Never Resting Brain: Simultaneous Representation of Two Alpha Related Processes in Humans

Eti Ben-Simon1,2,9, Ilana Podlipsky2,3, Amos Arieli4, Andrey Zhdanov2, Talma Hendler1,2,5*

1 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, 2 Functional Brain Center, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, 3 Department of Biomedical Engineering, Tel Aviv University, Tel-Aviv, Israel, 4 Neurobiology Department, Weizman Institute, Rehovot, Israel, 5 Department of Psychology, Tel Aviv University, Tel Aviv, Israel

Abstract

Brain activity is continuously modulated, even at “rest”. The alpha rhythm (8–12 Hz) has been known as the hallmark of the brain’s idle-state. However, it is still debated if the alpha rhythm reflects synchronization in a distributed network or focal generator and whether it occurs spontaneously or is driven by a stimulus. This EEG/fMRI study aimed to explore the source of alpha modulations and their distribution in the resting brain. By serendipity, while computing the individually defined power modulations of the alpha-band, two simultaneously occurring components of these modulations were found: An ‘induced alpha’ that was correlated with the paradigm (eyes open/eyes closed), and a ‘spontaneous alpha’ that was ongoing and unrelated to the paradigm. These alpha components when used as regressors for BOLD activation revealed two segregated activation maps: the ‘induced map’ included left lateral temporal cortical regions and the hippocampus; the ‘spontaneous map’ included prefrontal cortical regions and the thalamus. Our combined fMRI/EEG approach allowed to computationally untangle two parallel patterns of alpha modulations and underpin their anatomical basis in the human brain. These findings suggest that the human alpha rhythm represents at least two simultaneously occurring processes which characterize the ‘resting brain’; one is related to expected change in sensory information, while the other is endogenous and independent of the stimulus change.

Introduction

Since the discovery of Electroencephalography (EEG), attempts have been made to assign a functional meaning to the brain’s oscillatory neural activity. The frequency spectrum of scalp recorded EEG has typically been divided into a few bands ranging from delta (less than 3 Hz) to gamma (more than 30 Hz). Each band has been typically attributed to a certain brain state such as the level of consciousness or the degree of cognitive or perceptual activity, respectively [1,2]. Among the various frequency bands the alpha rhythm (8–12 Hz), received special attention since it was the first oscillation to be identified from scalp recordings. Hans Berger in 1929 found that the alpha power increases during eyes closed especially at rest and decreases with eyes open (i.e. the “Berger effect”) [1]. Subsequently, it has been acknowledged that task engagement such as perceptual judgment or increased attentiveness leads to a decrease in the alpha power [2,3].

The functional role of alpha has been debated; classically it is considered as the brain’s “idle rhythm”, sort of a standby state that allows the system to return more rapidly to goal oriented function when needed [4]. Interestingly, several recent imaging studies have supported the notion of an activated rest state by describing a network of activation that is being diminished during goal oriented tasks relative to no-task [3–7]. The idea of alpha as reflecting an idle state was supported by the findings of increased alpha power in posterior electrodes when eyes are closed and in motor cortex when limbs are at rest (also known as the mu rhythm [8]), as well as by studies showing increased alpha rhythm during meditation and other relaxation states [9]. Accordingly, the alpha rhythm was also found to be dominant in states of coma as well as in deep sleep stages [8,10]. Furthermore, alpha was shown to be negatively correlated with individual arousal levels [11], a fact which might explain the large inter-individual variability in the power and frequency of the alpha rhythm [12,13]. Yet, the debate over the neural function of alpha rhythm continues with recent theories that assign alpha a more active role in inhibitory control and timing of cortical processing [14], and as being involved in various brain functions such as memory and motor-action [15,16]. Altogether, although the knowledge on alpha rhythm function is increasing rapidly there are still open issues as for its neural source: is it focal or diffused and what is the basis for its modulations?

Studies in animals suggest that the thalamus is an important source in generation and modulation of cortical alpha rhythms[17] and exhibits a substantial relationship with the neocortex’s rhythmic activity [18]. However others, based on animal intracranial recordings, argue that alpha should not be attributed to a specific location but rather to diffuse distributed brain activation since it has been observed in widely separated locations.

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* E-mail: talma@tasmc.health.gov.il

These authors contributed equally to this work.
in different brain structures [15,16]. One way or another it is still unclear if the animal’s alpha reflects sufficiently the human’s alpha, especially if one considers it as the idle ongoing state of our mental working. Therefore, high spatial resolution studies in humans are essential in order to attain a valid concept regarding the distributed effect of the alpha rhythm.

In humans several EEG studies have pointed to more than a single origin for the alpha rhythm: one which is spontaneous, resulting from distributed sources and unassociated with any external stimulus, and another that is more localized and induced by a stimulus [15,16,19]. One drawback of the scientific effort so far in revealing the neural representations of these alpha rhythms is that the majority of studies were done with EEG which suffers from low spatial resolution (~1 cm). The recent use of combined electrical and cerebral blood flow neuroimaging methods provided the means to explore the alpha rhythm in-vivo in humans at a better spatial resolution than with EEG alone. Furthermore, since the alpha rhythm fluctuates rapidly, simultaneous rather than separate acquisition of these two imaging methods is crucial for a comprehensive view of the alpha correlates. Initial studies applying simultaneous EEG/fMRI recordings in humans revealed distributed BOLD activation correlated to power fluctuations in alpha rhythm. These activations generally included parieto-temporal areas in positive correlation and occipital areas in negative [20–22].

This EEG/fMRI study that was originally aimed at exploring the effects of eyes states (i.e. closed or open) on the alpha rhythm, serendipitously revealed two computationally different neural correlates of the alpha rhythm which might underlie different sources of its modulations; induced and spontaneous.

In order to differentiate between induced and spontaneous alpha modulations two components of the overall alpha power changes were computed: one taking into account the induced modulations by eyes states (i.e. close or open), and the other ongoing and unrelated to eyes states. By using simultaneous recording of EEG and fMRI we were able to achieve high temporal and spatial resolution. To account for the expected inter-subject variability in alpha ‘finger-print’ we used individually characterized alpha power peak and band [13].

Methods

Participants & Study Design

14 healthy volunteers (6 men and 8 women), aged 19–35 (mean 24.8±3.7), signed an informed consent for this study, approved by the Sourasky Medical Center Helsinki committee in Tel Aviv. This approval means that the study was done following the guidelines of the Helsinki Declaration. Subjects were equipped with earphones and asked by means of audio instructions to open and close their eyes every 30 seconds for a total time of 3 minutes. Subjects were told to lie as still as possible and follow the instructions. Sponge cushions were used to minimize head movements.

EEG acquisition

Continuous EEG data was recorded simultaneously with fMRI acquisition for 200 seconds. EEG was acquired using the MRI-compatible BrainAmp-MR EEG amplifier (Brain Products, Munich, Germany) and the BrainCap electrode cap with sintered Ag/AgCl ring electrodes providing 30 EEG channels, 1 ECG channel, and 1 EOG channel (Falk Minow Services, Herrsching-Breitbrunn, Germany). The electrodes were positioned according to the 10/20 system. The reference electrode was between Fz and Cz. Raw EEG was sampled at 5 kHz and recorded using the Brain Vision Recorder software (Brain Products).

EEG analysis

EEG data underwent the following processing stages

1. MR gradient artifacts removal. Artifacts related to the MR gradients were removed from all the EEG datasets using the FASTR algorithm implemented in FMRIB plug-in for EEGLAB, provided by the University of Oxford Centre for Functional MRI of the Brain (FMRIB). Briefly, the FASTR algorithm first corrects for possible minor jitters in the gradients’ occurrence delays, and then FASTR computes a template of the artifact based on the slices’ average, and subtracts it from the data. Following this process, residual artifacts are reduced using subtraction of Optimal Basis Set (OBS) constructed of first, most meaningful, Principle Components (PCAs) automatically determined from the plot of ordered eigenvalues of the artifacts’ matrix.

2. Cardiobalistic artifacts removal. Cardiobalistic artifacts were also removed using the FMRIB plugin, in two stages: a. Detection of QRS events is performed on the ECG channel using combined adaptive thresholding[23] and the Teager energy operator [24], followed by a correction algorithm, which aligns all events and corrects for false positives and negatives. b. Pulse Artifact Removal–The removal of pulse artifacts uses QRS events to subtract an artifact template from the data. This method is similar to the OBS algorithm used to remove the gradient residuals.

After these processing stages the EEG data was downsampled to 250 Hz and underwent a visual inspection of the EOG data for the presence of blinks at the time of instructions, in order to insure that the subjects closed and opened their eyes at those times. This examination led to the exclusion of 2 subjects. Two more subjects were excluded from the analysis due to movements in the scanner which were larger than 1mm. Thus our final analysis included 10 subjects.

Individual alpha band calculation. It was previously shown that alpha band frequency varies significantly across subjects[25] therefore it is desirable to estimate alpha band individually for each subject. Our experimental setup induces alpha wave activity facilitating individual characterization of subjects’ alpha band. In our analysis we derived the individual subjects’ most relevant frequencies from the EEG data with minimal assumptions as to the frequency of the presumed alpha band.

The EEG signal was expected to have, on average, high amplitude at the conventional alpha band frequencies (see Fig. 1). The individual alpha band was taken as the frequency band containing the highest energy of the signal across the experiment. The first step of the individual alpha band estimation was to calculate instantaneous power at each frequency of the EEG, using Stockwell transform[26] with frequency resolution of 1.25 Hz and time resolution of 1/250 sec (using Matlab 7.0.4, Mathworks Inc). The resulting instantaneous power was then averaged across the whole experiment at each electrode (see EEG spectrogram at Fig. 2).

In the search for the individual alpha band, the EEG spectrum was examined at each electrode, and a frequency (lower than 20 Hz) with the highest power was chosen as the alpha peak. Finally the five electrodes with the highest peaks were taken for further analysis. The distribution of alpha power across electrodes reveals that the greatest power is localized in occipital regions. Accordingly, Most of the chosen electrodes per subjects were located in the occipital-temporal area (see supplementary Table S1 for a list of the chosen electrodes). The individual subjects’ alpha band, across the chosen electrodes, was taken to be the alpha peak frequency ±1.25 Hz. This band width covered most of the alpha peak for most subjects (see supplementary Table S1 for different alpha characteristics of all subjects).
Continuous regressor generation. For each subject, the original EEG signal of the five chosen electrodes was band pass filtered to the individual subjects’ alpha band. At each of these electrodes instantaneous amplitude of the resulting signal was calculated by means of Hilbert transform and low pass filtered at 0.05 Hz to adopt it to the fMRI temporal resolution. Resulting signals were averaged across the five electrodes. The average signal was taken as the individual regressor for the fMRI analysis of each subject. For a summary of EEG analysis and regressor generation see Figure 2.

fMRI acquisition

Imaging was performed on a 3 T GE scanner (GE, Milwaukee, WI, USA). All images were acquired using a standard head coil. The scanning session included conventional anatomical MR images (T1-WI, T2-WI, T2-FLAIR), 3D spoiled gradient echo (SPGR) sequence (FOV = 250 mm, matrix size = 256x256, voxel size = 0.98x0.98x1) and functional T2*-weighted images (FOV = 200 mm, matrix size = 64x64, voxel size = 3x3x4, TR/TE = 2000/35, Slice thickness = 4 mm, 30 axial slices without gap).

fMRI analysis

SPM2 software (http://www.fil.ion.ucl.ac.uk/spm) was used for image preprocessing and voxel-based statistical analysis. First 20 seconds of data were discarded to allow steady state magnetization. Functional images were realigned to the first scan and normalized into standard MNI space. Spatial smoothing was performed using a Gaussian kernel (FWHM = 4 mm) and the signal was high-pass filtered at 1/128 s. To correlate the fMRI with the EEG data, the individual alpha time course (see EEG analysis) was used as a regressor in the design matrix, which also included a mean term.

Since an eyes open eyes closed paradigm induces alpha wave modulation it was necessary to determine whether the functional network derived from the EEG alpha regressor differs from the functional network revealed by the paradigm conditions. For that purpose an additional analysis was performed in which the design matrix was comprised only of the eyes open eyes closed conditions. The alpha regressor and the paradigm are strongly correlated, therefore the two functional networks, revealed by each of them, were largely similar. Hence, the next step of the analysis was to...
Figure 2. EEG analysis steps. 1. Gradient and cardioballistic artifact removal performed on raw EEG data; 2. Generation of spectrogram from the entire EEG signal; 3. Generation of EEG spectrum by averaging the spectrogram across the time of the experiment (200 sec); 4a. Selection of five electrodes with the highest alpha peak and selection of subject specific alpha band from the EEG spectrum; 4b. Calculation of instantaneous alpha amplitude throughout the experiment, at the chosen electrodes by means of band pass filtering at the chosen band and Hillbert transform; 5. Calculation of a regressor for fMRI analysis by convolution of the instantaneous alpha amplitude with HRF.

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calculate a paradigm-independent alpha regressor by introducing a confounding covariate of eyes open eyes closed conditions into the design matrix. This procedure removes the part of the alpha curve linearly explainable by the paradigm (the induced alpha part), and leaves the spontaneous fluctuations of alpha power occurring within conditions. For group analysis, a random-effects model was applied, and statistical inferences were considered significant at $p<0.02$, uncorrected.

**Results**

**Individually determined EEG spectrum**

Overall EEG revealed the expected peak of alpha in the dataset ranging from 7.5 to 12.25 Hz among the different subjects (see supplementary Table S1 for more details) and another peak is present at a frequency range that corresponds with gamma (40–80 Hz). A possible correlation between gamma and alpha time courses was examined over the course of the data analysis and no significant correlation was found. However, here we only present results that correspond to the alpha peak. Figure 1 denotes the individual spectra presented by different colors and the averaged peak shown in black. The spectra clearly demonstrate the relatively large variance among individuals in overall alpha power and frequency band in the data set.

**Bold activation in relation to induced alpha modulations**

We first examined the effect of induced alpha modulation on BOLD signal change, taking into account eyes state. Figure 3 (top row) demonstrates the corresponding alpha based group activation map ($n=10$, $p<0.02$ random effects, uncorrected). A positive correlation between the BOLD signal and the individual alpha regressor revealed a distributed network including activation in posterior and anterior Superior Temporal Sulcus (STS), more prominent on the left; the Supplementary Motor Area (SMA) and bilateral anterior Hippocampus (see supplementary Table S2). We then examined the effect of the paradigm (eyes open Vs eyes closed) on the BOLD signal, disregarding alpha. Figure 3 (bottom row) demonstrates the paradigm based group activation map ($n=10$, $p<0.02$ random effects, uncorrected). From comparing the activation maps in upper and lower rows one can clearly see the large similarity between the paradigm based and the induced-alpha, bold activation maps, implying that the paradigm activations masked over alpha based activations.

**BOLD activation in relation to spontaneous alpha modulation**

In order to reveal possible alpha modulation that is unrelated to eyes states we applied an analysis that aimed to computationally eliminate the effect of the paradigm on the alpha variation which resulted in the spontaneous alpha regressor. A positive correlation between the BOLD signal and the spontaneous alpha regressor revealed a distributed network including the Dorso Latreal Pre-Frontal Cortex, Caudate and Thalamic nuclei. This network is demonstrated in Figure 4 and in supplementary Table S3. A comparison of BOLD signal extracted from ROI at the spontaneous alpha network Vs ROI from induced alpha network is demonstrated in Figure 5.

**Negative correlation with alpha rhythm**

In order to reveal possible alpha modulation that is unrelated to eyes states we applied an analysis that aimed to computationally eliminate the effect of the paradigm on the alpha variation which resulted in the spontaneous alpha regressor. A positive correlation between the BOLD signal and the spontaneous alpha regressor revealed a distributed network including the Dorso Latreal Pre-Frontal Cortex, Caudate and Thalamic nuclei. This network is demonstrated in Figure 4 and in supplementary Table S3. A comparison of BOLD signal extracted from ROI at the spontaneous alpha network Vs ROI from induced alpha network is demonstrated in Figure 5.

**Discussion**

The main finding of this study is that the alpha rhythm detected in scalp EEG recordings was associated with two concurrent modulations that yielded segregated distributions of BOLD activation as revealed by the simultaneous fMRI: one that was closely linked to the difference between eyes open and eyes closed states and the other that was largely independent of these changing states (see Fig. 5). This finding emanates from our approach of computationally separating the spontaneous from the induced alpha modulations. Possibly, these two simultaneous organizations of alpha modulation have not been demonstrated before as other

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Figure 3. Induced alpha and paradigm related BOLD activation maps. Different slice views of BOLD activation group maps ($n=10$ random effect, $p<0.02$ uncorrected, min 15 voxels). Top row maps obtained by individual regressors of the induced alpha component. Low row maps obtained directly by the paradigm conditions (i.e. eyes closed Vs eyes open). Note the similarities between the two maps. Areas of main activation are denoted by numbers: L Middle Occipital Cortex (1), L Superior Temporal Sulcus (2), L Middle Temporal Gyrus (3), L Supplementary Motor Area (4), L Hippocampus (5).

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EEG studies combined with cerebral blood flow imaging have mainly concentrated on eyes-closed rest state thus revealing mainly the spontaneous alpha network [22,28]. Indeed, these studies report on alpha related BOLD activation that closely resembles the spontaneous alpha distribution in our study. In one attempt to measure the induced alpha rhythm by EEG/fMRI the large “Berger effect” due to alternating eyes states seemed to mask the possible existing spontaneous modulations [28].

Negative correlation to both induced and spontaneous alpha modulations were found predominantly in low-level visual areas in the occipital cortex [22,28]. Indeed, these studies report on alpha related BOLD activation that closely resembles the spontaneous alpha distribution in our study. In one attempt to measure the induced alpha rhythm by EEG/fMRI the large “Berger effect” due to alternating eyes states seemed to mask the possible existing spontaneous modulations [28].

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Figure 4. Spontaneous and negative alpha BOLD activation maps. A. Spontaneous alpha BOLD activation maps: Different slice views of BOLD activation group maps (n = 10 random effect, p<0.02 uncorrected, min 15 voxels) obtained by individual regressors of the spontaneous alpha component. Areas of activation are denoted by numbers: Dorso Medial Thalamus (1), Medial Prefrontal Cortex (2), Retrosplenial Cortex (3), Dorso Lateral Prefrontal Cortex (4), Amygdala (5). B. Negative alpha BOLD activation maps: Different slice views of BOLD activation group maps (n = 10 random effect, p<0.02 uncorrected, min 15 voxels) obtained by negative correlation to individual regressors of induced and spontaneous alpha components (red and green respectively). As expected negative correlation in both networks reveal predominantly visual areas. Areas of activation are denoted by numbers: primary Visual Cortex (1), high order visual areas (2).

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Activation related to spontaneous modulation of the alpha rhythm

In addition to distributed cortical activation, the spontaneous alpha modulations yielded a significant BOLD activation in the thalamus (see Fig. 4A), traditionally thought of as the main source of the alpha rhythm in the mammalian brain [17]. This conclusion
was based on cellular recordings in animals exhibiting thalamic oscillation in the 8–12 Hz, and further studies which revealed a substantial relationship between rhythmic thalamic activity and distributed cortical activity [18,32].

Neuroimaging studies have been inconsistent as to the thalamic origin of alpha. For example, a PET/EEG study on humans at rest described a positive correlation between alpha power and metabolic activity in bilateral thalamic nuclei [33], in accordance, more recent human EEG/MRI studies also revealed a positive correlation between BOLD activation in the thalamus and the power of scalp recorded alpha rhythm [20–22]. In contrast to these results an EEG/MRI rest study by Laufs et al[28] was inconclusive as to the role of thalamic nuclei in the generation of alpha rhythm, showing no thalamus alpha correlation. This difference in whole-brain combined measures might be related to the existence of more than one neural component of the alpha rhythm and to its sensitivity to individual's mental state.

Interestingly, in our study the thalamus was not part of the induced alpha network but rather of the spontaneous alpha network, suggests its involvement in the on-going stimulus independent modulations of alpha. It is therefore possible that the thalamus subserves the mechanism of alpha generation that concords with its role as an ongoing pace-maker. It was previously proposed that spontaneous modulations of the alpha rhythm, like a central pace-maker, might coordinate rhythmical activity in widely distributed cortical areas by synchronization [31], serving as a main contributor to the brain’s “self resonance” in on-going activity [15].

In contrast to the common view of the thalamus as a single alpha generator, some data point to the possibility that alpha rhythm might have non-thalamic sources. For example, in dogs it was shown that even after computationally eliminating thalamic activity the coherence of cortical alpha rhythms remains, albeit decreased [32]. Similarly, in humans, bilateral thalamic lesions did not abolish posterior alpha rhythm in eyes closed state [34]. These results correspond to a claim made lately by several researches that the alpha rhythm is driven by several neural generators [15,16].

Alpha rhythm and the ‘default brain’

It is noteworthy that in our study the BOLD activation network derived from the spontaneous alpha partly overlaps with the commonly described BOLD deactivation during goal directed tasks, also known as the “default brain” (e.g. sec [5–7,35] and for comparison Figure 4). This overlap corresponds with early ideas

Figure 5. BOLD time course related to spontaneous and induced alpha networks. BOLD time course of a single subject was extracted from induced alpha region of interest (ROI) in left STS (top, P < 0.0001) and from the spontaneous alpha network in the thalamus (bottom, P < 0.0001). The dashed line denotes the measured BOLD time course and the grey line denotes best fit to BOLD oscillations. It is evident that the BOLD time course extracted from the induced alpha network corresponds to the paradigm based alpha modulation while the time course based on spontaneous oscillations corresponds to the on-going alpha modulation.

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that the alpha rhythm reflects an ‘idle state’ of the brain [4]. Intriguingly, in a recent fMRI study the typical “default brain” activation was not affected by eyes position and was similar for eyes open and eyes closed. This finding lead to the assumption that the deactivation network is distinct from the alpha related network[6] since the latter changes with eyes state. However, our study suggests that any relation of alpha modulation to the “default brain” network is possible only if it is differentiated from the periodic effect of eyes state. A recent imaging study further supports this claim by showing computationally six spatiotemporal distinct rest related BOLD activations. A correlation of the various EEG bands to these BOLD networks revealed a strong relationship of alpha power with three networks, one of which corresponds to most regions of the commonly defined “default brain”. Intriguingly, this network also exhibited significant evidence of thalamo-cortical connectivity[36] similar to the spontaneous alpha network in the current study.

Activation related to induced modulation of the alpha rhythm

The ‘induced alpha’ network exhibits distributed BOLD activation in the SMA, STS, Hippocampus and Parahippocampal gyrus. Not surprisingly the induced alpha network largely overlaps with the paradigm driven BOLD activation to eyes closed versus eyes open (see Fig. 3 for comparison). Accordingly, the induced network resembles the findings of a recent fMRI rest study[37] in its eyes closed Vs eyes open contrast. It therefore can be concluded that the activation related to the induced alpha modulation closely corresponds to alternation in eyes states possibly relating to changes in visual input. Another suggestion for sensory related alpha generator comes from an EEG/PET study showing a significant correlation with the alpha rhythm during eyes closed in two areas of the brain: the thalamus and the STS [38]. Here we show that these activations derived from two separated components of the alpha rhythm, the thalamus from the spontaneous alpha while the STS from the induced alpha modulation.

The hippocampus was also part of the induced alpha network. This result is compatible with animal recordings in the hippocampus showing enhanced alpha signals with increased sensory stimulation [39]. Since different alpha frequencies were recorded depending on the sensory modality (visual vs. auditory stimuli) it was further suggested that the hippocampus serves a gating mechanism for alpha signals [15,16], modulating sensory input.

The induced alpha BOLD activations were largely lateralized to the left hemisphere (see supplementary Table S2). This alpha related functional asymmetry was previously reported by scalp recorded EEG in occipital and temporal regions ofawaked subjects at rest, both with eyes open and closed [10]. Creutzfeldt [40] suggested that there are distinct alpha generators in each hemisphere which share a common control mechanism; according to this view it might be suggested that the left generator is more involved in processes of sensory induced modulations.

Methodological considerations

Several limitations of our study should be noted. 1) The baseline condition alternating between the eyes open eyes closed condition might have hampered the sensitivity of our findings. It could be

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Supporting Information

Table S1 Individual alpha characteristics of studied subjects (n = 10)
Found at: doi:10.1371/journal.pone.0003984.s001

Table S2 Clusters of BOLD activation significantly correlated with induced alpha
Found at: doi:10.1371/journal.pone.0003984.s002

Table S3 Clusters of BOLD activation significantly correlated with spontaneous alpha
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Author Contributions
Conceived and designed the experiments: EBS TH. Performed the experiments: EBS AZ. Analyzed the data: EBS IP. Contributed reagents/materials/analysis tools: IP AA TH. Wrote the paper: EBS TH.
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