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Finding thalamic BOLD correlates to posterior alpha EEG

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ABSTRACT

Oscillatory electrical brain activity in the alpha (8–13 Hz) band is a prominent feature of human electroencephalography (EEG) during alert wakefulness, and is commonly thought to arise primarily from the occipital and parietal parts of the cortex. While the thalamus is considered to play a supportive role in the generation and modulation of cortical alpha rhythms, its precise function remains controversial and incompletely understood. To address this, we evaluated the correlation between the blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) signals in the thalamus and the spontaneous modulation of posterior alpha rhythms based on EEG–fMRI data acquired concurrently during an eyes-closed task-free condition. We observed both negative and positive correlations in the thalamus. The negative correlations were mostly seen within the visual thalamus, with a preference for the pulvinar over lateral geniculate nuclei. The positive correlations were found at the anterior and medial dorsal nuclei. Through functional connectivity analysis of the fMRI data, the pulvinar was found to be functionally associated with the same widespread cortical visual areas where the fMRI signals were negatively correlated with the posterior alpha modulation. In contrast, the dorsal nuclei were part of a distinct functional network that included brain stem, cingulate cortex and cerebellum. These observations are consistent with previous animal electrophysiology studies and the notion that the visual thalamus, and the pulvinar in particular, is intimately involved in the generation and spontaneous modulation of posterior alpha rhythms, facilitated by its reciprocal and widespread interaction with the cortical visual areas. We further postulate that the anterior and medial dorsal nuclei, being part of the ascending neuromodulatory system, may indirectly modulate cortical alpha rhythms by affecting vigilance and arousal levels.

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Introduction

In human EEG, alpha activity (i.e. electrical activity in the 8–13 Hz frequency range) is most prominent in occipital and parietal regions when the subject is resting wakefully with eyes closed, and is suppressed with opening of the eyes (Berger, 1929) or falling into sleep (Niedermeyer, 1997). The occipital dominance of alpha-band EEG activity is thought to reflect primarily cortical dendritic activity synchronized across a large part of the visual cortex, which is situated in the occipital lobe. The neural circuitry underlying this synchronization has not been firmly established and likely includes not only cortico-cortical but also thalamo-cortical connections. Specifically, the involvement of the thalamus remains difficult to assess non-invasively with scalp-recorded EEG alone due to its very low sensitivity to signal sources situated deeper in the brain, as is the thalamus.

Invasive electrophysiological recordings from animals have shed light on an important role of the visual thalamus in the generation, modulation and synchronization of alpha rhythms observed from the visual cortex (Hughes and Crunelli, 2005). During natural wakefulness, local field potentials (LFP) recorded from the visual cortex of dogs and cats exhibit robust oscillatory activity centered at 10 Hz (Chatila et al., 1993; Lopes da Silva et al., 1973; Lorincz et al., 2009). Like the human posterior alpha rhythm, its amplitude was shown to react in a similar fashion to opening and closing the eyes (Chatila et al., 1992). Importantly, alpha oscillations were also observed specifically within the visual thalamus, including both the lateral geniculate nucleus (LGN) and pulvinar (Pul). Comparison between the alpha rhythms recorded from the thalamic and cortical parts of the animal visual system showed a strong degree of phase-locking and amplitude covariation (Chatila et al., 1993; Lopes da Silva et al., 1973; Lopes da Silva et al., 1980; Lorincz et al., 2009). In addition, coherence analysis after simulated removal of the visual thalamus by parceling out its contributions to thalamo-cortical synchrony showed a significant decrease of intra-cortical alpha coherence (Lopes da Silva et al., 1980).

Extrapolating these findings from animals to humans, one may hypothesize that the reciprocal (i.e. feedforward and feedback) interactions between the visual thalamus and the visual cortex give rise to the human posterior alpha rhythm. A unique and non-invasive approach to test this hypothesis is to use concurrently recorded fMRI–EEG to search the entire brain for metabolic and/or hemodynamic correlates of

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the posterior alpha rhythm. This approach benefits from the whole brain coverage and relatively high spatial resolution provided by fMRI. Utilizing this approach, several groups have assessed the correlation between simultaneously acquired BOLD fMRI and alpha EEG primarily in the absence of overt subject activity (de Munck et al., 2007; Feige et al., 2005; Goldman et al., 2002; Laufs et al., 2003; Moosmann et al., 2003; Sadaghiani et al., 2010). Likewise, other groups combining positron emission tomography (PET) and EEG have also attempted to localize changes in regional cerebral blood flow (CBF) and cerebral metabolic rate of glucose consumption (CMRglu) that were correlated with the variation of alpha amplitude or power (Buchsbaum et al., 1984; Danos et al., 2001; Larson et al., 1998; Lindgren et al., 1999; Sadato et al., 1998). The results from these studies were generally consistent in cortical regions but notably variable in the thalamus. The correlation between the posterior alpha modulation and the BOLD, CBF or CMRglu signal in the thalamus has been reported to be positive (Danos et al., 2001; de Munck et al., 2007; Feige et al., 2005; Goldman et al., 2002; Moosmann et al., 2003; Sadaghiani et al., 2010; Sadato et al., 1998), negative (Larson et al., 1998; Lindgren et al., 1999; Moosmann et al., 2003) or near-zero (Laufs et al., 2003), as opposed to more reliably negative correlations in the visual cortex reported in most of these studies, except one (Laufs et al., 2003).

One possible source for the discrepancies among these studies relates to the structural and functional heterogeneity of the thalamus. Based on histology (Morel et al., 1997), the thalamus can be divided into a number of sub-regions (often called nuclei), many of which have been shown to serve specific functions (Sherman and Guillery, 2006). Numerous tracing studies in animals (Jones, 2007) have demonstrated uniquely specific connectional patterns of thalamic nuclei with cortical functional areas; in humans, this specificity has been confirmed with tract-tracing based on diffusion MRI (Behrens et al., 2003; Johansen-Berg et al., 2005), resting-state fMRI (Zhang et al., 2008) as well as by a recent electrophysiological study (Elias et al., 2012). For this reason, it is quite possible that individual thalamic sub-regions may also bear a unique relationship with alpha activity. Unfortunately, none of the previous neuroimaging studies was able to register its EEG–fMRI or EEG–PET correlation results to specific thalamic sub-regions, in part due to an inability to localize them to specific thalamic nuclei (e.g. LGN and Pul). Therefore, the precise nature of thalamic involvement in cortical alpha signals in humans remains poorly understood.

Toward filling this gap, we revisited the sub-cortical and cortical correlations between BOLD fMRI and alpha EEG using recent technical advances for artifact removal from concurrent fMRI–EEG recordings (Liu et al., 2012), high-field anatomical MRI (Duyn et al., 2007), physiological noise correction (Birn et al., 2008; Chang et al., 2009) and functional to structural image alignment (Saad et al., 2009). We aimed to answer a) whether BOLD signals within the visual thalamus were correlated (either negatively or positively) with the spontaneous modulation of posterior alpha rhythms, b) if so, to which nuclei of the visual thalamus (LGN or Pul) these correlations localized. To address the latter, the reference locations of LGN and Pul were respectively defined using a functional localizer with visual stimulation and high-resolution anatomical imaging, in addition to the use of a histology-based atlas of the thalamus (Morel, 2007). We also evaluated the intrinsic functional connectivity between the thalamus and the cortex to test whether those alpha-correlated thalamic and cortical regions would constitute a coherent functional network.

Methods and materials

Experimental design

In order to localize the neural circuitry underlying spontaneous modulation of posterior alpha rhythms, we measured simultaneous EEG and fMRI signals from 15 healthy volunteers under various experimental conditions and computed the correlation between the BOLD signal and the occipital EEG power at each volunteer's specific alpha frequency. The validity of this approach is based on the assumption that changes in alpha power have a metabolic correlate that leads to a BOLD effect through neurovascular coupling.

Three separate runs were performed to find the BOLD correlate to EEG alpha power, to measure an individual alpha frequency for each subject, and to functionally localize the LGN. Specifically, each subject was instructed to perform the following three tasks: 1) rest wakefully with eyes closed for 10 min, 2) rest while alternatingly keeping eyes closed or open in a self-paced manner (about 30 s for each period and 4 min in total), and 3) view checkerboard-patterned stimuli (full-screen, black-and-white, 6 Hz reversal frequency) presented with a block design (30 s on and 30 s off repeated for 3 cycles) combined with a continuous fixation task (pressing a button to report random color changes of a central dot). Some subjects participated in multiple scans of the same protocol on the same or a different day. At the end of each 10-min resting session, we explicitly asked the subject for feedback about his/her ability to stay wakeful during the entire scan. The session was excluded from further analysis if the subject reported falling asleep or feeling drowsy or if excessive head motion was observed. In total, this study included 35 scans for eyes-closed rest, 21 scans for the eyes-closed–eyes-open task and 21 scans for the visual stimulation.

To co-register functionally defined regions (e.g. alpha-BOLD correlated areas) to specific thalamic nuclei, we also performed high-resolution structural imaging based on GRE phase data and used a histology-based atlas of the thalamus. The former was used to describe the in vivo anatomical contrast and details, while the latter was used to identify the names of the nuclei underlying the thalamic alpha-BOLD correlation.

Environmental light exposure was minimized throughout the experiment. All of the subjects had normal or corrected-to-normal vision and gave informed written consent in accordance with a protocol approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health.

Data acquisition

We acquired concurrent EEG (32-channel EEG, international 10–20 montage, two unipolar electrodes for electrocardiogram (ECG) and electrooculography (EOG), 16-bit BrainAmp MR, BrainProducts GmbH, Germany) and BOLD fMRI using a single-shot gradient echo (GRE) echo-planar imaging (EPI) sequence on a 3 T Signa MRI system (General Electric Health Care, Milwaukee, WI, USA) equipped with a 16-channel receive-only coil array (NOVA Medical, Wilmington, MA, USA).

Continuously acquired EEG data were referenced to the FCz channel and sampled at 5 kHz with a resolution of 0.5 μV/bit and an analog bandwidth from 0.1 to 250 Hz. The EEG sampling clock was synchronized with an external reference signal extracted from the 10 MHz master clock of the MRI scanner. The onset time of every EPI slice acquisition was also recorded based on a 5 V TTL signal from the scanner. Cardiac and respiratory signals were recorded using a pulse oximeter on the left index finger and a pneumatic belt around the upper abdomen, respectively.

The GRE-EPI data were acquired with 90° flip angle (FA), 30 ms echo time (TE), 1.5 s repetition time (TR), 30 axial slices with 4 mm thickness and no inter-slice gap, 220×165 mm^2 field of view (FOV) for 64×48 matrix and sensitivity encoding (SENSE) parallel imaging with an acceleration factor of two (rate-2) as described earlier (de Zwart et al., 2002). The last imaging volume was acquired with slightly longer TE to measure the spatial variation of the B_0 field. T_1-weighted anatomical images covering the whole head were acquired with 3-D magnetization prepared rapid gradient echo (3-D MPRAGE) (FA = 12°, TE = 2.25 ms, TR = 5 ms, inversion time = 725 ms, 200 sagittal slices, 1 mm^3 isotropic resolution, rate-2 SENSE).