

Cortical and Subcortical Correlates of Electroencephalographic Alpha Rhythm Modulation

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Feige, Bernd, Klaus Scheffler, Fabrizio Esposito, Francesco Di Salle, Jürgen Hennig, and Erich Seifritz. Cortical and subcortical correlates of electroencephalographic alpha rhythm modulation. *J Neurophysiol* 93: 2864–2872, 2005. First published December 15, 2004; doi:10.1152/jn.00721.2004. Neural correlates of electroencephalographic (EEG) alpha rhythm are poorly understood. Here, we related EEG alpha rhythm in awake humans to blood-oxygen-level-dependent (BOLD) signal change determined by functional magnetic resonance imaging (fMRI). Topographical EEG was recorded simultaneously with fMRI during an open versus closed eyes and an auditory stimulation versus silence condition. EEG was separated into spatial components of maximal temporal independence using independent component analysis. Alpha component amplitudes and stimulus conditions served as general linear model regressors of the fMRI signal time course. In both paradigms, EEG alpha component amplitudes were associated with BOLD signal decreases in occipital areas, but not in thalamus, when a standard BOLD response curve (maximum effect at ~6 s) was assumed. The part of the alpha regressor independent of the protocol condition, however, revealed significant positive thalamic and mesencephalic correlations with a mean time delay of ~2.5 s between EEG and BOLD signals. The inverse relationship between EEG alpha amplitude and BOLD signals in primary and secondary visual areas suggests that widespread thalamocortical synchronization is associated with decreased brain metabolism. While the temporal relationship of this association is consistent with metabolic changes occurring simultaneously with changes in the alpha rhythm, sites in the medial thalamus and in the anterior midbrain were found to correlate with short time lag. Assuming a canonical hemodynamic response function, this finding is indicative of activity preceding the actual EEG change by some seconds.

INTRODUCTION

Rhythmic electrical potential fluctuations measurable on the human scalp were the first direct evidence for the link between electrophysiological processes in the brain and behavior.

Berger (1929, 1930) observed that the most prominent of these rhythms, the alpha rhythm, is largest in a state of relaxed wakefulness when eyes are closed and shows a sudden reduction when eyes are opened. It is remarkable that the largest amplitude of the electroencephalogram is not associated with a state of increased information processing but rather with a (temporary) lack of information throughput. It was later shown that most primary sensory and motor cortical areas express

similar rhythms in phases of temporally reduced information processing during waking. Pfurtscheller and Aranibar (1977) therefore coined the term “idling rhythms.”

The occipital alpha rhythm constitutes the idling rhythm of the visual cortical areas; however, its amplitude does not simply depend on the amount of visual stimulation but also on visual imagery (Luria 1966), vigilance (Niedermeyer and Lopes da Silva 1993), and visual attention (Babiloni et al. 2004; Worden et al. 2000). This results from the fact that the thalamus is involved in the active gating of different sensory as well as cortico-cortical channels (cf. Steriade et al. 1997). Changes in the alpha rhythm mark changes in the gating of visual information, either locally because other modalities are temporally more important or globally, as vigilance changes.

While the origin of the alpha rhythm can be localized within the primary and secondary visual areas of the occipital and partly parieto-occipital cortex using multi-channel electroencephalographic (EEG) or magnetoencephalographic (MEG) derivations (Ciulla et al. 1999; Hari et al. 1997; Manshanden et al. 2002; Michel et al. 1992; Patel et al. 1999; Williamson et al. 1997), the brain regions participating in the state fluctuations expressed in variations of the alpha rhythm as well as their functional role within these changes are not yet conclusively described.

The thalamus is the main subcortical candidate area to show such fluctuations. Its nuclei relay sensory information from all modalities except olfaction on the way to the primary cortical areas; the thalamocortical relay nucleus for the visual system, the lateral geniculate nucleus, has strong and reciprocal connections to primary visual cortex forming the massive so-called optic radiation. Moruzzi and Magoun (1949) found a rhythm resembling alpha in frequency and reactivity in the thalamic pulvinar in the cat. Lopes da Silva et al. (1973) found coherent alpha rhythms in lateral geniculate nuclei, pulvinar, and visual cortex of awake, behaving dogs.

Later Steriade and Llinás (1988) described the mechanism of a different high-amplitude EEG rhythm of similar frequency that is characteristic for stage 2 sleep: Sleep spindle oscillations are driven by feedback loops between inhibitory cells in the thalamic reticular nucleus and thalamocortical neurons. Thalamocortical cells exhibit a burst mode firing pattern at the

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spindle frequency when inhibited by the reticular nucleus; this rhythm is entrained on the connected cortical areas. High EEG amplitudes occur if large areas of directed neuronal structures at a small distance to the EEG electrodes are synchronized. If viewed in a similar framework, the large amplitude of the alpha rhythm would result from a coherent cortical drive from the thalamus coincident with a lack of other input. Recently, Hughes et al. (2004) proposed oscillations induced by activation of the metabotropic glutamate receptor mGluR1a as a mechanism for the promotion of EEG alpha and theta by the lateral geniculate. However, it is not yet conclusively known to which degree intracortical synchronization mechanisms participate in the generation or selection of the alpha rhythm (Lopes da Silva et al. 1997).

Regional brain metabolic variations coincident with alpha amplitude changes can be experimentally examined by simultaneously acquiring EEG and neuroimaging data including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Most PET studies have used cross-sectional experimental designs comparing different alpha levels across different subjects (Danos et al. 2001; Larson et al. 1998; Lindgren et al. 1999). However, PET has been rarely used to examine intraindividual correlations between EEG and metabolic measures (Sadato et al. 1998).

With the recent advent of technology for simultaneous measurement of EEG and fMRI (cf. Salek-Haddadi et al. 2003 for a review), it has become feasible to examine the intraindividual correlation of spontaneous rhythms and metabolism on a time scale of seconds. This relatively high temporal resolution also allows investigation into the different functional roles of brain areas by examining differences in their temporal relationship with EEG alpha variations.

In the occipital cortex, previous studies correlating EEG alpha amplitudes and metabolic measures have typically found negative correlations among alpha amplitude and blood flow (Sadato et al. 1998), glucose metabolic rate (Danos et al. 2001), and BOLD signal (Goldman et al. 2002; Moosmann et al. 2003). Although the findings vary in terms of participation of other cortical areas, this means that overall metabolism in primary and secondary visual areas is decreased while EEG alpha amplitude is increased. Laufs et al. (2003) reported parietal but no occipital negative correlation with EEG alpha amplitude in their fMRI study.

Subcortical associations with EEG alpha amplitude are less well established. For instance, Sadato et al. (1998) found a positive intrasubject correlation with regional cerebral blood flow in pons, left midbrain, hypothalamus, right thalamus, and right amygdala. At the same time, intersubject comparisons found both negative (Larson et al. 1998; Lindgren et al. 1999) and positive (Danos et al. 2001) correlations of thalamic glucose metabolic rate with alpha amplitude. Using fMRI, Goldman et al. (2002) and Moosmann et al. (2003) found positive correlation between EEG alpha amplitude and BOLD in thalamus, whereas Laufs et al. (2003) did not.

The preceding studies, however, did not exploit the methodological power of combined EEG and fMRI data acquisition to examine differences in temporal relation to alpha occurrence; they assumed neural activity changes occurring simultaneously with EEG changes and a canonical hemodynamic response function (HRF). Furthermore, all previous studies assessed alpha amplitude on the basis of spectral band power in

occipital bipolar derivations, which capture a mixture of activity originating from widely separated brain areas. The partially contradictory findings may have been caused by the failure to specifically extract the occipital alpha rhythm. In addition, because previous studies did not include task paradigms, subjects were left in the scanner for several minutes, usually with closed eyes, which leads to uncontrolled changes in vigilance state and an unclear distinction between wake-state fluctuations and sleep onset processes.

In the current study, we therefore recorded topographical EEG within the MR scanner concurrently with functional MR scans in combination with a visual paradigm (opening and closing the eyes in regular intervals) and an auditory paradigm (auditory stimulation ON-OFF with eyes kept open). Opening and closing the eyes is the most powerful modulator of occipital alpha amplitude, allowing both increase in the observed variation in alpha and examination of the respective influence of visual stimulation and occipital alpha on cortical and subcortical areas. The auditory paradigm was performed as an experimental control condition, for this paradigm avoids the possible confounding effect of visual system variation and stimulates a different major sensory pathway, the thalamocortical relay nuclei of which are located adjacent to those of the visual system. Independent component analysis (ICA) (Bell and Sejnowski 1995; Lee et al. 1999; Makeig et al. 1999, 2002) was used to selectively extract occipital alpha time series. ICA optimizes temporal independence of topographically linearly separated time series and is therefore ideally suited to minimize the mixing of different electrophysiological components as well as artifacts observed at every single EEG derivation (e.g., Jung et al. 2000). In addition to voxel-based linear modeling, we used cross-correlation analysis in thalamic and visual system regions of interest to characterize different temporal relationships with respect to occipital EEG alpha amplitude.

METHODS

Seven healthy right-handed subjects were included (23–40 yr, 5 male, 2 female). Alcohol, caffeine, or nicotine consumption within 24 h before the experiment was disallowed. Prior to the experiment, subjects gave their written informed consent. The study was approved by the ethics committee of the Freiburg University Hospital.

The fMRI data were acquired on a 1.5 T Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany). Two fMRI measurements consisting of 245 axial single-shot gradient-recalled echoplanar image whole-brain volumes were acquired (number of slices = 25; TE = 61 ms; slice thickness = 5 mm; matrix 64×64 pixels; field of view 180×180 mm²; volume acquisition time = 2,750 ms; silent interval interval = 2,500 ms). The first five scans were discarded for spin saturation; in the remaining scans, blocks of 10 scans were alternately assigned to one of two conditions. In the first “eyes open/closed” run, subjects were instructed via headphones when to open and close their eyes (cf. Fig. 1); in the second “auditory stimulation” run, an auditory stimulation with a 1,000-Hz sine tone carrier tone at 90 dB sound pressure level pulsed with a repetition rate of 5 Hz and a duty cycle of 50% was switched on and off alternating every 10 scans while subjects kept their eyes open. After the functional scans, an anatomical magnetization-prepared rapid gradient-echo sequence was recorded (Mugler and Brookeman 1990) (160 sagittal slices with 224×256 voxels, $1.2 \times 1.0 \times 1.0$ mm³). Because other researchers have previously experienced cases of electrode heating with three-dimensional imaging sequences, the electrode cap was removed before anatomical volume acquisition.

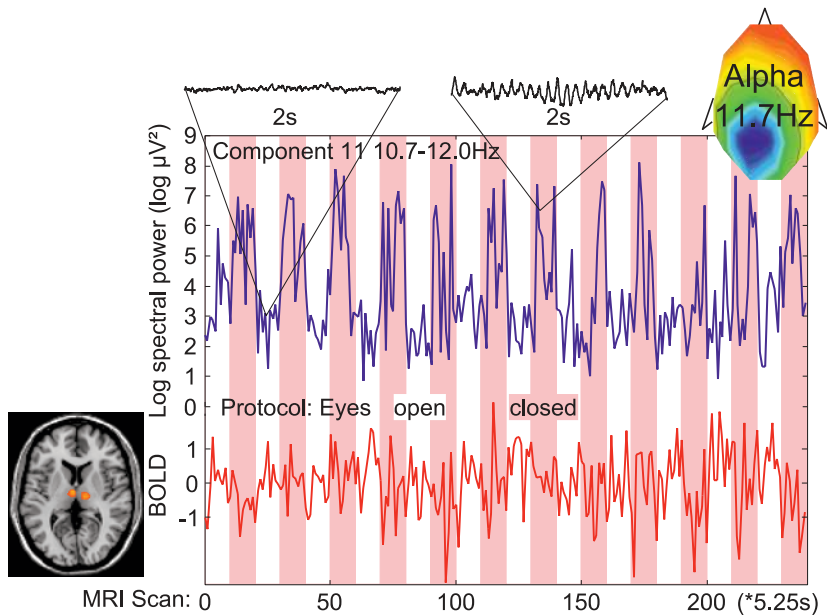


FIG. 1. Recording paradigm superimposed with alpha component and blood-oxygen-level-dependent (BOLD) time courses in the eyes open/closed paradigm for 1 of the subjects. *Top right inset:* the topography of the alpha independent component analysis (ICA) component for this subject. The strong variation of occipital electroencephalographic (EEG) alpha amplitude with opening and closing of the eyes can be seen; however, there is substantial additional variability within each condition. As an illustration of BOLD signal variations, a thalamic region of interest was used that was both affected by opening and closing the eyes and by occipital alpha (cf. Fig. 5). Shown in the lower trace is the z -transformed BOLD time course in this region of interest.

The electrophysiological traces were acquired using a 32-channel MR-compatible EEG amplifier (BrainAmps MR, BrainProducts GmbH, Munich, Germany). The standard “BrainCap” electrode cap with sintered Ag-AgCl ring electrodes included 29 EEG, 2 electrocardiogram (ECG; left lower and near-midline upper chest) and 1 electrooculogram (EOG) electrode (below the right eye). Recording impedances were kept <5 k Ω . All signals were recorded against a reference just in front of the Cz electrode; signal ground was connected to an electrode just behind Cz. Signals were filtered between 0.1 and 200 Hz, sampled at 500 Hz, and stored on disk for off-line processing.

Extraction of inter-scan EEG epochs

The EPI gradient switching caused strong artifacts (peak-to-peak amplitude ~ 5 V) in the EEG traces. To process the artifact-free EEG segments, the scan artifact onsets were detected by filtering all EEG channels between 52 and 200 Hz, rectification, averaging across channels, and determining the first peak exceeding 400 μ V. The next 3000 ms were skipped (“refractory period” of the detector), and the process was repeated until all scan onsets were detected. The time between consecutive scan onsets detected this way was $5,249.8 \pm 1.5$ ms across all 16 runs, which shows both the temporal stability of the scanning and the reliability of the scan onset detection in the EEG. Analysis of longer time windows showed that the 404 ms after each scan reliably contained a subsiding oscillating artifact and that a similar, rising artifact sometimes appeared ≤ 250 ms before the start of the next scan. For this reason, sections of EEG data starting 404 ms after the scan time and ending 250 ms before the next scan (1,848 ms) were extracted for further processing. The first four inter-scan EEG epochs were discarded to obtain 240 epochs just preceding the corresponding functional scan.

Identification of ICA components

Extended ICA (Bell and Sejnowski 1995; Lee et al. 1999; Makeig et al. 1999, 2002) was performed using the Salk Institute C implementation (<http://www.cnl.salk.edu/~enghoff/>) on the concatenated 490 inter-scan EEG epochs of both runs and 29 EEG channels, resulting in 29 ICA components. The combination of map (topography) and weight vectors for each component was normalized so that the absolute map maximum was either +1 or -1 . By multiplication of the weights matrix with the original EEG, a time activation curve

was extracted for each component. Due to the map normalization, the activation curve simply corresponds to the signal at the electrode where the component is strongest. Component logarithmic (base e) spectral power was calculated for each EEG segment by averaging two Welch-windowed FFT spectra obtained from 512-point windows overlapping by half. The resulting spectral resolution was 0.98 Hz. In addition to the analysis of activation time courses, the topographies of all components of all subjects ($29 \times 7 = 203$ topographies) were partitioned into 30 clusters using a robust medoid-based version of the K-means algorithm. One cluster medoid clearly showed the parieto-occipital distribution known for occipital alpha; all seven members of this cluster were confirmed to have a spectral power peak between 8 and 11 Hz and to be responsive to opening/closing of the eyes. Two of the components in this cluster belonged to the same subject, and one subject had no member component. The latter subject instead had two lateralized occipital components with spectral characteristics and eye closure responsivity typical for the occipital alpha rhythm.

After ICA component selection, spectral power of all alpha components of the given subject was integrated across all frequency bins within the alpha band (8–12 Hz) for each epoch, log-transformed and used as “alpha” regressor for the same subject’s fMRI time series. The regressor therefore quantifies the alpha-band power of the alpha components within each inter-scan interval. Figure 1 shows the alpha component time course for one of the subjects together with the BOLD time course in the indicated thalamic region superimposed on the protocol.

fMRI analysis

The fMRI datasets were analyzed with BrainVoyager (Brain Innovation B.V., Maastricht, The Netherlands) and were preprocessed using intra-session slice alignment, interslice time correction, linear detrending of BOLD time series, spatial alignment with the anatomical scans and warping into Talairach space.

Multi-subject general linear model analyses (GLM using the iteratively reweighted least squares method) of individually z -transformed voxel time courses were calculated separately for the two experiments across all seven subjects using the stimulation protocol (1 for auditory stimulation or eyes open and 0 for silence or eyes closed, respectively) and alpha spectral power as regressors. The regressors were preprocessed by first normalizing them to the interval [0, 1] (subtracting the minimum and dividing by the maximum value across all time points) and then convolving with a canonical HRF using the

program “waver” from the AFNI suite (<http://afni.nimh.nih.gov/>). For the stimulation, or “protocol” regressor, the following standard HRF parameters were used: delay time, 2 s; rise time, 4 s; fall time, 6 s; undershoot, 0.2; restore time, 2 s. For the alpha regressor, to account for the fact that the EEG alpha was recorded 2.5 s before the fMRI scan, delay time was set to 0 and rise time to 3.5 s. The peak amplitude was set to 1.0. With a TR of 5.25 s, the effect of all standard BOLD effect models for low-frequency regressors (several seconds period time) is very similar to simply delaying the time series by one scan time.

To be able to perform cross-correlation analyses with the alpha regressor also in the eyes open/closed experiment, in which the alpha and “protocol” regressors were interdependent, we calculated a “protocol”-independent (orthogonalized) alpha regressor by subtracting the part of the alpha curve linearly explainable by the “protocol” (Gram-Schmidt orthogonalization) for each subject. This procedure removes the systematic alpha differences between conditions and only leaves the generally faster spontaneous fluctuations of alpha amplitude occurring within conditions. To treat both paradigms equivalently, a protocol-orthogonalized alpha regressor was also derived for the auditory experiment.

In addition to the voxel-based analysis, averaged fMRI signals were derived for each of the 119 regions of interest (ROIs) defined by the Montreal Neurological Institute (MNI) Talairach data set using the AFNI program “3dROIstats” and entered into the statistical software suite “R” (R Development Core Team 2004). The corresponding signal time courses were individually transformed using a robust version of the z -transform [median absolute deviation with asymptotically normal consistency, function `mad()`]. Statistical testing was done using a linear mixed effects model with the two regressors and random effects grouped by subject. This model implements a within-subject repeated measures analysis by accounting for possibly different intercepts of the target variable across subjects while globally estimating the influence of the regressors.

Statistical significance was set at $P < 0.05$. For the whole brain volume of 1,010,205 mm³ this was achieved by considering cluster sizes >324 mm³ at a voxel threshold of $P < 0.001$ (Monte-Carlo simulation using the AFNI program “AlphaSim”). For the thalamic activation, a conjunction analysis (cf. Friston et al. 1999) was addi-

tionally used to show the partial overlap of eyes open/closed correlation and EEG alpha correlation in medial thalamus. In the auditory paradigm, we employed a confirmative correlation analysis restricted to the thalamic volume activated in the visual paradigm. To achieve $P < 0.05$, small-volume correction (Worsley et al. 1996) on the volume of 570 mm³ then requires a voxel threshold of $P < 0.001$.

Three-dimensional rendering was done using the freely available “blender” software (<http://www.blender3d.org/>). Surface mesh data of anatomical structures as well as of statistically significant functional clusters was generated using BrainVoyager and imported for rendering. Cortex and brain stem surface meshes were derived from the Talairach-transformed anatomical data set of one of the subjects participating in the study; the thalamus surface was derived from the MNI Talairach data set.

RESULTS

Correlations of occipital alpha amplitude with protocol

To characterize the interdependency of the two regressors, a mixed-effects linear model was calculated across the seven subjects seeking to explain the occipital alpha amplitude by the protocol trace. As expected, alpha power was significantly larger during the eyes closed than during the eyes open condition [$t(8; 1,672) = -14.06, P = 1.6e-42$]. For the auditory paradigm, occipital alpha rhythm was slightly increased in the auditory stimulation condition [$t(8; 1,672) = 3.06, P = 0.002$].

Correlations in the simultaneous protocol and occipital alpha model

Figure 2 shows the partial correlations with the protocol and the alpha regressor, respectively, in a “glass brain” view for both paradigms.

Regarding the protocol correlations, primary visual areas and the thalamic lateral geniculate nuclei were found to be deactivated when eyes were closed. A strong frontocentral

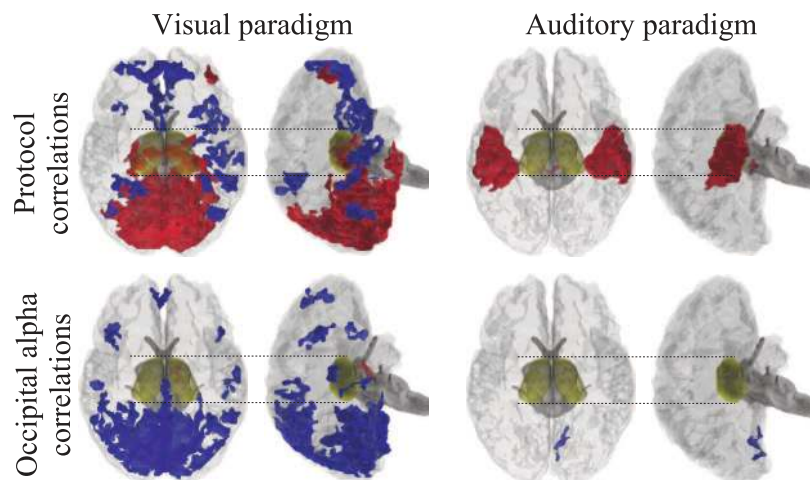


FIG. 2. Protocol correlations (top) and correlations with occipital EEG alpha power (bottom) with the “eyes open/closed” (left) and “auditory stimulation ON-OFF” (right) protocols. The thalamus is highlighted in yellow for better visibility; positive correlations are included in red, negative in blue. The anticorrelations with opening the eyes extending from a frontocentral cluster bilaterally to the back of the head (left) are probably the result of the associated eye and lid movements. The auditory stimulation plot (right) was done with a cluster size set to 200 instead of 324 mm³ with the effect of retaining, in addition to the auditory cortical areas, a third cluster in the inferior colliculi showing the alignment precision of functional and anatomical data. Apart from a single cluster in the anterior right mesencephalon, only negative correlations with alpha power are seen in this analysis (bottom). The area deactivated during increased alpha includes the calcarine and fusiform gyri as well as medial parietal cortex (Brodmann area 7; only significant in the visual paradigm); compared with the distribution of “eyes open” activation in the top row, the alpha-related deactivation comprises the same areas with the addition of the parietal part and a larger temporal extension. In the auditory paradigm (right), qualitatively, the same distribution of BOLD signal change is found, however, quantitatively to a smaller extent. Only a single cluster in the right calcarine sulcus reached significance at whole brain correction level.

TABLE 1. Protocol and electroencephalographic (EEG) alpha amplitude correlations

Region	Eyes Open/closed				Auditory Stimulation			
	Protocol		Alpha EEG		Protocol		Alpha EEG	
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>
Brodman area 17	9.68	0.000	-4.36	0.000	-3.60	0.000	-3.38	0.001
Brodman area 18	10.12	0.000	-5.04	0.000	-1.41	0.158	-3.84	0.000
Brodman area 37	-1.44	0.151	-5.15	0.000	-0.06	0.950	-3.68	0.000
Cuneus	8.83	0.000	-6.52	0.000	-1.48	0.139	-3.63	0.000
Fusiform Gyrus	2.12	0.034	-4.49	0.000	-0.77	0.444	-3.24	0.001
Inferior Occipital Gyrus	4.23	0.000	-3.76	0.000	-1.36	0.175	-3.61	0.000
Lingual Gyrus	14.10	0.000	-6.92	0.000	-1.45	0.146	-3.29	0.001
Middle Occipital Gyrus	2.34	0.019	-4.29	0.000	-1.38	0.168	-3.61	0.000

Correlations with protocol and EEG alpha amplitude in the eyes open/closed (left), and auditory stimulation on/off (right) experiments obtained using simultaneous general linear model analysis (GLM) with the two regressors when assuming a canonical hemodynamic response function (HRF) for both regressors. Montreal Neurological Institute (MNI)-derived Talairach volumes of interest are included where the EEG alpha effect was significant at $P \leq 0.001$ in both experiments. Note that despite the generally strong effects observed for the simple visual task, some of the strongly alpha-related areas show only weak or no correlation with the visual paradigm. EEG alpha effects in thalamic regions do not reach significance in this analysis.

negative correlation with eye opening was identified as an eye movement artifact because the corresponding voxel time courses showed steep and abrupt signal changes at the eye movement times. For the auditory paradigm, the correlation with stimulus blocks shows the expected strong activation of auditory cortex during presentation of sound stimuli. In addition, a cluster smaller than the threshold of 324 mm³ appears within the inferior colliculi. This is the only cluster additionally appearing when the volume threshold is reduced to 200 mm³. Because these anatomical structures are small, a larger activated volume cannot be expected. According to AlphaSim, the odds for a cluster of this size to occur by chance within the whole brain volume, given our voxel threshold of $P < 0.001$, are 0.38.

The distribution of negative correlations with EEG alpha amplitude is similar in both paradigms, albeit much weaker in the auditory paradigm in which the eyes were always open. In the eyes open/closed experiment, it clearly extends more parietally than the correlation with simple visual activity. In the auditory paradigm, the distribution is qualitatively similar but the correlation is much weaker due to the lower amount of alpha variations. In both paradigms, Talairach ROI analysis (Table 1) showed negative correlations at $P \leq 0.001$ in Brodmann areas 17, 18, and 37. Brodmann areas 19 (peristriate cortex) and 7 (medial parietal cortex) reached $P \leq 0.001$ only in the visual paradigm; in the auditory paradigm, a tendency for negative BOLD effect was present for area 19 ($P = 0.004$) but not for area 7 ($P = 0.4$).

Positive correlation with EEG alpha amplitude was found in a small region in the right anterior midbrain ($x/y/z$ coordinates: 10 -7 -10 mm), which appears as a smaller residuum of the more extended positive correlations found in the "orthogonalized alpha" analysis in the following text.

To verify that the observed correlations with occipital EEG alpha amplitude were not related to artifacts of opening and closing the eyes, and that it is feasible to use only the protocol-orthogonalized alpha regressor in correlation models, we repeated the whole-brain statistics as shown in the preceding text in three additional calculations involving protocol-orthogonalized alpha: First in a simultaneous model with protocol as in the preceding text; second, using orthogonalized alpha alone; third, using only the eyes-closed sections of the paradigm,

additionally dropping the two scans at the transition points that could be influenced by the transient motor act. All three analyses showed very similar results to those shown in the preceding text (see Supplementary Figure¹). The fact that entering protocol as an additional regressor to protocol-orthogonalized alpha leads to only minimal differences indicates that despite the spatial overlap of eyes open/closed and alpha-related variance, unexplained protocol variance does not contribute much to the error term when evaluating models including only orthogonalized alpha.

Correlations with the orthogonalized alpha regressor

One interesting and functionally significant reason for the failure of the previous analysis to find thalamic correlations with occipital alpha would be a deviation in temporal relationship from the assumptions made in that analysis. We therefore performed cross-correlation analyses between three selected ROIs from the MNI Talairach atlas and both protocol and protocol-orthogonalized occipital alpha amplitude (both without convolution with the putative HRF). The ROIs are chosen to represent possibly different types of relationships to the occipital alpha rhythm and its regulation: Brodmann area 17 (primary visual cortex), the lateral geniculate nuclei (thalamic visual relay), and the thalamus as a whole. The whole thalamus was used in this analysis to avoid more detailed presumptions about its parts.

Figure 3 shows the results in the eyes open/ closed paradigm. The correlations in primary visual cortex are strongest for lag 1 (=1 TR) for both the protocol and orthogonalized alpha regressor, consistent with a deactivation of this area coincident in time with closing the eyes and with alpha power increase given a canonical HRF. The lateral geniculate nuclei (LGN) show a significant correlation only with protocol, i.e., with opening the eyes, but none with alpha. The thalamus shows a similar correlation pattern as LGN and Brodmann area 17 with respect to opening the eyes but a distinct significant correlation with alpha at lag 0. This corresponds to a mean delay from EEG to fMRI of only 2.5 s, indicating that the

¹ The Supplementary Material for this article (a figure) is available online at <http://jn.physiology.org/cgi/content/full/00721.2004/DC1>.

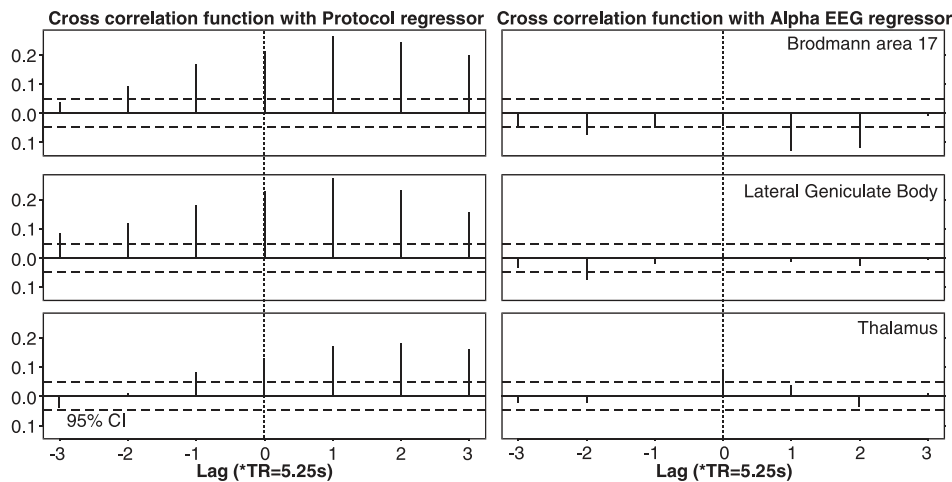


FIG. 3. Cross-correlation plots between BOLD variations in 3 cortical and subcortical regions and hemodynamic response function (HRF)-unconvolved protocol (*left*)/orthogonalized alpha (*right*). The indicated confidence interval assumes white noise and applies to the test of a single variable. For Brodmann area 17 (*top row*), the optimal shift is 1 for both regressors, compatible with neural changes occurring simultaneously with protocol/occipital alpha changes if a canonical HRF is assumed. In the lateral geniculate nuclei (*middle row*), the cross-correlation with protocol is very similar to that in Brodmann area 17, whereas correlation with alpha amplitude is not seen. Across the whole thalamus (*bottom row*), the cross-correlation with protocol is weaker but similar to that in the visual system areas above, whereas correlation with alpha amplitude occurs in an isolated fashion at lag 0.

corresponding metabolic activity increase precedes EEG alpha increases if a canonical HRF is assumed. At the same time, all observed protocol correlations become significant at lag 1, which indicates that the corresponding changes in neural activity occur simultaneously with opening or closing the eyes under the same assumption.

Figure 4, *right*, shows the result of mapping the subcortical fMRI correlations with the orthogonalized alpha regressor at lag 0. For comparison, subcortical correlations with the HRF-convolved eyes open/closed protocol are displayed on the *left*. As demonstrated in the conjunction analysis shown in Fig. 5, the thalamic region between ventral lateral and medial dorsal nuclei ($x/y/z$ coordinates, volume: $-14 -17 + 12$ mm, 345 mm³; $+4 -13 + 7$ mm, 225 mm³) significantly correlates positively with both opening the eyes and orthogonalized alpha power. However, while the activation extends in ventroposterior direction to the LGN for the visual activation, the alpha correlation extends in ventroanterior direction, displaying a second focus in the anterior midbrain anterior to the red nuclei and medial to the subthalamic nuclei (between coordinates $+2 -15 -17$ up to $-7 -12 -6$ mm), possibly encompassing the medial and anterior parts of the subthalamic region. It includes the medial aspect of substantia nigra and extends on the right side toward the substantia innominata of Reichert. In a confirmatory analysis with small volume correction using the thalamic volume activated in the visual paradigm, a positive correlation with protocol-orthogonalized alpha was found in the right thalamus in the auditory paradigm; this is shown on the right side of Fig. 5 ($x/y/z$ coordinates: $+2 -13 + 10$ mm).

To exclude the possibility that the thalamic correlation was due to eye movement artifacts or other transient effects related to opening and closing the eyes, we used the thalamic region from the conjunction analysis as region of interest in an additional set of post hoc GLM analyses performed separately on the eyes-open and eyes-closed sections of the protocol and excluding the transition periods between the sections. Transition periods were defined as the two scans following the instruction to open or close the eyes. In each case, the ROI fMRI signal was modeled as a function of the orthogonalized alpha regressor without HRF convolution using a multisubject GLM. Results for the full data set (including all scans as in the preceding text) were $t(8; 1,672) = 5.62$, $P = 2e-8$; for eyes closed, $t(8; 658) = 6.78$, $P = 3e-11$; and for eyes open, $t(8; 676) = 2.87$, $P = 0.004$. This means that even if we excluded the transition periods we found correlations within the eyes closed sections but also, to a smaller extent, during the eyes open sections of the paradigm.

DISCUSSION

In the current study, we have examined the correlation between occipital EEG alpha rhythm, selectively extracted using ICA, and fluctuations in the BOLD effect during two simple experimental paradigms. These included first opening and closing the eyes and second auditory stimulation versus silence with eyes kept open. The paradigms were designed to keep the subjects in a stable awake state and to provide reference metabolic data of two important sensory pathways

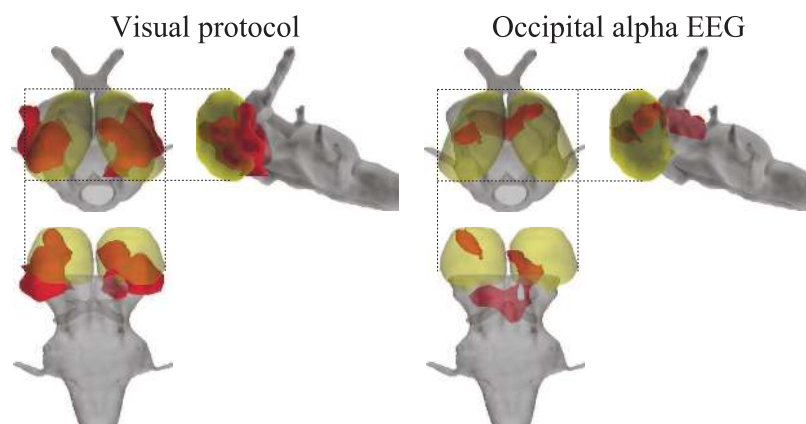


FIG. 4. Glass-brain views of correlations with HRF-convolved subcortical protocol (eyes open/closed, *left*) and unconvolved orthogonalized alpha (*right*). Statistical threshold was strictly set according to whole brain correction as before. Only positive correlations were found. As also seen in the conjunction analysis in Fig. 5, both correlations are colocalized in the thalamic region between ventral lateral and medial dorsal nuclei; the protocol correlation additionally includes the lateral geniculate nuclei, whereas the alpha correlations extend anteriorly and downward into the mesencephalon, in a region medial to the subthalamic nuclei and anterior to the red nuclei, possibly encompassing the substantia nigra.

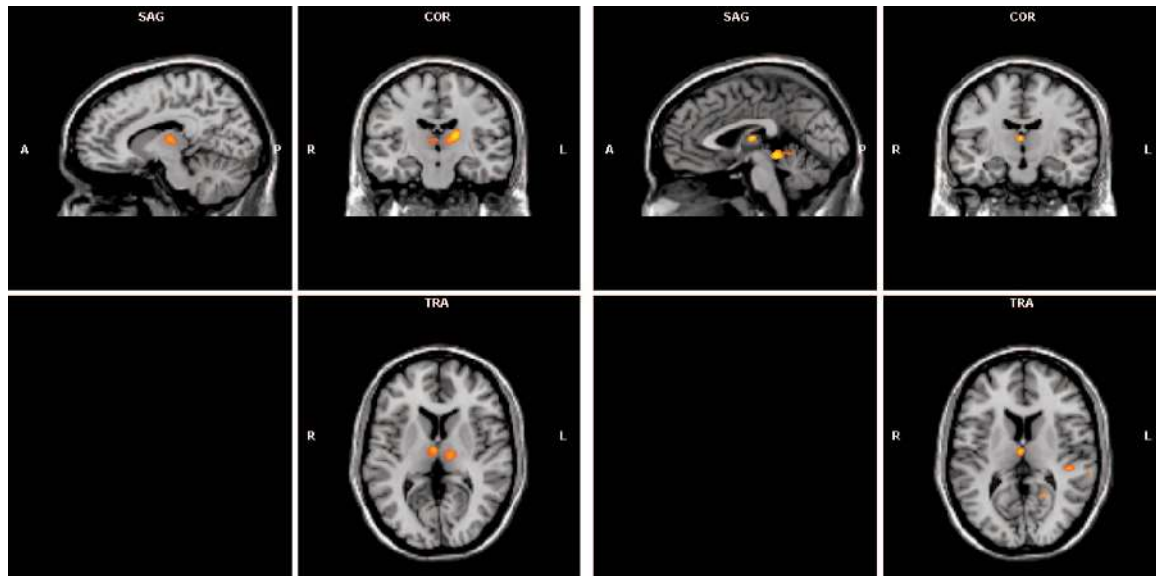


FIG. 5. *Left*: conjunction analysis between protocol (eyes open/closed) and orthogonalized alpha at lag 0 ($x/y/z$ slice coordinates: $+6 -17 + 8$ mm, whole brain correction, only positive correlation); *right*: correlation with (protocol-orthogonalized) alpha amplitude at lag 0 for the auditory paradigm (slice coordinates: $+2 -14 + 11$ mm, small volume correction, only positive correlation, voxel threshold $P < 0.001$).

with different relation to the generation of occipital alpha: while occipital alpha is a rhythm of the visual system and is characterized by its reactivity toward opening and closing the eyes, the task-irrelevant auditory stimulation used in our paradigm showed only a weak positive correlation with occipital alpha amplitude. This cross-modal influence can be interpreted as a suppression of the visual system during auditory stimulation (Pfurtscheller 1992). However, no significant negative BOLD effect was seen in visual areas during auditory stimulation.

Cortical correlations with occipital alpha

We found negative correlations of the BOLD signal with occipital alpha amplitude in primary and secondary visual areas in both the visual and the auditory stimulation paradigm. These results are in line with the negative alpha correlations found in other studies correlating brain metabolic markers and EEG alpha amplitude (Buchsbaum et al. 1984; Goldman et al. 2002; Moosmann et al. 2003; Sadato et al. 1998). These areas also closely correspond to the sources of occipital alpha rhythm in EEG and MEG localization studies (Ciulla et al. 1999; Hari et al. 1997; Manshanden et al. 2002; Michel et al. 1992; Patel et al. 1999; Williamson et al. 1997). The pattern of cortical deactivation corresponded between the two experimental paradigms, although the effect was stronger in the visual than the auditory experiment, where alpha variation was weaker. Within the accuracy limits of our study and assuming a canonical HRF, the temporal relationship was compatible with a simultaneous occurrence of the neural deactivation and occipital alpha power increase. We cannot rule out that part of the alpha amplitude fluctuation was secondary to variations in visual input as they occur during normal eye blinks. However, it is well known that alpha variations can also result from changes in visual imagery (Luria 1966), vigilance (Niedermeyer and Lopes da Silva 1993), and visual attention (Babiloni et al. 2004; Worden et al. 2000). It is not yet known whether the coincidence of metabolic downregulation and large-scale

synchronization has active functional aspects; brain rhythms such as alpha have been hypothesized to have a functional role in the regulation of network properties (e.g., for gain regulation) (Lopes da Silva et al. 1974). Alternatively, it is known that the generators of the waking spontaneous rhythms alpha and mu can be driven by rhythmic input compatible to their resonant frequency (steady-state response studies with visual, somatosensory stimuli) (cf. Narici and Romani 1989; Singh et al. 2003). Therefore the appearance of large-amplitude waves on the scalp could well be the expression of a default oscillatory state entered in the absence of small-scale differential information processing activity.

The apparent contradiction of electrophysiological alpha “activity” occurring while the corresponding sensory channel is temporarily inactive first puzzled Hans Berger. Recent research has brought up a related question: with the current indications that BOLD signal change is most strongly related to the amplitude of local field potential variations and to the synaptic input of an area (whether excitatory or inhibitory) (Logothetis and Wandell 2004; Logothetis et al. 2001; Mathiesen et al. 1998), it might be expected that the EEG amplitude as macroscopic sum of local field potentials would correlate positively with regional metabolic activity as indicated by the BOLD effect. Apparently, however, the large-scale synchronized dendritic polarization that leads to the high amplitude of the alpha rhythm can well coincide with a reduced regional metabolic activity level.

Subcortical correlations

Subcortical electrophysiological correlates of the alpha rhythm were originally found in the thalamic pulvinar (Lopes da Silva et al. 1973; Moruzzi and Magoun 1949) and LGN (Lopes da Silva et al. 1973). Today, the mechanisms of generation of the thalamic rhythm as well as the exact contribution of intracortical connectivity to the cortical oscillations that determine the EEG alpha rhythm are still unknown. As the occipital alpha rhythm amplitude is increased during transient

reduction of visual information throughput, a negative correlation between alpha amplitude and BOLD effect in the LGN or a positive correlation in the inhibitory reticular nucleus could have been expected. It is interesting to note that we did not find BOLD effect correlations with occipital alpha amplitude in pulvinar, LGN, or thalamic reticular nucleus.

In the current study, clear activation of the respective thalamocortical relay nuclei was observed to be associated with opening the eyes (LGN) and with the presentation of auditory stimulation (medial geniculate nuclei). Just as in primary visual cortex, the temporal relationship of LGN fluctuations to opening and closing the eyes was compatible with, to the limits of our study, simultaneous activation and a canonical HRF. At the same time, in contrast to cortical parts of the early visual system, the LGN showed no correlation with occipital alpha EEG amplitude. However, a thalamic region located only ~10–15 mm more anteriorly and superiorly correlated positively with occipital alpha in a way that could not be detected when assuming a canonical HRF (corresponding to a time delay of ~6 s between EEG and BOLD effect) but only if a smaller delay was assumed (in our study, the delay was 2.5 s on average). This could be due to an actual difference in the local HRF; however, the nearby thalamocortical nuclei showed no signs of a markedly different HRF. Another possibility is that the activity in this region actually precedes the occurrence of occipital EEG alpha in time.

The regions positively correlating with occipital EEG alpha with this characteristic comprised sites in the medial thalamus (in the area of the intralaminar nuclei) and in the anterior midbrain (in the area of the substantia nigra). This corresponds to the PET study of Sadato et al. (1998), who found a positive intrasubject correlation between EEG alpha amplitude and regional cerebral blood flow in pons, left midbrain and hypothalamus. The two previous combined EEG/fMRI studies reporting positive correlation between EEG alpha and thalamic metabolism (Goldman et al. 2002; Moosmann et al. 2003) did not cover this brain area. Laufs et al. (2003) found neither a correlation in the thalamus nor in the midbrain. This discrepancy is conceivably due to the different temporal relationship to EEG alpha fluctuations that was not accounted for previously.

Our results point toward a leading role of a mesencephalic-medial thalamic network in the regulation of the brain state characterized by high EEG alpha amplitudes. In this brain state, primary and secondary visual as well as parietal cortical areas are downregulated. The mesencephalon plays an important role in the regulation of the autonomous aspects of behavior; it is possible that spontaneous upregulation of a pathway for active behavior results in concomitant downregulation of visual areas.

Based on his observation of strongly increased cortical spontaneous rhythms seconds after single-pulse stimulation of the intralaminar region in cats and monkeys, Jasper (1949) considered the midline and intralaminar thalamic nuclei as diencephalic relay of the ascending reticular activating system. While the direct “midline pacemaker theory” for EEG alpha waves was later rejected on the grounds of more precise physiological knowledge (Andersen et al. 1967; Steriade and Llinás 1988), the importance of this thalamic area for arousal and consciousness is often stressed (Newman 1995; Van der Werf et al. 2002).

Regarding mesencephalic connections, the intralaminar and medial thalamic nuclei are modulated by serotonergic fibers ascending from the dorsal and median raphe nuclei (Ishida and Kitano 1977; Monckton and McCormick 2002) as well as by cholinergic fibers, most probably from the pedunculopontine nuclei (Dringenberg and Olmstead 2003; Paré et al. 1988; Steriade et al. 1988). In the current study, no correlation with the posterior midbrain location of these nuclei was observed; rather, we found a positive correlation in the anterior midbrain (substantia nigra, ventral tegmental area) that is mostly dopaminergic. Studies on thalamic dopamine receptor distribution are scarce; recently, however, Rieck et al. (2004) examined the dopamine D2 receptor distribution in human thalamus both in vitro (using [¹²⁵I]epidepride radioligand labeling) and in vivo (using [¹⁸F]fallypride PET) and found increased binding specifically in the midline and intralaminar nuclei. It is therefore possible that the mesencephalic-medial thalamic network we found to correlate positively with occipital EEG alpha amplitude is a dopaminergic central modulator of brain state.

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GRANTS

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