting-state activity of brainstem nuclei as well as brainstem–cortex functional connectivity at the single-subject level and compare the results to those obtained at group level at 3 T [1]. We also show that identification of nuclei can be greatly aided by fractional anisotropy (FA) maps created from the DTI data, suggesting a strong structure-function correlation in these nuclei.

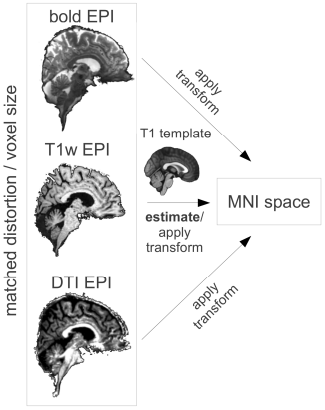

Fig. 1: Spatial normalization scheme. Due to their matched distortion and voxel size, the transformation to MNI space can be estimated for the T_1-weighted image and applied to BOLD/DTI.

Methods: Three volunteers gave informed consent and were scanned on a Siemens 7 T whole-body scanner (Siemens Healthcare, Erlangen, Germany) equipped with SC72 body gradients using a custom-built 32-channel receive array and birdcage transmit coil. Subjects were instructed to keep their eyes open and remain still during scanning. Functional data were acquired with a BOLD-weighted gradient-echo single-shot EPI using the Simultaneous Multi-Slice technique [2] with multiband factor 2 and the following protocol parameter values: 1.2×1.2mm^2 voxel size (FOV=192×192 mm), 126 1.5-mm thick oblique sagittal slices, TR=3.5 s, TE=23 ms, flip=80°, no p.F., BW=1562 Hz/pix, nominal echo-spacing=0.76 ms, *R*=4 in-plane (GRAPPA) acceleration using 128 FLEET-EPI reference lines [4] and 100 measurements. Matched T_1-weighted EPI data (using TR=8 s, TE-23 ms, flip-90°, 7/8 p.F.) were acquired using a slab-selective FOCI adiabatic inversion and a permutation of the slice ordering to achieve 20 inversion times per slice in an acquisition time of 2 min 58 s. T_1 values were fit to these inversion recovery curves to produce a T_1 map for the image volume, from which a synthetic T_1-weighted volume closely resembling the contrast of the MNI template was generated [5]. Finally, diffusion weighted data were also acquired with a matched protocol (using monopolar diffusion gradients, TR=4.3 s, TE=64.8 ms) including 60 diffusion directions with a b-value of ~1000 s/mm^2 and 7 interspersed T_2-weighted (non-diffusion weighted, b0) images, 2 repetitions, acquisition time/repetition ~ 5 min [6]. Fat suppression was achieved by reversal of the excitation gradient. Spatial preprocessing consisted of affine coregistration and non-linear warping of the T_1w-EPI to the ICBM152 MNI template. The same transformation was then applied to BOLD and DTI data. After cropping to retain only the brainstem, BOLD data were analyzed using masked ICA [1] to detect activity of brainstem nuclei at the single-subject level. Results obtained by low-dimensional mICA (d=37) were then compared to group level results from our previous 3-T study (n=50) [1] by means of spatial cross-correlation coefficients. Furthermore, a high-dimensional mICA followed by an inversion of the un-mixing matrix on the whole-brain data was used to assess brainstem-cortex functional connectivity. Fractional anisotropy (FA) maps were derived from DTI tensor reconstruction and used to aid identification of nuclei.

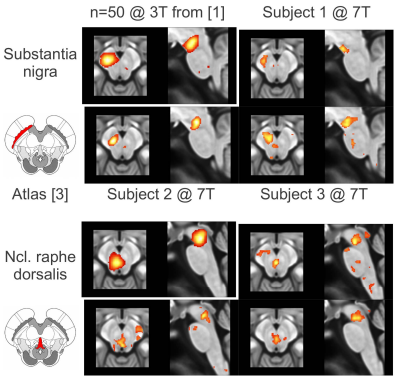

Fig. 3: Comparison of group mICA components obtained on a 3 T scanner with single subject results obtained at 7 T.

Results: mICA successfully detected on the single subject level a number of previously described brainstem nuclei, whose identification was greatly aided by FA maps. This is illustrated for *Ncl. raphe med.* in **Fig. 2**. Reproducibility analysis showed good reproducibility of components from our 3-T study in single subjects: 10 / 7 / 8 nuclei showed significant correlation coefficients with 3T components in subject 1 / 2 / 3 (**Fig. 3**). Connectivity analysis revealed previously described cortical networks in a number of brainstem nuclei, like the default mode network for lateral pontine nuclei and a network consisting of insular, mid-cingulate and primary visual areas for the ventral tegmental area (**Fig. 4**).

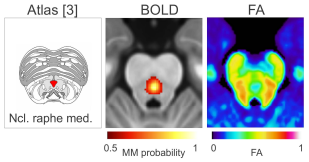

Fig. 2: Identification of activation clusters aided by functional anisotropy maps.

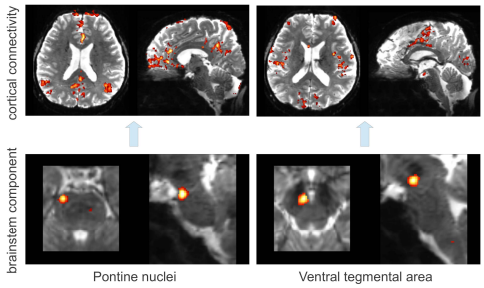

Fig. 4: Cortical connectivity of two brainstem nuclei.

Discussion: Our results show the feasibility of functional brainstem imaging on the single-subject level with a purely EPI-based imaging approach at 7 T.

Conclusion: Assessing activity and functional connectivity of brainstem nuclei on the single-subject level may soon give us a deeper understanding of individual differences in pain processing, autonomic regulation and other functions localized in the brainstem.

References: [1] Beissner F et al. (2013) Neuroimage. In press. [2] Setsompop *et al.* (2012) *MRM* **67**:1210. [3] Naidich et al. Springer. Wien; 2008. [4] Polimeni *et al.* (2013) *ISMRM* p.2646. [5] Renvall V et al. Abstract #6537 ISMRM 2014. [6] Heidemann et al. NeuroImage, 60(2), 967–978. **Acknowledgements:** Supported by German Research Foundation (BE4677/1-1), NIBIB K01-EB011498 and NCRR P41-RR14075, Instrumentarium Science Foundation, Swedish Cultural Foundation in Finland (11/7793-1166).