Self-Regulation of the Thalamus with Real-Time fMRI Neurofeedback Enhances Correlation of Thalamic BOLD Activity and EEG Alpha Rhythm

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Target audience: Researchers and clinicians interested in the use of multimodal fMRI and EEG techniques for non-invasive brain neuromodulation, as well as in mechanisms of rhythmic neural activity and functions of the human thalamus.

Purpose: Temporal correlations between posterior EEG alpha rhythm and BOLD fMRI activity of the thalamus have been a subject of considerable attention. Studies by simultaneous EEG-fMRI, e.g. [1-4], have raised concerns about reliability and spatial accuracy of detecting such correlations. Real-time fMRI neurofeedback (rtfMRI-nf) with simultaneous EEG is a promising approach for non-invasive modulation of deep-lying brain structures and investigation of related EEG activity [5,6]. Here we report the first study utilizing rtfMRI-nf training of the thalamus with simultaneous EEG recordings. We demonstrate that rtfMRI-nf training targeting the anterior (AN) and mediodorsal (MD) thalamic nuclei [7] is accompanied, in healthy participants, by a significant enhancement in temporal correlation between thalamic BOLD activity and EEG alpha rhythm.

Methods: Ten healthy subjects (5 females) participated in the study. The experiments were conducted on a GE Discovery MR750 3T MRI scanner with an 8-channel receive-only head coil. A single-shot gradient echo EPI sequence with FOV/slice =240/2.9mm, *TR/TE*=2000/30ms, SENSE=2, image matrix 96x96, flip=90°, 34 axial slices, was employed for fMRI. Concurrent EEG recordings were performed using a 32-channel MR-compatible EEG system (Brain Products GmbH). The rtfMRI-nf was implemented using a custom developed real-time system with a neurofeedback GUI (Fig. 1a). It was based on fMRI activity in the target ROI (Fig. 1d), which included bilateral AN and MD nuclei defined anatomically using TT atlas in AFNI [8]. The experimental protocol included seven runs, and each run (except Rest) consisted of 40 s long blocks of **A**ttend, **H**appy Memories, and **C**ount conditions (Fig. 1b). The red rtfMRI-nf bar (Fig. 1a) was displayed for all three conditions during Runs 1-4, and its height was updated every 2 s. For Happy Memories conditions, the participant was instructed to feel happy by evoking happy autobiographical memories while trying to raise the level of the red bar. For Attend conditions, the subject was asked to rest while watching the red bar. For Count conditions, the subject was asked to mentally count back by subtracting a given integer from 300 while watching the red bar. EEG data analysis was performed in BrainVision Analyzer 2. EEG artifacts were removed using the average artifact subtraction and ICA. Time-frequency analysis was conducted using continuous wavelet transform with 8 ms temporal and 0.25 Hz frequency resolution. The EEG alpha band was defined individually for each subject as [IAF–2…IAF+2] Hz, where IAF is the individual alpha peak frequency. Average EEG alpha power $P(t)$ for O1, O2, and Oz electrodes was computed at each time point. Normalized power was defined as $\ln(P(t))$. It was converted to z-scores and convolved with HRF to yield an EEG-alpha-based fMRI regressor. fMRI data processing was performed in AFNI. Psychophysiological interaction (PPI) analysis [9] was conducted within the GLM framework to evaluate task-dependent differences in correlations between the EEG-alpha-based regressor and fMRI data.

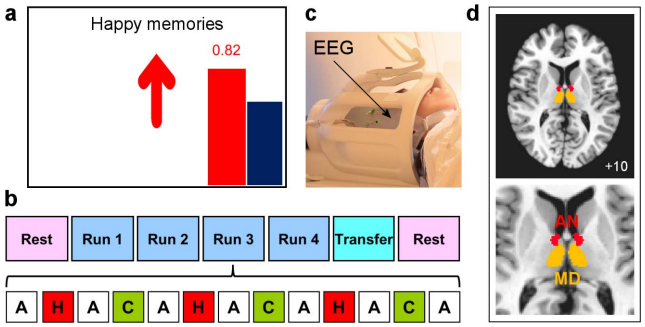

Fig. 1. a) GUI screen with neurofeedback bar (red) and zero-level bar (blue); b) experimental protocol with **A**ttend, **H**appy, and **C**ount condition blocks; c) EEG-fMRI setup; d) Target ROI for rtfMRI neurofeedback: anterior (AN) and mediodorsal (MD) nuclei of the thalamus.

Results: Fig. 2a shows that the participants were able to successfully activate both AN and MD using retrieval of happy autobiographical memories with rtfMRI-nf. This ability persisted during the Transfer run without rtfMRI-nf. Fig. 2b exhibits a group statistical map of the PPI interaction term describing the difference in correlations with the EEG-alpha-based regressor between the Happy and Attend conditions (p<0.03, uncorr., min. cluster 200 voxels). Two neurofeedback runs with the highest AN/MD activity were concatenated and included in the analysis from each subject. A significant positive effect is observed in the thalamus area. This effect is present for both medial and lateral parts of the thalamus. Fig. 2c shows a map of Happy vs Attend fMRI contrast (p<0.005, uncorr, min. cluster 200 voxels) for comparison.

Conclusion: Our results demonstrate, for the first time, that modulation of thalamic BOLD activity by means of rtfMRI-nf is accompanied by a significant enhancement in temporal correlation between this activity and posterior EEG alpha rhythm. This observation further supports the important role of the thalamus in generation and modulation of the alpha rhythm. Our findings suggest that non-invasive rtfMRI neuromodulation with simultaneous EEG recordings is a promising tool for studies of human brain function.

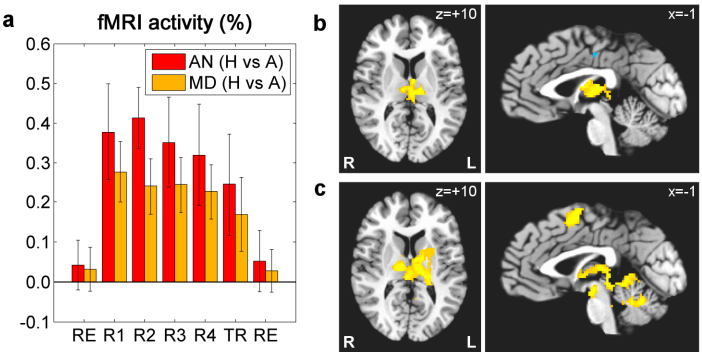

Fig. 2. a) Average Happy vs Attend fMRI activities of AN and MD during the neurofeedback training; b) PPI interaction [EEG-alpha-based regressor] x [Happy – Attend] maps; c) Happy vs Attend fMRI activity maps (see text for details).

References: [1] R.I. Goldman et al. *NeuroReport* 2002, 13:2487. [2] H. Laufs et al. *PNAS* 2003, 100:11053. [3] B. Feige et al. *J Neurophysiol* 2005, 93:2864. [4] Z. Liu et al. *NeuroImage* 2012, 63:1060. [5] V. Zotev et al. *PLoS ONE* 2011, 6:e24522. [6] V. Zotev et al. *Proc ISMRM* 2013, 0521. [7] K.H. Taber et al. *J Neuropsy Clin Neurosci* 2004, 16:127. [8] R.W. Cox. *Comput Biomed Res* 1996, 29:162. [9] K.J. Friston et al. *NeuroImage* 1997, 6:218.