Mapping Activation in the Human Brainstem at 7 T with High Spatial and Temporal Resolution Using RASER and SSBA

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Target audience: researchers interested in pulse sequence development, image reconstruction, and fMRI data analysis, as well as application-oriented neuroscientists, orofacial pain clinicians, psychologists, and psychiatrists.

Introduction: In previous fMRI studies using RASER (Rapid Acquisition with Sequential Excitation and Refocusing)[1, 2], it has been shown that this emerging imaging technique provides high quality fMRI data. Among several beneficial characteristics of RASER, it has been observed that this imaging method is less sensitive to physiological noise, which arise from fluctuations of the main magnetic field (e.g., caused by respiratory movements of the chest wall) compared to EPI-based techniques. Furthermore, RASER is a purely T_2-weighted sequence. The detected BOLD response is thought to be more specific to the site of neural activity compared to T_2^*-weighted sequences, that allows better spatial distinction of focal neuronal correlates. Therefore, mapping activity in the brainstem therefore benefits highly from the use of RASER. We demonstrate in this paper that neural correlates of pain processing of the human trigeminal neuronal circuit can be mapped with high spatial and temporal resolution.

Method: RASER is based on so-called spatiotemporal (st) encoding using a frequency-swept excitation pulse to sequentially excite transverse magnetization replacing the phase-encoding in a conventional EPI readout. T_2-weighting is achieved by refocusing the transverse magnetization with two 180°-pulses. The RASER FOV was zoomed in onto the brainstem. The acquisition was accelerated in the phase-encoded third dimension by a factor of two and reconstructed using GRAPPA[2, 4]. Superresolution was employed to increase signal-to-noise ratio and reduce power-deposition.[2, 5]

The acquisition time for a whole 3D image exceeds the period of the stimulation paradigm. In order to generate activation maps from time series with an undersampled BOLD response the post-processing technique SSBA[3] is used. In SSBA, periodic signal modulation, such as the BOLD response, are represented as peaks in the pseudo-spectral dimension, which is obtained by Fourier-transformation of the complex-valued image time series along the temporal dimension. The amplitude of the relative signal change is derived from the spectral peak at the apparent (aliased) paradigm frequency. As a result of undersampling of the BOLD response in the third phase-encoded dimension, the spectral peak of the BOLD response is shifted by a number of voxels determined by how often the paradigm is aliased in the respective spatial dimension. This spatial shift is corrected for in SSBA. The *F*-score ids calculated from the magnitude spectra by calculating the ratio of the peak variance of the BOLD response relative to variance of the frequency adjacent to the peak. The registration of the RASER images and the *F*-maps was performed using FLIRT (SPM8, Wellcome Trust Centre for Neuroimaging, UCL, London, UK).

Experimental: Experiments were performed on a 7 T scanner (Siemens, Erlangen, Germany) using a volume head coil with 32 receive and 16 transmit channels (VirtuMed, Minneapolis, Minnesota). Twelve volunteers participated after written consent. B_1-shimming was applied to minimize flip angle variations across the brain[6]. A T_1-weighted anatomy was acquired. RASER parameters were: CHIRP-pulse (*R*-value 100, duration of 16.32 ms) for excitation, spatial resolution 1.5 mm isotropic, reconstructed matrix 109x32x20, T_E = 65 ms, shot-to-shot T_R = 750 ms, volume-to-volume T_R = 7.5 s.

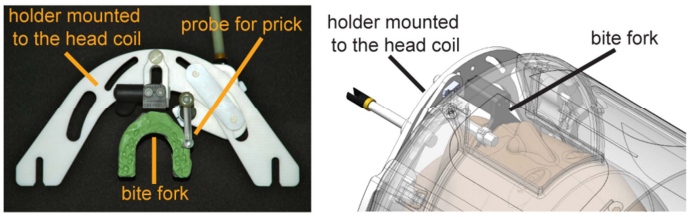

Fig. 1: stimulus device for applying reproducible pricks to the gingiva

The stimulus consisted of a 20 s rest period followed by a series of 10 pricks of the gingiva on top right side and a 60 s after sensation period without stimulation. The inter-stimulus interval (ISI) between pricks was 2 s and 10 s. Each ISI was scanned 3 times. The six scans were acquired in a randomized order. To prick the gingiva with the same pressure, a bite fork holding a pointed, but dull probe which can moved by an extension rod to apply pricks to the gingiva from outside the magnet was mounted onto the head coil (Fig. 1).[7] Subjects reported their pain rating by pressing response buttons after each prick. The scale for the ratings ranged from 0 (no pain, only touch) to 10 (worst pain). The pressure of the probe was adjusted for each subject to ensure that the rating remained within the range of 1 to 6 throughout the experiment.

Results: Fig. 2 shows the activation maps representing the BOLD response correlating with the periodicity of the pricks. A mask was generated by averaging all *F*-maps of all scans for each subject and thresholded at a confidence level of 95%. Based on this mask, it was ensured that activation in the brainstem largely overlap between subjects. The data of 4 subjects were discarded since accurate registration failed. Significant activation for both ISIs of 10 s and 2 s is found in the trigeminal nucleus (V2), the chief sensory nucleus, the periaqueductal grey and the posteromedial nucleus of the thalamus (Fig. 2).

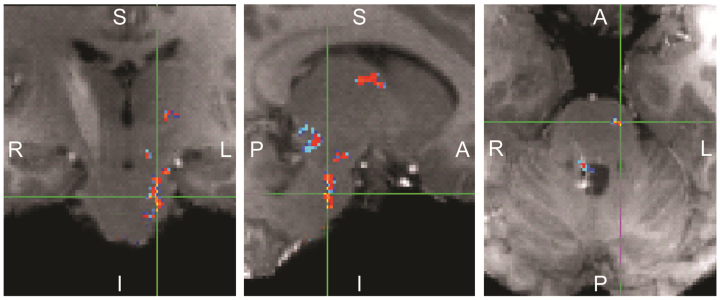

Fig. 2: activation maps (average *F*-maps of 8 subjects thresholded at a confidence level of 95%) for an ISI of 10 s (blue) and 2 s (red)

Discussion: The main advantage of using a 3D-imaging method in which the third dimension is phase-encoded in subsequent scans is that the BOLD response is sampled at a higher rate determined by the scan-to-scan repetition time than the volume-to-volume T_R The accurate amplitude of the BOLD response can be extracted from the 3D-RASER time coursers using SSBA. In contrast, with a multi-slice 2D imaging technique using the same volume-to-volume T_R of 7.5 s the BOLD response of an event-related paradigm design is underestimated or even completely missed if the slice of interest is not acquired exactly when the BOLD response occurs. This concept is confirmed by reproducing the activation maps obtained for the fully-sampled 10 s with the under-sampled 2 s prick paradigm (Fig. 2) for regions processing touch sensation.

References: **1.** Goerke U *et al*., *NeuroImage* **54**: 350 (2011); **2.** Goerke U *et al.*, *Proc. Intl. Soc. Magn. Reson. Med.* **21**: 2282 (2013); **3.** Goerke U, Ugurbil K, *Proc. Intl. Soc. Mag. Reson. Med.* **17**: 19 (2009); Goerke U, Ugurbil K, *Proc. Intl. Soc. Magn. Reson. Med.* **19** (2011); **4.** Griswold MA *et al*., *MRM* **47**: 1202 (2002); **5.** Ben-Eliezer N *et al*., *Magn. Reson. Imaging* **30**: 1401 (2012); **6.** van de Moortele P-F *et al*., *MRM* **54**: 1503 (2005); **7.** Moana EJ et al. *BMC Neuroscience* **11**: 142 (2010). *Financial support by the KECK Foundation and the NIH grants P30 NS057091, P30 NS5076408, P30 NS076408, P41 RR008079, P41 EB015894, and S10 RR026783 is acknowledged.*