RESEARCH ARTICLE

Real-time fMRI neurofeedback of the mediodorsal and anterior thalamus enhances correlation between thalamic BOLD activity and alpha EEG rhythm

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Abstract

Real-time fMRI neurofeedback (rtfMRI-nf) with simultaneous EEG allows volitional modulation of BOLD activity of target brain regions and investigation of related electrophysiological activity. We applied this approach to study correlations between thalamic BOLD activity and alpha EEG rhythm. Healthy volunteers in the experimental group (EG, $n = 15$) learned to upregulate BOLD activity of the target region consisting of the mediodorsal (MD) and anterior (AN) thalamic nuclei using rtfMRI-nf during retrieval of happy autobiographical memories. Healthy subjects in the control group (CG, $n = 14$) were provided with a sham feedback. The EG participants were able to significantly increase BOLD activities of the MD and AN. Functional connectivity between the MD and the inferior precuneus was significantly enhanced during the rtfMRI-nf task. Average individual changes in the occipital alpha EEG power significantly correlated with the average MD BOLD activity levels for the EG. Temporal correlations between the occipital alpha EEG power and BOLD activities of the MD and AN were significantly enhanced, during the rtfMRI-nf task, for the EG compared to the CG. Temporal correlations with the alpha power were also significantly enhanced for the posterior nodes of the default mode network, including the precuneus/posterior cingulate, and for the dorsal striatum. Our findings suggest that the temporal correlation between the MD BOLD activity and posterior alpha EEG power is modulated by the interaction between the MD and the inferior precuneus, reflected in their functional connectivity. Our results demonstrate the potential of the rtfMRI-nf with simultaneous EEG for noninvasive neuromodulation studies of human brain function.

KEYWORDS

alpha rhythm, anterior nucleus, dorsal striatum, EEG-fMRI, mediodorsal nucleus, memory, neurofeedback, precuneus, real-time fMRI, thalamus

1 | INTRODUCTION

Understanding the mechanisms of generation and modulation of alpha EEG rhythms is a fundamental problem in neuroscience that awaits its comprehensive solution. Despite considerable progress, such mechanisms remain poorly understood due to their complexity (Başar, 2012). On the neuronal level, rhythmic electrical activity in the alpha band (8–13 Hz) in a normal brain arises from complex interactions among thalamocortical and cortico-cortical neuronal circuits (Hughes & Crunelli, 2005). On the macroscopic level, alpha EEG rhythms reflect complex

interplay between globally coherent and locally dominated dynamic processes, leading, respectively, to functional integration and functional specialization (Nunez, Wingeier, & Silberstein, 2001).

Simultaneous EEG-fMRI studies (Mulert & Lemieux, 2010) employing resting-state paradigms have provided important insights into properties of alpha EEG activity (de Munck et al., 2007; DiFrancesco, Holland, & Szaflarski, 2008; Feige et al., 2005; Goldman, Stern, Engel, & Cohen, 2002; Gonçalves et al., 2006; Laufs et al., 2003; Liu et al., 2012; Moosmann et al., 2003; Omata, Hanakawa, Morimoto, & Honda, 2013; Wu, Eichele, & Calhoun, 2010). These studies have revealed

negative temporal correlations between fluctuations in posterior alpha EEG power, convolved with the hemodynamic response function (HRF), and blood-oxygenation-level-dependent (BOLD) activity in the occipital cortex, particularly in the primary (V1) and secondary (V2) visual areas. Negative alpha-BOLD correlations are also observed in the visual areas of the thalamus, including the lateral geniculate nucleus (LGN) and the ventrolateral pulvinar (Liu et al., 2012). In contrast, positive temporal correlations between posterior alpha EEG power and BOLD activity have been detected in the dorsal parts of the thalamus, usually within and around the mediodorsal nucleus (MD) (de Munck et al., 2007; DiFrancesco et al., 2008; Goldman et al., 2002; Liu et al., 2012; Omata et al., 2013; Wu et al., 2010). Such positive correlations between metabolic activity in the thalamus and alpha EEG power, also observed in EEG-PET, are often cited as evidence of the important role played by the thalamus in generation and modulation of alpha rhythms (Schreckenberger et al., 2004). However, important questions remain. Scalp EEG has low sensitivity to neuronal activities in deep subcortical areas. Therefore, the positive alpha-BOLD correlations, observed for the MD, must be supported by cortical regions, interacting with the MD and participating in generation or modulation of posterior alpha rhythm. Resting EEG-fMRI studies have not been able to identify such regions. Further complicating interpretation is the fact that the MD (unlike the LGN) has no significant neuronal connections to the occipital cortex, and has limited neuronal connectivity to the parietal cortex (Kasdon & Jacobson, 1978; Selemon & Goldman-Rakic, 1988). Spontaneous BOLD fluctuations in the MD and in the occipital/parietal regions appear to be uncorrelated in healthy subjects at rest (Allen et al., 2011; Kim, Park, & Park, 2013). Overall, underlying mechanisms of the positive alpha-BOLD correlations for the thalamus remain unknown.

Resting-state EEG-fMRI experimental paradigms have two limitations. First, they rely on spontaneous fluctuations in EEG and BOLD activities. This reduces the experiments' sensitivity to specific EEG-fMRI effects of interest. Second, a participant's actual mental state at any moment during rest cannot be controlled or measured accurately. This leads to large between-subject and within-subject variabilities in resting-state results. These limitations are evident in the above-mentioned resting EEG-fMRI studies of alpha rhythm, which showed both insufficient sensitivity (Feige et al., 2005; Laufs et al., 2003; Moosmann et al., 2003), and large between-subject variability (de Munck et al., 2007; Gonçalves et al., 2006).

In this study, we investigate correlations between BOLD activity of the thalamus and posterior alpha EEG rhythm using the new multimodal approach we introduced recently, real-time fMRI neurofeedback with simultaneous EEG (Zotev et al., 2016). Real-time fMRI neurofeedback (rtfMRI-nf) (Birbaumer, Ruiz, & Sitaram, 2013; Thibault, Lifshitz, & Raz, 2016; Weiskopf, 2012) enables noninvasive volitional modulation of BOLD activities of small precisely defined regions deep inside the brain. The rtfMRI-nf modulation leads to an enhancement in functional connectivity between the target region and its task-specific network (Zotev et al., 2011; Zotev, Phillips, Young, Drevets, & Bodurka, 2013). Electrophysiological activities of cortical regions belonging to the network can be probed using simultaneous (passive) scalp EEG recordings.

Therefore, combination of the rtfMRI-nf and simultaneous EEG makes it possible to examine correlations between BOLD activity of the target region and related EEG activity (Zotev et al., 2016).

The rtfMRI-nf with simultaneous EEG approach has the potential to overcome the limitations inherent to resting-state EEG-fMRI. With rtfMRI-nf, BOLD activities of the target region and associated network can be significantly enhanced and modulated in a controlled manner. This increases signal-to-noise ratio and provides greater sensitivity for EEG-fMRI effects of interest. Because an rtfMRI-nf signal is a real-time measure of task performance, consistency of both individual and group results can be improved with sufficient training. Therefore, the rtfMRI-nf with simultaneous EEG offers new opportunities for studying relationships between electrophysiological and hemodynamic processes in the human brain. This approach can also help to identify promising target measures for EEG neurofeedback (EEG-nf) (Gruzelier, 2014), brain-computer interfaces (Cavazza et al., 2014), and simultaneous multimodal rtfMRI-EEG-nf (Mano et al., 2017; Perronnet et al., 2017; Zotev, Phillips, Yuan, Misaki, & Bodurka, 2014).

For this study, we selected the target region of interest (ROI) for rtfMRI-nf as the combination of the MD and the anterior nucleus (AN). The reason is that BOLD activity fluctuations in both the MD and the AN exhibit the strongest positive temporal correlations with posterior alpha EEG power at rest, according to the recent EEG-fMRI study (Liu et al., 2012). Both the MD and AN are parts of the limbic thalamus (Taber, Wen, Khan, & Hurley, 2004; Wolff, Alcaraz, Marchand, & Coutureau, 2015). The MD has major reciprocal connections with the prefrontal cortex and the anterior cingulate cortex. It also receives inputs from the amygdala, basal forebrain, entorhinal cortex, temporal polar cortex, substantia nigra, and cerebellum (Mitchell, 2015; Taber et al., 2004). Importantly, the MD subdivisions function as parts of the basal ganglia-thalamocortical circuits (Alexander, Crutcher, & DeLong, 1991). The AN has major reciprocal connections with the anterior and posterior cingulate cortices, and the hippocampal complex. It also receives input from the mamillary complex (Child & Benarroch, 2013; Taber et al., 2004). Both the MD and AN play important roles in memory, including episodic memory (Child & Benarroch, 2013; Taber et al., 2004; Wolff et al., 2015). The MD also contributes to a variety of other brain functions, including emotion, motivation, executive function, learning, and decision-making (Mitchell, 2015; Taber et al., 2004).

Because the MD and AN thalamic nuclei are prominently involved in the episodic memory function, they are activated during recall of autobiographical memories, as demonstrated by meta-analyses of fMRI memory studies (Spreng, Mar, & Kim, 2009; Svoboda, McKinnon, & Levine, 2006). We previously used an experimental paradigm involving retrieval of happy autobiographical memories together with rtfMRI-nf to achieve volitional modulation of the amygdala and associated emotion regulation network, including the MD (Zotev et al., 2011, 2016). Importantly, episodic memory retrieval strongly activates the posterior nodes of the fMRI default mode network (DMN), including the precuneus/posterior cingulate and the left and right angular gyri (Sestieri, Corbetta, Romani, & Shulman, 2011; Spreng et al., 2009). EEG source analysis studies have shown that the posterior DMN regions exhibit increased alpha EEG power during self-referential thoughts (Knyazev,

FIGURE 1 Experimental paradigm for real-time fMRI neurofeedback modulation of the thalamus with simultaneous EEG recordings. (a) Target region of interest (ROI) used to provide the rtfMRI-nf signal for the experimental group (EG). The target ROI consists of two thalamic nuclei: the anterior nucleus (AN, red) and the mediodorsal nucleus (MD, orange). The nuclei are defined anatomically according to the stereotaxic atlas of the human brain by Talairach and Tournoux. They are projected in the figure onto the standard anatomical template TT_N27 in the Talairach space. The cross-section of the whole thalamus is shown in a darker grey color. (b) Generation of the sham feedback signal for the control group (CG). The sham signal waveform is computed for a 40-s-long condition block as a random linear combination of seven Legendre polynomials. (c) A 32-channel MR-compatible EEG system used to perform EEG recordings simultaneously with fMRI data acquisition. (d) Occipital (O1, O2, Oz) and parietal (P3, P4, Pz) EEG channels commonly used to study posterior alpha EEG activity [Color figure can be viewed at wileyonlinelibrary.com]

Slobodskoj-Plusnin, Bocharov, & Pylkova, 2011) and retrieval of autobiographical memories (Knyazev et al., 2015).

We conducted the rtfMRI-nf with simultaneous EEG experiment to test two main hypotheses. First, we hypothesized that healthy participants would be able to significantly increase BOLD activities of the MD and AN thalamic nuclei using the rtfMRI-nf during retrieval of happy autobiographical memories. Second, we hypothesized that performance of the rtfMRI-nf task would be accompanied by significant enhancements in temporal correlations between the MD and AN BOLD activities and posterior alpha EEG power. We also expected to identify cortical regions supporting these correlation effects.

2 | MATERIALS AND METHODS

2.1 | Participants

The study was conducted at the Laureate Institute for Brain Research, and was approved by the Western Institutional Review Board (IRB). All the participants provided written informed consent as approved by the IRB. All study procedures were performed in accordance with the principles expressed in the Declaration of Helsinki.

Thirty-four healthy volunteers participated in the study. The participants underwent a psychological evaluation by a licensed clinician and were both medically and psychiatrically healthy. Five subjects exhibited

excessive head motions during scanning, and their data were not included in the analyses. The participants were randomly assigned to either the experimental group (EG, $n = 15$, 9 females) or the control group (CG, $n = 14$, 8 females). The EG participants followed an experimental procedure with rtfMRI-nf based on BOLD activity of the thalamus, as described in detail below. The CG participants followed the same procedure, but were provided, without their knowledge, with a sham feedback unrelated to any brain activity. The subjects' average age was 29 ($SD = 6$) years for the EG and 29 ($SD = 10$) years for the CG.

2.2 | Experimental paradigm

The experimental paradigm involved targeted modulation of BOLD activity of the AN and MD thalamic nuclei using rtfMRI-nf during retrieval of happy autobiographical memories and recording of concurrent EEG activity (Figure 1).

The target ROI for the rtfMRI-nf for the EG consisted of the AN and MD nuclei, depicted in Figure 1a. They were defined anatomically as the AN and MD regions specified in the stereotaxic atlas of the human brain by Talairach and Tournoux (1988). The target ROI was transformed to each subject's individual fMRI image space and used as a mask to compute the average ongoing BOLD activity of the target region. The rtfMRI-nf signal provided to the EG participant was based on this activity. It was presented to the subject inside the MRI scanner

FIGURE 2 Protocol for the rtfMRI-nf experiment. (a) Real-time GUI display screens for three experimental conditions: Happy Memories, Attend, and Count. The variable-height rtfMRI-nf bar (red) is shown during each condition, and its height is updated every 2 s. The fixed blue bar denotes the zero level. (b) Protocol for the rtfMRI-nf experiment includes seven runs, each lasting 8 min 46 s: Rest (RE), Run 1 (R1), Run 2 (R2), Run 3 (R3), Run 4 (R4), Transfer (TR), and Rest (RE). The experimental runs (except the Rest) consist of 40-s-long blocks of Happy Memories (H), Attend (A), and Count (C) conditions. No bars are shown during the Transfer run [Color figure can be viewed at wileyonlinelibrary.com]

in the form of a variable-height thermometer-style red bar on the screen, as described below. By controlling the height of the rtfMRI-nf bar, the EG participant was able to directly modulate BOLD activity of the target region in real time.

The sham feedback signal for the CG was computer-generated as illustrated in Figure 1b. It was defined, for each 40-s-long condition block, as a linear combination of seven Legendre polynomials with randomly selected coefficients, projected from the $[-1..+1]$ interval onto the $[0..40]$ s time interval. The random number generator was initialized to a random seed value at the beginning of each experiment. Such sham feedback signal definition yielded a smooth waveform (Figure 1b), which was used to set the height of the red bar in real time. It appeared to provide meaningful real-time information to the CG participant. However, the waveform's shape (temporal profile) was random, and it also varied randomly across the condition blocks and across the subjects. We did not select the sham neurofeedback approach that employs an rtfMRI signal from a control brain region (Zotev et al., 2011), because the thalamus has extensive neuronal connections to various cortical areas and subcortical structures.

2.3 | Experimental protocol

Prior to the rtfMRI-nf session, each participant was given detailed instructions that included an overview of the experiment and an explanation of each experimental task. The participant was asked to think of and write down three happy autobiographical memories, keeping them private. It was suggested that he/she use those three memories at the beginning of the experiment to evaluate their effects, and then explore various other happy autobiographical memories as the training progressed to enhance emotional memory experience and improve rtfMRI-nf performance. The participants were encouraged to keep their eyes open and pay attention to the display screen throughout each experimental run.

The experimental protocol is illustrated in Figure 2. It included three conditions: Happy Memories, Attend, and Count. The real-time GUI display screens for these conditions are shown in Figure 2a. Each condition was specified by visual cues that included a color symbol at the center of the screen and a text line at the top. As mentioned above, the rtfMRI-nf signal was represented by the variable-height red bar (Figure 2a). We chose to have it displayed and updated during all three experimental conditions to reduce variations in visual stimulation and visual attention levels across the conditions. The bar height was updated every 2 s, and was also indicated by the numeric value shown above the bar. The blue bar was fixed and denoted the zero level.

For the Happy Memories condition blocks, the participants were instructed to evoke and contemplate happy autobiographical memories while simultaneously trying to raise the red rtfMRI-nf bar on the screen as high as possible (Figure 2a, left). For the Attend condition blocks, the subjects were asked to relax while paying attention to the fluctuating red bar without attempting to control it (Figure 2a, middle). For the Count condition blocks, the participants were instructed to mentally count back from 300 by subtracting a given integer while watching the red bar without trying to control it (Figure 2a, right). Because during the Happy Memories condition the subjects were asked to volitionally control the rtfMRI-nf signal, we also refer to it as the rtfMRI-nf task. The Attend condition served as a baseline attention task, and the Count condition was a cognitive control task.

The rtfMRI-nf experiment included seven fMRI runs (Figure 2b) each lasting 8 min 46 s. During the initial and final Rest runs, the participants were asked to relax and rest while looking at the fixation cross. The five task runs—Run 1, Run 2, Run 3, Run 4, and the Transfer run—consisted of alternating 40-s long blocks of Happy Memories, Attend, and Count conditions (Figure 2b). Each Happy Memories or Count condition block was preceded by an Attend condition block. During the four rtfMRI-nf runs (Runs 1–4), the participants performed the three experimental tasks as indicated by the GUI display with the rtfMRI-nf

bar (Figure 2a). During the Transfer run, the participants performed the same tasks, except that no bars were shown on the screen for any of the conditions. The Transfer run was included in order to evaluate whether the participants' learned ability to control BOLD activity of the target ROI generalized beyond the actual rtfMRI-nf training. The Happy Memories conditions did not differ across Runs 1–4. The Count conditions involved counting back from 300 by subtracting 3, 4, 6, 7, and 9 for Run 1, Run 2, Run 3, Run 4, and the Transfer run, respectively. The display range for the rtfMRI-nf signal was -2% to $+2\%$ for all conditions.

2.4 | Data acquisition

All experiments were conducted on the General Electric Discovery MR750 3T MRI scanner with a standard 8-channel receive-only head coil (Figure 1c). A single-shot gradient echo EPI sequence with FOV/slice = $240/2.9$ mm, $TR/TE = 2000/30$ ms, flip angle = 90° , 34 axial slices per volume, slice gap = 0.5 mm, SENSE acceleration $R = 2$ in the phase encoding (anterior-posterior) direction, acquisition matrix 96×96 , sampling bandwidth = 250 kHz, was employed for fMRI. Each fMRI run lasted 8 min 46 s and included 263 EPI volumes (the first three EPI volumes were excluded from data analysis to account for fMRI signal reaching a steady state). Physiological pulse oximetry and respiration waveforms were recorded simultaneously with fMRI. The EPI images were reconstructed into a 128×128 matrix, yielding $1.875 \times 1.875 \times 2.9$ mm³ fMRI voxels. A T1-weighted 3D MPAGE sequence with FOV/slice = $240/1.2$ mm, $TR/TE = 5.0/1.9$ ms, $TD/TI = 1400/725$ ms, flip angle = 10° , 128 axial slices per slab, SENSE $R = 2$, acquisition matrix 256×256 , sampling bandwidth = 31.2 kHz, scan time = 4 min 58 s, was used for anatomical imaging. It provided structural brain images with $0.94 \times 0.94 \times 1.2$ mm³ voxel size.

EEG recordings were performed simultaneously with fMRI (Figure 1c) using a 32-channel MR-compatible EEG system from Brain Products, GmbH. The EEG system clock was synchronized with the MRI scanner 10 MHz clock using the Brain Products' SyncBox. EEG data were acquired with 0.2 ms temporal and 0.1 μ V measurement resolution (16-bit 5 kS/s sampling) in $0.016 \dots 250$ Hz frequency band with respect to FCz reference. All technical details of the EEG-fMRI system configuration and data acquisition were reported previously (Zotev, Yuan, Phillips, & Bodurka, 2012). Similar to our recent study (Zotev et al., 2016), the EEG recordings in this work were passive, that is, no EEG information was used in real time as part of the experimental procedure.

2.5 | Real-time data processing

The rtfMRI-nf was implemented using the custom real-time fMRI system utilizing real-time functionality of AFNI (Cox, 1996; Cox & Hyde, 1997) as described previously (Zotev et al., 2011). A high-resolution MPAGE structural brain image and a short EPI dataset (5 volumes) were acquired at the beginning of each rtfMRI-nf experiment. The last volume of the EPI dataset was used as a reference EPI volume defining the subject's individual EPI space. The target ROI, defined in the

Talairach space (Figure 1a), was transformed to the individual EPI space using the MPAGE image data. The resulting ROI in the EPI space contained, on the average, 260 voxels. During the subsequent fMRI runs (Figure 2b), the AFNI real-time plugin was used to perform volume registration of each acquired EPI volume to the reference EPI volume (motion correction) and export the mean value of fMRI signal for the target ROI in real time. The custom developed GUI software was used to further process the exported fMRI signal values and display the ongoing rtfMRI-nf information (Figure 2a).

The rtfMRI-nf signal was defined as the fMRI percent signal change with respect to a selected baseline. For each Happy Memories or Count condition, an average of fMRI signal values for the preceding 40-s-long Attend condition block (Figure 2b) was used as the baseline. For each Attend condition, the baseline was calculated as an average of fMRI signal values in the same Attend condition block acquired prior to the current fMRI signal value. Specifically, for the first volume in the Attend block, the percent signal change was set to zero; for the second volume, the fMRI signal value from the 1st volume was used as the baseline; for the third volume, the baseline was computed as an average of the fMRI signal values from the first and second volumes; and so on. Thus, the rtfMRI-nf signal for the Attend conditions represented percent signal changes for fluctuating fMRI signal values with respect to the incrementally updated Attend baseline. To reduce effects of fMRI noise and physiological artifacts, a moving average of the current and two preceding rtfMRI percent-signal-change values (Zotev et al., 2011) from the same condition block was computed. (The recorded cardiac and respiratory waveforms were not used in the real-time processing). This moving average was used to set the height of the red rtfMRI-nf bar on the screen (Figure 2a) for the EG. The height of the red bar and the numeric value above it were updated every $TR = 2$ s. To provide sham feedback for the CG, the actual rtfMRI-nf values for the Happy Memories and Count conditions were substituted with the computer-generated sham feedback signal values (Figure 1b). An example of the rtfMRI-nf signal time course for one EG participant is shown in Supporting Information, Figure S1.

2.6 | fMRI data analysis

Offline analysis of the fMRI data was performed in AFNI as described in detail in Supporting Information, S1.1. It involved fMRI pre-processing with cardiorespiratory artifact correction (Glover, Li, & Ress, 2000), slice timing correction, and volume registration. A standard fMRI activation analysis for each task run involved solution of a general linear model (GLM) with the Happy Memories and Count block-stimulus regressors. Average GLM-based fMRI percent signal changes were then computed for the AN and MD ROIs (Figure 1a), and for the LGN ROI (Supporting Information, S1.1). A standard fMRI functional connectivity analysis with the MD ROI as the seed region was performed within GLM framework specifically for the Happy Memories conditions in each task run. The GLM also included time courses of fMRI motion parameters and average fMRI time courses of bilateral ROIs within white matter (WM) and ventricle cerebrospinal fluid (CSF) as nuisance covariates (Jo, Saad, Simmons, Milbury, & Cox, 2010). An fMRI

functional connectivity analysis with the AN ROI as the seed region was performed in a similar way (Supporting Information, S1.1).

In addition to the standard fMRI activation and functional connectivity analyses, we conducted similar analyses (Supporting Information, S1.1) that included the fMRI time course of the ROI encompassing the primary (V1, BA 17) and secondary (V2, BA 18) visual areas as a nuisance covariate. We refer to this ROI as V1/V2. BOLD activities of these areas exhibit strong negative correlations with posterior alpha EEG power (Feige et al., 2005). The inclusion of this additional covariate yielded fMRI results that were less dependent on variations in visual attention.

2.7 | EEG data processing

Offline processing of the EEG data, acquired during fMRI, was performed in BrainVision Analyzer 2.1 software as described in detail in Supporting Information, S1.2. Removal of EEG artifacts was based on the average artifact subtraction and independent component analysis (Bell & Sejnowski, 1995; McMenamin et al., 2010). Channel Cz was selected as a new reference. Following the artifact removal, the EEG data were downsampled to 8 ms temporal resolution.

The alpha EEG band was defined individually for each participant as $[IAF - 2 \dots IAF + 2]$ Hz, where IAF is the individual alpha peak frequency. The IAF was determined by inspection of average EEG spectra for the occipital and parietal EEG channels (Figure 1d) across the Attend condition blocks in the four rtFMRI-nf runs (Figure 2b).

2.8 | Alpha envelope correlation analysis

To study amplitude modulation of alpha EEG activity across the EEG array, we conducted analyses of temporal correlations between alpha amplitude envelopes for all channel pairs. After the artifact removal, EEG signals from all channels (8 ms temporal resolution) were bandpass filtered (48 dB/octave) in the individual alpha band, defined above, to extract their alpha activities. The Hilbert transform was applied to obtain the analytic signal, and its magnitude defined the alpha envelope time course for each channel. Temporal correlation between the alpha envelopes for each pair of channels was analyzed for each experimental condition in each of the five task runs (Figure 2b). Each analysis included a segmentation with 4.096 s interval, a complex FFT with 0.244 Hz spectral resolution, and the Coherence transform implemented in Analyzer 2.1. The transform was used to compute a magnitude-squared correlation coefficient for two channels' time courses at a given frequency as a squared magnitude of their cross-covariance value normalized by their auto-covariance values at the same frequency. The results were averaged for the low frequency range [0.244...1.46] Hz, and a square root of the average was calculated. We refer to the resulting quantity as the alpha envelope correlation (AEC). The AEC was computed for each pair of EEG channels. Differences in the average AEC values between experimental conditions (Figure 2b) were used to evaluate task-specific variations in correlated amplitude modulation of alpha rhythm across the EEG array.

2.9 | Occipital alpha power analysis

To facilitate comparison of our EEG-fMRI results to those of the previous studies that investigated BOLD correlates of occipital alpha EEG power (DiFrancesco et al., 2008; Feige et al., 2005; Goldman et al., 2002; Liu et al., 2012), we focused on alpha power for the occipital channels O1, O2, Oz (Figure 1d). (All the analyses were later repeated for the parietal channels P3, P4, Pz.) EEG signal power was computed using a continuous wavelet transform with Morlet wavelets for [0.25...15] Hz frequency range with 0.25 Hz frequency resolution and 8 ms temporal resolution. Normalized occipital alpha EEG power (Gasser, Bächer, & Möcks, 1982) was defined for each time point as $\alpha O = \ln(P(O1)) + \ln(P(O2)) + \ln(P(Oz))$, where P is the EEG signal power in the individual alpha band defined above. The normalized occipital alpha power values were averaged for 200-ms-long time bins, linearly detrended, and converted to z scores across each run. To account for possible modulating effects of eye movements (de Munck et al., 2007), including eye blinking and occasional eye closing, on the alpha EEG power, we orthogonalized the z score time course for each run with respect to the corresponding EEG eye-blinking covariate (Supporting Information, S1.3). We used the resulting z score time courses, denoted as $z(\alpha O)$, to define EEG-based regressors for EEG-fMRI analyses. Average differences in the z scores between experimental conditions were used to evaluate task-specific variations in the normalized occipital alpha EEG power.

2.10 | EEG-fMRI temporal correlation analysis

To study task-specific temporal correlations between alpha EEG power and BOLD activity, we performed psychophysiological interaction (PPI) analyses (Friston et al., 1997; Gitelman, Penny, Ashburner, & Friston, 2003) adapted for EEG-fMRI (Zotev et al., 2014, 2016). In these analyses, we tested the hypothesis that temporal correlations between the occipital alpha EEG power and BOLD activities of the AN and MD would be stronger during the Happy Memories conditions with rtFMRI-nf than during the control conditions (Attend, Count) for the EG, but not for the CG.

EEG-based regressors for the PPI analyses were defined as illustrated in Figure 3. The time course of z scores of the normalized occipital alpha EEG power, $z(\alpha O)$, was computed for each run as described above. The HRF ("Cox special," maximum at 6 s) was calculated with 200 ms sampling using the waver AFNI program. Convolution of the $z(\alpha O)$ time course with the HRF produced the EEG-based regressor, employed as a PPI correlation regressor (Figure 3a). To define a PPI interaction regressor, the $z(\alpha O)$ time course was first multiplied by a selected contrast function, and then convolved with the HRF. An EEG-based PPI interaction regressor for the Happy versus Attend condition contrast was defined as illustrated in Figure 3b,c. An EEG-based PPI interaction regressor for the Happy versus Count condition contrast was defined as illustrated in Figure 3d,e. These EEG-based PPI regressors were sub-sampled to middle time points of fMRI volumes, linearly detrended, and used as stimulus regressors in the PPI analyses of the EEG-fMRI data within GLM framework.

FIGURE 3 Definition of EEG-based regressors for the psychophysiological interaction (PPI) analyses of EEG-fMRI data. A general linear model (GLM) for a PPI analysis includes one PPI correlation regressor, one PPI interaction regressor, block-design stimulus regressors, and nuisance covariates. The PPI regressors are defined here using the time course of the normalized occipital alpha EEG power (αO) converted to z scores across each run. (a) Convolution of the EEG power z scores (cyan, 200 ms sampling) with the hemodynamic response function (HRF) yields the EEG-based PPI correlation regressor (red). (b) Definition of the [Happy – Attend] contrast function. It is equal to +1 for the Happy Memories (H) condition blocks, –1 for the following Attend (A) condition blocks, and 0 for all other points. The condition blocks are depicted schematically in Figure 2b. (c) Convolution of the EEG power z scores multiplied by the [Happy – Attend] contrast function (cyan) with the HRF yields the EEG-based PPI interaction regressor for the Happy vs Attend condition contrast (red). (d) Definition of the [Happy – Count] contrast function. It is equal to +1 for the Happy Memories (H) condition blocks, –1 for the Count (C) condition blocks, and 0 for all other points. (e) Convolution of the EEG power z scores multiplied by the [Happy – Count] contrast function (cyan) with the HRF yields the EEG-based PPI interaction regressor for the Happy vs Count condition contrast (red) [Color figure can be viewed at wileyonlinelibrary.com]

In addition to the EEG-based PPI regressors, we defined fMRI-based PPI regressors using the average fMRI time course of the visual cortex V1/V2, as described in Supporting Information, S1.4. We refer to them as fMRI-visual PPI correlation covariate and fMRI-visual PPI interaction covariate (for the Happy vs Attend or Happy vs Count condition contrast). These waveforms were used as nuisance covariates in the PPI analyses of the EEG-fMRI data.

Each PPI analysis involved a solution of a GLM model with two EEG-based PPI regressors by means of the 3dDeconvolve AFNI

program. The PPI correlation term described the correlation of the EEG-based regressor with the fMRI time course across all three experimental conditions. The PPI interaction term described the difference in correlations of the EEG-based regressor with the fMRI time course between the Happy Memories condition and the selected control condition (Attend or Count). The fMRI data and motion parameters were bandpass filtered between 0.01 and 0.1 Hz. The GLM design matrix for each task run included four stimulus regressors, ten nuisance covariates, and five polynomial terms for modeling the baseline. The stimulus regressors included: the EEG-based PPI interaction regressor; the EEG-based PPI correlation regressor; the Happy Memories block-stimulus regressor; the Count block-stimulus regressor. The nuisance covariates included: time courses of the six fMRI motion parameters (together with the same time courses shifted by one TR); the time course of the WM ROI; the time course of the CSF ROI; the fMRI-visual PPI interaction covariate; the fMRI-visual PPI correlation covariate. The last two nuisance covariates (Supporting Information, S1.4) accounted for PPI interaction and correlation effects that could be attributed to temporal variations in the average BOLD activity of the visual cortex V1/V2. Each PPI analysis, conducted in this way, yielded GLM-based R^2 -statistics and t -statistics maps for the EEG-based PPI interaction and correlation terms, which we used to compute voxel-wise PPI interaction and correlation values. The resulting maps were normalized using the Fisher r -to- z transform, then transformed to the Talairach space, re-sampled to $2 \times 2 \times 2 \text{ mm}^3$ isotropic voxel size, and spatially smoothed (5 mm FWHM). See Supporting Information, S1.5 for additional technical details of the PPI analyses.

Independent-samples t tests were conducted to evaluate significance of the EG versus CG group differences in the PPI interaction effects for the Happy versus Attend and the Happy versus Count condition contrasts. The results were corrected for multiple comparisons by controlling the family-wise-error (FWE). The correction was based on Monte Carlo simulations implemented in the AlphaSim AFNI program.

3 | RESULTS

3.1 | Thalamic BOLD activity

Results of the offline fMRI activation analysis for the AN and MD ROIs are exhibited in Figure 4a for the EG and in Figure 4b for the CG. For statistical testing, each participant's BOLD activity levels were averaged across the four rtfMRI-nf runs (Runs 1–4). The average BOLD activity levels for the Happy Memories conditions (H vs A) for the AN ROI were significant for the EG ($t(14)=5.82, p < .00004$) and showed a significant EG versus CG group difference ($t(27)=3.14, p < .004$). The corresponding average BOLD activity levels for the MD ROI were also significant for the EG ($t(14)=4.86, p < .0003$) and exhibited a significant group difference ($t(27)=2.38, p < .024$). (When results for the two ROIs were tested, the Bonferroni-corrected $p < .05$ corresponded to uncorrected $p < .025$). For the Transfer run (TR), the BOLD activity levels (H vs A) for the EG were somewhat lower (Figure 4a), but did not differ significantly from the average BOLD activity levels across the four rtfMRI-nf runs (AN, TR vs NF: $t(14)=-1.48, p < .162$; MD, TR vs NF: $t(14)=-0.87, p < .402$), indicating transfer of the training effects.

FIGURE 4 BOLD activity levels for the anterior and mediodorsal thalamic nuclei during the rtfMRI-nf experiment. (a) Average fMRI percent signal changes for the anterior nucleus (AN) and the mediodorsal nucleus (MD) for the experimental group (EG). The two nuclei were parts of the target ROI for the rtfMRI-nf (Figure 1a). Each bar represents a mean GLM-based fMRI percent signal change for the corresponding ROI with respect to the Attend baseline for the Happy Memories (H vs A) or Count (C vs A) conditions in a given run, averaged across the group. The error bars are standard errors of the means (sem) for the group average. The experimental runs and condition blocks are depicted schematically in Figure 2b. (b) Corresponding average fMRI percent signal changes for the AN and MD for the control group (CG) [Color figure can be viewed at wileyonlinelibrary.com]

Average BOLD activity levels for the LGN positively correlated with those for the MD in either group, as described in Supporting Information, S2.2 and Figure S2).

3.2 | Functional connectivity changes

Figure 5 shows the statistical maps for the EG versus CG group difference in fMRI functional connectivity of the MD during the Happy Memories conditions with rtfMRI-nf. The single-subject functional connectivity analyses included the average fMRI time course of the visual cortex V1/V2 as a nuisance covariate. (The analyses without this covariate provided similar results). Each subject's MD functional connectivity maps were averaged for the last two rtfMRI-nf runs (Runs 3 and 4; see Section 4). Similar fMRI connectivity analyses were conducted for the AN as the seed region. The group difference statistical maps in Figure 5 were thresholded at $t(27) = \pm 2.77$ (uncorr. $p < .01$) and clusters containing at least 81 voxels were retained to yield FWE corrected $p < .025$ (to account for testing results for the two seed ROIs). The cluster properties are reported in Table 1, separately for the MD and the AN analyses. According to Figure 5a, the MD functional connectivity with the right medial precuneus (BA 31) was significantly enhanced during the rtfMRI-nf task for the EG compared to the CG. In contrast,

the MD functional connectivities with three prefrontal regions and the substantia nigra were significantly reduced for the EG relative to the CG (Figure 5b–d and Table 1).

3.3 | Alpha envelope correlations

Results of the AEC analysis are exhibited in Figure 6. An example of the alpha amplitude envelope is shown in Figure 6a. The AEC changes between the Happy Memories conditions with rtfMRI-nf and Attend conditions (H vs A) in each task run were computed for each pair of EEG channels. The average AEC change across all channel pairs ($n = 406$ for 29 EEG channels) was also computed for each run and each participant. The AEC changes are compared in Figure 6b–d with fMRI activity levels (marked with *) for the MD ROI corresponding to the part of the total MD BOLD activity that did not exhibit temporal correlation with the average BOLD activity of the visual cortex V1/V2. It was determined from the GLM-based fMRI activation analysis that included the average fMRI time course of the V1/V2 as a nuisance covariate. The average individual AEC changes across all EEG channel pairs (also averaged for Runs 3,4) showed significant positive correlation with the corresponding MD fMRI activity* levels for the EG ($r = 0.56$, $p < .031$, Figure 6b), but not for the CG (Figure 6d). Partial

FIGURE 5 Functional connectivity of the mediodorsal nucleus during the rtfMRI-nf task compared between the groups. fMRI functional connectivity analyses were performed for the Happy Memories conditions in each run using the mediodorsal nucleus (MD) ROI as the seed. The results were averaged for the last two rtfMRI-nf runs (Runs 3,4) for each participant. Statistical maps for the experimental versus control group difference (EG vs CG) in the average MD functional connectivity are shown for four regions (Table 1): (a) the right medial precuneus (BA 31); (b) the left anterior cingulate (BA 32); (c) the left inferior frontal gyrus (BA 47); (d) the left precentral gyrus (BA 6). The maps are projected onto the TT_N27 template in the Talairach space. Following the radiological notation, the left hemisphere (L) is shown to the reader's right. The crosshairs mark locations of the statistical peaks for the group difference (Table 1) [Color figure can be viewed at wileyonlinelibrary.com]

correlation between the same measures controlled for the LGN fMRI activity* (Supporting Information, Figure S2) was more positive and significant for the EG ($r(12) = 0.67$, $p < .008$), but not for

TABLE 1 Functional connectivities of the mediodorsal and anterior nuclei during the rtfMRI-nf task compared between the groups

Region	Laterality	x, y, z (mm)	t score	Size (vox.)
<i>Mediodorsal nucleus</i>				
Inferior frontal gyrus (BA 47)	L	-37, 20, -3	-4.84	217
Anterior cingulate (BA 32)	L	-9, 17, -10	-4.80	131
Precentral gyrus (BA 6)	L	-31, -9, 58	-4.35	100
Substantia nigra	R	11, -17, -8	-3.92	98
Precuneus (BA 31)	R	7, -69, 22	+3.86	98
<i>Anterior nucleus</i>				
Caudate head	L	-15, 19, 4	-4.60	217
Lentiform nucleus	L	-31, -5, -6	-4.62	82

Note. Abbreviations: BA = Brodmann areas; L = left; R = right; x, y, z = Talairach coordinates. FWE-corrected $p < .025$ (size—cluster size, minimum 81 voxels for uncorrected $p < .01$). Statistical results for the experimental versus control group differences (EG vs CG) in fMRI functional connectivities of the mediodorsal nucleus (MD) and anterior nucleus (AN) during the Happy Memories conditions with rtfMRI-nf are shown. The functional connectivity analyses were performed separately for the MD and the AN as seed regions. Location of the point with the peak group difference t score ($df = 27$) and the number of voxels are specified for each cluster obtained after FWE correction for multiple comparisons in each analysis.

the CG ($r(11) = -0.23$, $p < .446$). According to Figure 6c, the individual AEC changes for the EG showed positive correlations with the MD fMRI activity* levels for many channel pairs (red segments, $r > 0$, $p < .01$, uncorr.). For the CG, no correlations reached the $p < .01$ statistical threshold. In contrast to the result for the MD in Figure 6b, correlation between the average AEC changes and fMRI activity* levels for the AN ROI was not significant (AN, EG, NF: $r = 0.23$, $p < .402$).

3.4 | Alpha-BOLD mean value correlations

Figure 7 examines correlations between the mean individual changes in the occipital alpha EEG power z scores, $z(\alpha O)$, and the corresponding fMRI activity* levels for the MD ROI. The fMRI activity* has the same meaning as in Figure 6. The plots on the left show correlation results for the rtfMRI-nf runs (NF, with the data averaged for Runs 3,4). The plots on the right show correlation results for the Transfer run (TR) without nf. According to Figure 7a, the individual Happy versus Attend (H vs A) occipital alpha power changes for the EG exhibited significant positive correlations with the MD fMRI activity* levels both for the rtfMRI-nf runs (NF: $r = 0.70$, $p < .004$) and for the Transfer run (TR: $r = 0.59$, $p < .021$). No significant correlations were found for the CG (Figure 7b). Partial correlation between the same measures controlled for the LGN fMRI activity* (Supporting Information, Figure S2) was more significant for the EG (NF: $r(12) = 0.87$, $p < .0001$), but not for the CG (NF: $r(11) = 0.06$, $p < .848$). Compared to the results for the MD in Figure 7a, correlations between the individual occipital alpha power changes and fMRI activity* levels for the AN ROI were less significant (AN, EG, NF: $r = 0.61$, $p < .015$; TR: $r = 0.29$, $p < .295$).

FIGURE 6 Amplitude modulation of alpha EEG rhythm during the rtfMRI-nf training and its correlation with BOLD activity of the medial-dorsal nucleus. (a) Envelope of alpha EEG activity obtained via the Hilbert transform. Temporal correlation between alpha envelopes for a pair of EEG channels is referred to as the alpha envelope correlation (AEC). (b) Significant positive correlation between the individual AEC changes for the Happy versus Attend conditions (H vs A), averaged across all EEG channel pairs ($n = 406$), and the corresponding fMRI activity* levels (H vs A) for the medial-dorsal nucleus (MD) ROI. The results are for the experimental group (EG), and each data point corresponds to one participant. The fMRI activity (marked with *) is the part of the total MD BOLD activity that did not exhibit temporal correlation with the average BOLD activity of the visual cortex V1/V2 (see text). Each participant's data are averaged for the last two rtfMRI-nf runs (Runs 3,4). (c) Correlations between the individual AEC changes (H vs A) and the corresponding MD fMRI activity* levels (H vs A) for EEG channel pairs for the EG. Each red segment denotes a pair of EEG channels for which the correlation is positive ($r > 0$, $p < .01$, uncorr.). Negative correlations ($r < 0$) did not reach the $p < .01$ statistical threshold. Each participant's data are averaged for Runs 3,4. (d) Lack of correlation between the individual AEC changes, averaged across all channel pairs, and the corresponding MD fMRI activity* levels for the control group (CG) [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | Alpha-BOLD temporal correlations

Average values of the PPI interaction effects for the AN and MD ROIs are exhibited in Figure 8a. The PPI interaction effects for the Happy versus Attend (H vs A) and Happy versus Count (H vs C) condition contrasts were determined from separate whole-brain PPI analyses using the regressors illustrated in Figure 3. Voxel-wise PPI interaction values were averaged within the AN and MD ROIs for each run and across the four rtfMRI-nf runs (Runs 1–4) for each participant.

According to Figure 8a, the average PPI interaction effects for the AN and MD were positive for the EG and negative for the CG. A non-zero PPI interaction indicates that the EEG-based PPI correlation regressor (Figure 3a) cannot accurately explain the EEG-related variance in the BOLD activity across all conditions, because its correlation with the BOLD time course depends on the condition. Such condition-dependent variance is modeled by the competing EEG-based PPI interaction regressor for a given contrast (Figure 3c,e). The positive PPI interaction effects for the AN and MD (Figure 8a) mean that temporal correlations between the occipital alpha EEG power ($z(\alpha O)$, convolved with the HRF) and BOLD activities of these regions were more positive

during the Happy Memories conditions with rtfMRI-nf than during the control conditions (Attend or Count) for the EG. These effects are illustrated in Figure 8b, which compares actual single-subject EEG-based regressor and BOLD activity of the AN across experimental conditions in a single rtfMRI-nf run.

Importantly, all four EG versus CG group differences in the PPI interaction effects shown in Figure 8a were significant. (When results for the two ROIs and two contrasts were tested, the Bonferroni-corrected $p < .05$ corresponded to uncorrected $p < .0125$). Comparison of the PPI interaction effects for the EG (Figure 8a) to zero level (instead of the CG) revealed one PPI effect that was significant (EG, AN, H vs C: $t(14) = 5.42$, $p < .0001$), and one PPI effect that trended toward significance after correction (EG, MD, H vs A: $t(14) = 2.81$, $p < .014$). The regression of the fMRI-visual PPI covariates (Supporting Information, S1.4) generally improved significance of the PPI results for the AN and MD, as described in Supporting Information, S2.3 and Figure S3).

For the Transfer run for the EG, the mean PPI interaction values (not shown) did not differ significantly from the corresponding PPI

FIGURE 7 Correlations between variations in the mean occipital alpha EEG power and BOLD activity of the mediadorsal nucleus during the rtfMRI-nf experiment. (a) Significant positive correlations between the mean individual Happy versus Attend (H vs A) changes in z scores of the normalized occipital alpha EEG power, $z(\alpha O)$, and the corresponding fMRI activity* levels for the MD ROI for the experimental group (EG). As in Figure 6, the fMRI activity* is the part of the total MD BOLD activity that did not show temporal correlation with the average BOLD activity of the visual cortex V1/V2. Each data point corresponds to one participant. The plot on the left (NF) shows correlation for the participants' individual data averaged for the last two rtfMRI-nf runs (Runs 3,4). The plot on the right (TR) shows correlation for the Transfer run without nf. (b) Lack of correlations between corresponding measures for the control group (CG) [Color figure can be viewed at wileyonlinelibrary.com]

interaction values averaged for the four rtfMRI-nf runs (Figure 8a), suggesting transfer of the training effects. Moreover, the individual PPI interaction values (H vs A) for the MD ROI significantly correlated with the corresponding changes in fMRI functional connectivity strength between the MD and the inferior precuneus, as described in Supporting Information, S2.4 and Figure S4).

Figure 9 shows whole-brain statistical maps for the EG versus CG group difference in the EEG-based PPI interaction effects for the Happy versus Attend condition contrast. The voxel-wise PPI interaction values were averaged across the four rtfMRI-nf runs (Runs 1–4) for each participant. The statistical maps in Figure 9 were thresholded at $t(27) = \pm 2.77$ (uncorrected $p < .01$) and clusters containing at least 81 voxels were retained (FWE-corrected $p < .025$ to account for testing PPI results for the two contrasts). The cluster properties are described in Table 2. The results in Figure 9 and Table 2 reveal the largest cluster in the thalamus area (volume $\sim 13 \text{ cm}^3$ in the Talairach space), which includes the MD, the AN, the medial pulvinar, and the dorsal parts of the caudate body.

Whole-brain statistical maps for the EG versus CG group difference in the EEG-based PPI interaction effects for the Happy versus Count condition contrast are exhibited in Figure 10. The data were thresholded and clusterized as described above for Figure 9, and the cluster properties are specified in Table 3. The results in Figure 10 and

Table 3 show the largest cluster (volume $\sim 30 \text{ cm}^3$) covering the thalamus area and extending to the dorsal striatum. This cluster includes the AN, the anterior and posterior parts of the MD, the medial pulvinar, the ventrolateral nucleus (VL), the entire caudate body, and the entire putamen.

We repeated the analyses, reported in Figures 7–10, using the parietal alpha EEG power (for channels P3, P4, Pz), and they yielded similar results.

4 | DISCUSSION

In this study, we investigated the feasibility of volitional regulation of BOLD activity of the MD and AN thalamic nuclei using the rtfMRI-nf. We employed simultaneous EEG to evaluate the effects of such non-invasive thalamic modulation on posterior alpha EEG rhythm.

Posterior alpha rhythm is generated by multiple and functionally diverse neuronal sources. MEG equivalent current dipole source localization studies have shown that the strongest dipole-modeled sources of posterior alpha rhythm are distributed around the parieto-occipital sulcus and around the calcarine sulcus (Hari, Salmelin, Mäkelä, Salenius, & Helle, 1997; Manshanden, de Munck, Simon, & Lopes da Silva, 2002). The parieto-occipital alpha sources can be located on either side

FIGURE 8 Changes in temporal correlations between occipital alpha EEG power and BOLD activities of the anterior and mediodorsal nuclei across experimental conditions. (a) Average values of the psychophysiological interaction (PPI) effects for the anterior (AN) and mediodorsal (MD) thalamic nuclei for the experimental group (EG) and the control group (CG). Time courses of z scores of the normalized occipital alpha EEG power, $z(\alpha O)$, were used in the PPI analyses as illustrated in Figure 3. The EEG-based PPI interaction effect for the Happy versus Attend condition contrast is denoted in the figure as “H vs A,” and the EEG-based PPI interaction effect for the Happy vs Count condition contrast is denoted as “H vs C.” The voxel-wise PPI interaction values were averaged within the AN and MD ROIs (Figure 1a) and across the four rtfMRI-nf runs (Runs 1–4) for each participant. Each bar represents a group average. The error bars are standard errors of the means (sem). The t scores and p values in the figure correspond to the EG versus CG group difference ($df = 27$). (b) Illustration of the PPI effects for the EG using single-subject data. The top plot shows positive correlation between the EEG-based regressor and the fMRI time course for the AN ROI during three Happy Memories (H) condition blocks in one nf run (Figure 2b) concatenated together in the figure. The middle plot demonstrates lack of correlation between these time courses during three concatenated Attend (A) condition blocks, following the Happy Memories blocks in the same run. The bottom plot shows negative correlation between these time courses during three concatenated Count (C) condition blocks in the same run [Color figure can be viewed at wileyonlinelibrary.com]

of the sulcus—in the precuneus (BA 7, 31) and in the adjacent occipital cortex (V3, BA 19) (Hari et al., 1997). Interestingly, positive correlations between global alpha EEG power and glucose metabolism (PET) were found in the same parieto-occipital regions (Schreckenberger et al., 2004). The parieto-occipital sources of alpha rhythm have been implicated in cognitive and memory functions, including working memory (Tuladhar et al., 2007) and episodic memory (Seibert, Hagler, & Brewer, 2011). The calcarine alpha sources are located in the visual areas V1/V2 (Portin, Salenius, Salmelin, & Hari, 1998; Portin, Vanni, Virsu, & Hari, 1999). They are involved in the more basic visual functions, such as pattern detection (Portin et al., 1998) and visual attention (Yamagishi et al., 2003). Alpha EEG signals measured by the occipital and parietal scalp EEG channels (Figure 1d) are superpositions of signals from the parieto-occipital and calcarine sources of alpha activity.

In this study, we focused on correlations between posterior alpha EEG power and BOLD activity of the MD/AN during the autobiographical memory recall. Such correlations are more likely to be associated with the parieto-occipital alpha sources involved in the memory function. Modulation of posterior alpha power by visual attention, associated more closely with the calcarine alpha sources in the visual areas V1/V2, is a confounding factor in our work. Therefore, we took several

steps to reduce between- and within-subject variations in visual attention and to account for such variations in the data analysis. First, the CG participants were provided with the sham feedback (Figure 1b), that required visual attention levels similar to those for the rtfMRI-nf (EG). All major conclusions in the study are drawn from the EG versus CG group comparisons (Figures 4–10). Second, the variable-height red rtfMRI-nf bar was displayed during all three experimental conditions (Figure 2a) to reduce variations in visual attention across the conditions. Third, the time course of the occipital alpha EEG power (αO) was orthogonalized with respect to the time course of the eye-blinking activity also reflecting occasional eye closing. Fourth, the average fMRI time course of the visual cortex V1/V2 was used to define nuisance covariates for the fMRI activation and functional connectivity analyses, as well as for the PPI analyses of EEG-fMRI correlations. Thus, any effects that could be attributed to temporal variations in the average V1/V2 activity were explicitly regressed out in the GLMs.

During the rtfMRI-nf training, the EG participants were able to successfully upregulate BOLD activity of the target brain region consisting of the AN and MD thalamic nuclei (Figure 4). The rtfMRI-nf training effects were specific to the EG, and generalized beyond the actual rtfMRI-nf training (Figure 4a). The MD functional connectivity

FIGURE 9 Enhancement in temporal correlation between occipital alpha EEG power and BOLD activity during the rtfMRI-nf task relative to the Attend task compared between the groups. Statistical maps for the experimental versus control group difference (EG vs CG) in the EEG-based PPI interaction effect for the Happy vs Attend condition contrast are shown. Time courses of z scores of the normalized occipital alpha EEG power, $z(\alpha O)$, and the [Happy – Attend] contrast function were used to define the PPI regressors as illustrated in Figure 3a–c. The PPI interaction results for the four rtfMRI-nf runs (Runs 1–4) were averaged for each participant. The maps are projected onto the TT_N27 template in the Talairach space, with 3 mm separation between axial slices. The number adjacent to each slice indicates the z coordinate in mm. The left hemisphere (L) is to the reader's right. Peak t statistics values for the group difference and the corresponding locations are specified in Table 2 [Color figure can be viewed at wileyonlinelibrary.com]

during the rtfMRI-nf task was enhanced (for the EG compared to the CG) for the right medial precuneus (BA 31), and reduced for several prefrontal regions (Figure 5 and Table 1). The functional connectivity between the MD and the precuneus in our study reflects involvement of both regions in the autobiographical memory recall. Importantly, this functional connectivity was enhanced by the rtfMRI-nf for the EG, as evidenced by the significant EG versus CG group difference (Figure 5a).

Performance of the rtfMRI-nf task was accompanied by amplitude modulation of alpha EEG activity (Figure 6). The stronger the MD BOLD activity was modulated for the EG, the stronger correlated modulation of alpha amplitude was observed throughout the EEG array (Figure 6b). We estimate from the linear fit in Figure 6b that a 1% MD BOLD activity (with the average V1/V2 activity kept constant) would correspond to an increase in the average alpha envelope correlation (AEC) across the array by 0.09. The positive correlation effect for the EG was observed for many channel pairs (Figure 6c), particularly those involving channels Pz and P4, located over the medial and right lateral precuneus. The correlation pattern in Figure 6c is consistent with the fMRI functional connectivity results in Figure 5a and the PPI interaction results in Figure 9.

During the rtfMRI-nf task, changes in the mean occipital alpha EEG power (αO) significantly correlated with the mean MD BOLD activity levels for the EG (Figure 7a, left). The correlation was also significant for the Transfer run (Figure 7a, right), during which no visual nf

information was provided. Based on the linear fit in Figure 7a (left), we estimate that a 2.3% MD BOLD activity (with the average V1/V2 activity kept constant) might lead to a significant increase ($z = 1.65$, one-tailed $p < .05$) in the mean occipital alpha power. Importantly, the observed increase in alpha power with increasing MD BOLD activity cannot be attributed to a reduction in visual attention, because the mean LGN BOLD activity levels during the rtfMRI-nf task positively correlated with the mean MD BOLD activity levels (Supporting Information, S2.2 and Figure S2).

Overall, our analysis suggests that the more accurately activities of the main visual areas (LGN, V1, V2) are controlled and accounted for, the stronger positive correlations are observed between alpha EEG activity measures (AEC or power changes) and BOLD activity of the MD. For example, the correlation results for the EG, reported in Figures 6b and 7a, become more significant if the mean LGN BOLD activity levels are partialled out. Interestingly, significance of the results in Figures 5a, 6b, and 7a increased across the nf runs, likely because the EG participants became more proficient at controlling the rtfMRI-nf signal as the training progressed. Therefore, the average results for the last two nf runs (Runs 3,4) are exhibited in Figures 5–7. The PPI interaction results in Figures 8–10 did not show an obvious trend across the nf runs, probably because the PPI results are more strongly affected by residual artifacts and noise in both EEG and fMRI data. Therefore, the average PPI interaction effects across all four nf runs (Runs 1–4) are reported in Figures 8–10.

TABLE 2 Enhancement in temporal correlation between occipital alpha EEG power and BOLD activity during the rtfMRI-nf task relative to the Attend task compared between the groups

Region	Lateral- ity	x, y, z (mm)	t score	Size (vox.)
<i>Thalamus/dorsal striatum</i>				
Mediodorsal nucleus (MD)	R	5, -13, 14	5.81	1591
Mediodorsal nucleus (MD)	L	-5, -21, 15	4.59	—/—
Caudate body	L	-15, -17, 22	5.49	—/—
Caudate body	R	16, -16, 20	4.83	—/—
Pulvinar, medial	R	5, -23, 10	4.87	—/—
<i>Frontal lobe</i>				
Superior frontal gyrus (BA 6)	R	5, 5, 54	4.47	465
Inferior frontal gyrus (BA 45)	R	33, 27, 5	5.09	388
Middle frontal gyrus (BA 9)	R	25, 37, 34	4.50	348
Middle frontal gyrus (BA 6)	R	39, -3, 52	4.46	213
Superior frontal gyrus (BA 9)	L	-29, 43, 28	4.14	179
Middle frontal gyrus (BA 6)	L	-25, -3, 62	4.51	116
<i>Limbic lobe</i>				
Cingulate gyrus (BA 23)	L	-3, -33, 28	3.82	115
Posterior cingulate (BA 30)	L	-7, -43, 22	4.84	97
Anterior cingulate (BA 32)	L	-7, 27, 25	3.62	96
<i>Parietal lobe</i>				
Precuneus (BA 31)/ posterior cingulate	R	6, -70, 25	4.75	732
Precuneus (BA 7)	L	-28, -69, 48	4.63	150
Angular gyrus (BA 39)	R	47, -67, 30	3.99	147
Precuneus (BA 7)	R	3, -53, 48	3.36	96
<i>Temporal lobe</i>				
Inferior temporal gyrus (BA 20)	R	63, -27, -16	4.28	122
<i>Other</i>				
Insula (BA 13)	L	-39, 7, 16	4.35	217
Declive (cerebellum)	R	37, -67, -22	4.01	167
Pyramis (cerebellum)	R	13, -77, -30	4.18	115

Note. Abbreviations: BA = Brodmann areas; L = left; R = right; x, y, z = Talairach coordinates.

FWE-corrected $p < .025$ (Size—cluster size, minimum 81 voxels for uncorrected $p < .01$).

—/— denotes the local maximum within the same cluster.

Statistical results for the experimental versus control group difference (EG vs CG) in the EEG-based PPI interaction effect for the Happy versus Attend condition contrast are shown. Location of the point with the peak group difference t score ($df = 27$) and the number of voxels are specified for each cluster obtained after FWE correction for multiple comparisons. For the largest cluster in the thalamus/dorsal striatum area, local t score maxima are also specified.

The main result of this study is the observation of enhanced temporal correlation between thalamic BOLD activity and alpha EEG rhythm during the rtfMRI-nf training. The positive PPI interaction effects for the AN and MD ROIs for the EG (Figure 8a) indicate the more positive temporal correlations between the occipital alpha EEG power (convolved with the HRF) and BOLD activities of these nuclei during the rtfMRI-nf task compared to the control tasks. These effects were specific to the EG, and generalized beyond the actual rtfMRI-nf training. Similar PPI effects were observed for the parietal alpha EEG power. Taken together, the results in Figures 6–8 demonstrate both mean value correlations and enhanced temporal correlations between the MD BOLD activity and the modulation of alpha EEG rhythm, suggesting a profound connection between the two processes.

The PPI interaction group-difference results in Figure 9 and Table 2, corresponding to the Happy versus Attend condition contrast, reveal the strongest effect in the right MD at (5, -13, 14). This is consistent with the right lateralization of MD BOLD activity in fMRI autobiographical memory studies (Spreng et al., 2009; Svoboda et al., 2006). The results in Figure 9 and Table 2 also show significant effects in many brain regions known to have connections to the MD, including the dorsolateral prefrontal cortex (DLPFC, specifically BA 9 and BA 6 with $|x| > 20$ mm), the ventrolateral prefrontal cortex (BA 45), the anterior cingulate cortex (BA 32), the caudate body, and the cerebellum. The involvement of the DLPFC and the dorsolateral caudate suggests an engagement of the “prefrontal” basal ganglia-thalamocortical circuit (Alexander et al., 1991; Grahn, Parkinson, & Owen, 2008). This circuit is a closed loop connecting the DLPFC and the parvocellular subdivision of the MD nucleus (MDpc) as follows: DLPFC $\Rightarrow$ caudate $\Rightarrow$ globus pallidus/substantia nigra $\Rightarrow$ MDpc $\Rightarrow$ DLPFC. The main cluster in Figure 9 also includes the medial pulvinar, which has extensive connections to the prefrontal cortex (Bridge, Leopold, & Bourne, 2016). There are no significant effects in the ventrolateral pulvinar or the LGN.

The second largest cluster in Figure 9 and Table 2 has the maximum effect within the right medial precuneus (BA 31) at (6, -70, 25) and extends down to the posterior cingulate cortex (BA 30). As mentioned above, the precuneus/posterior cingulate region is the main posterior node of the DMN. Figure 9 and Table 2 also show a cluster in the right angular gyrus (BA 39), closely corresponding to the right lateral DMN node. Thus, the results in Figure 9 and Table 2 demonstrate an enhancement in temporal correlation between the occipital alpha EEG power and BOLD activity not only for the thalamus, but also for the posterior (medial and right lateral) DMN nodes. The latter finding is consistent with results of the EEG-only studies that showed increased alpha EEG power within the posterior DMN regions during self-referential processing (Knyazev et al., 2011, 2015). It is also consistent with the results of the EEG-PET study (Schreckenberger et al., 2004) that showed positive correlations between global alpha EEG power and glucose metabolism under lorazepam challenge in the precuneus (BA 7, 31).

The PPI group-difference results in Figure 10 and Table 3 correspond to the Happy versus Count condition contrast. Unlike the Attend condition, the Count condition is the cognitive task that shares some characteristics with the Happy Memories task. It activates the MD (Figure 4), which is involved in the working memory function, and the

FIGURE 10 Enhancement in temporal correlation between occipital alpha EEG power and BOLD activity during the rtfMRI-nf task relative to the Count task compared between the groups. Statistical maps for the experimental versus control group difference (EG vs CG) in the EEG-based PPI interaction effect for the Happy versus Count condition contrast are shown. Time courses of z scores of the normalized occipital alpha EEG power, $z(\alpha O)$, and the [Happy – Count] contrast function were used to define the PPI regressors as illustrated in Figure 3a,d,e. The PPI interaction results for the four rtfMRI-nf runs (Runs 1–4) were averaged for each subject. The maps are projected onto the TT_N27 template in the Talairach space, with 3 mm separation between axial slices. The number adjacent to each slice indicates the z coordinate in mm. The left hemisphere (L) is to the reader's right. Peak *t* statistics values for the group difference and the corresponding locations are specified in Table 3 [Color figure can be viewed at wileyonlinelibrary.com]

parietal regions involved in numerical processing and working memory (Zotev et al., 2011). Therefore, the PPI results in Figure 10 and Table 3 are less sensitive to the general effects of memory performance (particularly related to the MD) and more sensitive to the specific effects of the rtfMRI-nf that distinguish it from the sham feedback. The prominent involvement of the caudate body and the DLPFC confirms the engagement of the “prefrontal” basal ganglia-thalamocortical circuit discussed above. The significant effects in the ventrolateral nucleus (VL), the putamen, and the supplementary motor area (SMA, medial BA 6) indicate an engagement of the “motor” basal ganglia-thalamocortical circuit (Alexander et al., 1991; Grahn et al., 2008). This circuit is a closed loop connecting the SMA and the VL nucleus pars oralis (VLo) as follows: SMA $\Rightarrow$ putamen $\Rightarrow$ globus pallidus/substantia nigra $\Rightarrow$ VLo $\Rightarrow$ SMA.

The results in Figure 10 and Table 3 also show a cluster in the right temporo-parietal area (BA 39) corresponding approximately to the right angular gyrus cluster (BA 39) in Figure 9 and Table 2. Another cluster with the maximum effect in the left precuneus (BA 19) has the center of mass at (−34, −76, 32) in the left angular gyrus (BA 39). Therefore, the PPI group-difference results in Figure 10 and Table 3 show positive effects in the temporo-parietal regions in the general vicinities of the lateral posterior DMN nodes.

The caudate and the putamen, together constituting the dorsal striatum, serve as the basal ganglia's interface to the cortex. They play important roles in learning, including skill learning and learning from feedback (Grahn et al., 2008; Yin & Knowlton, 2006). Notably, the

caudate body and the putamen are associated with the more basic stimulus-response learning (Yin & Knowlton, 2006), while the caudate head is involved in the more advanced action-outcome learning (Grahn et al., 2008). Self-regulation studies using rtfMRI-nf have shown engagement of these regions (Lawrence et al., 2014; Scharnowski et al., 2015; Sulzer et al., 2013; Veit et al., 2012). The basal ganglia-thalamocortical circuits, including the “prefrontal” and “motor” circuits mentioned above, enable parallel processing and integration (Alexander et al., 1991), and play crucial roles in the learning cycle (Birbaumer et al., 2013; Yin & Knowlton, 2006). The results in Figure 10 and Table 3 demonstrate that BOLD activities of these circuits' regions correlate with the posterior alpha EEG activity. This finding is not surprising, because these circuits are engaged during the rtfMRI-nf procedure targeting the MD BOLD activity, which positively correlates with alpha EEG power. However, the correlation effects in the caudate and putamen (Figure 10) may also reflect a more profound connection between oscillations in the basal ganglia and in the cortex (Brittain & Brown, 2014). For example, oscillatory connectivity in the alpha band has been observed between the subthalamic nucleus and temporo-parietal cortical regions (Litvak et al., 2011).

Our results suggest that the functional connectivity between the MD and the inferior precuneus (BA 31) plays an important role during the described rtfMRI-nf procedure. Such connectivity was enhanced during the rtfMRI-nf task for the EG compared to the CG for the parietal regions, with the statistical maximum at (7, −69, 22) within the right

TABLE 3 Enhancement in temporal correlation between occipital alpha EEG power and BOLD activity during the rtfMRI-nf task relative to the Count task compared between the groups

Region	Laterality	x, y, z (mm)	t score	Size (vox.)
<i>Thalamus/dorsal striatum</i>				
Pulvinar, medial	L	−1, −27, 6	7.41	3757
Ventrolateral nucleus (VL)	L	−18, −9, 12	6.81	—//—
Caudate body	R	11, −5, 18	6.17	—//—
Caudate body	L	−13, −5, 22	6.13	—//—
Putamen	R	27, 3, 14	5.28	—//—
Putamen	L	−27, −3, 14	5.05	—//—
Anterior nucleus (AN)	R	9, −7, 13	5.04	—//—
Anterior nucleus (AN)	L	−8, −5, 13	4.35	—//—
<i>Frontal lobe</i>				
Middle frontal gyrus (BA 9)	L	−41, 19, 32	5.23	980
Middle frontal gyrus (BA 6)	L	−29, 3, 52	5.63	736
Middle frontal gyrus (BA 9)	R	35, 25, 22	4.14	250
Medial frontal gyrus (BA 6)	L	−5, −13, 58	4.76	91
<i>Limbic lobe</i>				
Cingulate gyrus (BA 24)	R	17, 1, 42	4.99	580
Cingulate gyrus (BA 32)	L	−9, 17, 42	4.34	193
<i>Parietal lobe</i>				
Precuneus (BA 19)	L	−31, −79, 38	4.75	194
<i>Temporal lobe</i>				
Middle temporal gyrus (BA 39)	R	41, −73, 28	3.92	102

Note. Abbreviations: BA = Brodmann areas; L = left; R = right; x, y, z = Talairach coordinates.
FWE-corrected $p < .025$ (size—cluster size, minimum 81 voxels for uncorrected $p < .01$).

—//— denotes the local maximum within the same cluster.

Statistical results for the experimental versus control group difference (EG vs CG) in the EEG-based PPI interaction effect for the Happy vs Count condition contrast are shown. Location of the point with the peak group difference t score ($df = 27$) and the number of voxels are specified for each cluster obtained after FWE correction for multiple comparisons. For the largest cluster in the thalamus/dorsal striatum area, local t score maxima are also specified.

medial precuneus (Figure 5a and Table 1). This locus is spatially close to the parieto-occipital sulcus (Figure 5a). Modulation of this region's BOLD activity (together with that of the MD) may conceivably affect, directly or indirectly, the main dipolar sources of alpha EEG rhythm in the vicinity of the parieto-occipital sulcus, discussed above. Indeed, temporal correlation between the occipital alpha EEG power and BOLD activity was enhanced during the rtfMRI-nf task for the EG relative to the CG for the posterior DMN nodes, with the maximum at (6, −70, 25) within the right medial precuneus (Figure 9 and Table 2). This location is remarkably close to the above-mentioned point of the

strongest MD connectivity enhancement. Furthermore, the PPI interaction effect for the MD significantly correlated, for the Transfer run for the EG, with the enhancement in the MD-precuneus functional connectivity (Supporting Information, S2.4 and Figure S4A). Taken together, these findings suggest that the temporal correlation between the MD BOLD activity and posterior alpha EEG power is modulated by the interaction between the MD and the inferior precuneus, reflected in their functional connectivity.

The rtfMRI-nf targeting the MD and/or AN, provided during a memory task (episodic, working, spatial, and so on), can conceivably be used for the memory function training. Such training may be relevant in neuropsychiatric disorders characterized by autobiographical memory disturbances, including depression and PTSD. For example, the rtfMRI-nf can be used to increase BOLD activity of the MD during recall of happy autobiographical memories and/or reduce such activity in response to traumatic memories or rumination. The ability of the rtfMRI-nf to alter functional connectivity between the MD and the posterior DMN (Figure 5a) may be particularly important in treatment of depression, which is characterized by abnormally elevated resting fMRI connectivity between these regions (Greicius et al., 2007; Hamilton, Farmer, Fogelman, & Gotlib, 2015).

Our findings suggest that EEG-nf based on modulation of alpha EEG power would naturally complement the rtfMRI-nf targeting the MD/AN. Studies utilizing EEG-nf for upregulation of alpha (or upper alpha) EEG power have demonstrated improvements in participants' cognitive and memory performance, including working memory and short term memory (Escolano et al., 2014; Hanslmayr, Sauseng, Doppelmayr, Schabus, & Klimesch, 2005; Hsueh, Chen, Chen, & Shaw, 2016; Nan et al., 2012; Zoefel, Huster, & Herrmann, 2011). Changes in resting fMRI functional connectivity following alpha EEG-nf training have also been reported (Kluetsch et al., 2014; Nicholson et al., 2016). Interestingly, most alpha EEG-nf studies did not employ specific cognitive tasks or predefined mental strategies during the training. Using alpha EEG-nf during a particular cognitive or memory task would conceivably improve training of the related function compared to the non-specific training scenario. For example, upregulation of posterior alpha EEG power using EEG-nf during recall of happy autobiographical memories could specifically enhance episodic memory of emotional events. Such EEG-nf approach can be used as a supplementary technique in combination with the rtfMRI-nf of the MD/AN. The two methods can also be used simultaneously as rtfMRI-EEG-nf (Zotev et al., 2014) to enable simultaneous regulation of thalamic BOLD activity and alpha EEG rhythm.

5 | CONCLUSION

We demonstrated, for the first time, that healthy participants can learn to successfully upregulate BOLD activities of the mediodorsal and anterior thalamic nuclei using the rtfMRI-nf. We observed that such regulation enhanced temporal correlation between thalamic BOLD activity and alpha EEG power. We also identified the posterior DMN nodes as cortical regions supporting this correlation effect. Our results

confirm the fundamental role of the thalamus, particularly the medio-dorsal nucleus, in modulation of alpha EEG rhythm. They also demonstrate the potential of the rtfMRI-nf with simultaneous EEG for noninvasive neuromodulation studies of human brain function.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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