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MRI-constrained spectral imaging of benzodiazepine modulation of spontaneous neuromagnetic activity in human cortex

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Spontaneous electromagnetic brain rhythms have been widely used in human neuropharmacology, but their applicability is complicated by the difficulties to localize their origins in the human cortex. Here, we used a novel multi-modal non-invasive imaging approach to localize lorazepam (30 μg/kg *i.v.*) modulation of cortical generators of spontaneous brain rhythms. Eight healthy subjects were measured with 306-channel magnetoencephalography (MEG) in a double-blind, randomized, placebo-controlled (saline), crossover design. For anatomically realistic source modeling, wavelet-transformed MEG data were combined with high-resolution MRI to constrain the current locations to the cortical mantle, after which individual data were co-registered to surface-based coordinate system for the calculation of group statistical parametric maps of drug effects. The distributed MRI-constrained MEG source estimates demonstrated decreased alpha (10 Hz) activity in and around the parieto-occipital sulcus and in the calcarine sulcus of the occipital lobe, following from increased $GABA_A$-inhibition by lorazepam. Anatomically constrained spectral imaging displays the cortical loci of drug effects on oscillatory brain activity, providing a novel tool for human pharmacological neuroimaging.

Introduction

Spontaneous rhythmic brain activity, observed in magnetoencephalography (MEG) and electroencephalography (EEG), is thought to reflect oscillatory events essential for normal brain function. The frequency–power distribution of these rhythms (alpha 8–12 Hz, beta 15–25 Hz, gamma 30–80 Hz) correlates with the state of the consciousness, making them an essential tool for clinical monitoring and diagnosis. As MEG and EEG signals probably reflect postsynaptic currents in cortical pyramidal neurons (Hämäläinen et al., 1993; Nunez, 1981), dynamic changes in spontaneous brain rhythms help monitoring specific neuronal effects of clinically relevant centrally acting drugs. Benzodiazepines, which mediate their inhibitory actions *via* the ionotropic gamma-aminobutyric acid ($GABA_A$) receptors, result in an increase of beta and decrease of alpha activity (Coenen and van Luijtelaar, 1991; Visser et al., 2003). Unfortunately, localizing the cerebral sources of MEG/EEG activity is complicated, limiting the applicability of spontaneous brain rhythms in neuropharmacological imaging.

A number of applications for source-localization of MEG/EEG activity exist. The majority of existing efforts have concentrated on estimating the cerebral sources of event-related potentials or magnetic fields, which represent averaged epochs of EEG or MEG activity, respectively, phase-locked to an external stimulus or internal event. However, source localization of brain spontaneous activity, emerging from distributed oscillators, is complicated using focal source estimation methods such as equivalent current dipole (ECD) modeling (Hämäläinen et al., 1993), which has been widely used for localizing (more focal) sources of event-related MEG or EEG activity. Consequently, more diffuse source estimates for source modeling of brain oscillatory activity have been recently applied (David et al., 2002; Gross et al., 2001; Hauk et al., 2002; Jensen et al., 2005; Lachaux et al., 2002). However, none of these methods applied exact information of the individual shape of the cortical surface, which varies greatly among different subjects, for reducing the MEG/EEG solution space to the cortical gray matter, which is the most likely origin of brain oscillations (Dale and Sereno, 1993). Therefore, a non-invasive method to

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estimate MEG power sources directly in the cortical surface utilizing anatomical MRI constraints was recently developed (Lin et al., 2004). This method combines a cortically constrained minimum norm estimate (MNE) (Dale et al., 2000; Hämäläinen and Ilmoniemi, 1984) and spectral analysis employing complex Morlet wavelets (Tallon-Baudry and Bertrand, 1999; Varela et al., 2001). Here, we utilized this method to localize cortical changes in spontaneous MEG activity, following from an administration of the 3-hydroxy benzodiazepine derivative *lorazepam*, a drug that is extensively used in clinical practice (Ameer and Greenblatt, 1981).

Methods

Eight nonsmoking right-handed healthy subjects (4 females; age 20–29 years; weight 54–76 kg) participated in the study, after a medical examination and blood tests to exclude subjects with physical or mental health problems (Symptom Checklist (SCL-90) (Derogatis et al., 1973)). Self-reportedly, subjects consumed no more than five drinks/week, and used no medications for 2 weeks, no alcohol for at least 48 h, and no caffeine for 12 h before the recordings. All subjects gave informed written consent and institutional ethical committee approval was obtained.

All subjects arrived at the laboratory at 8 AM after an overnight fast. A catheter was placed in the right antecubital vein for injecting either 30 μg/kg of lorazepam (Ativan® 4 mg/ml, Wyeth Lederle) or placebo (saline) in a randomized, double-blind, placebo-controlled crossover design (two sessions separated by a week). During the 306-channel MEG recording (band-pass 0.03–100 Hz, sampling rate 600 Hz; Elekta Neuromag, Helsinki, Finland), which started 5 min after the infusion, subjects were instructed to sit quietly in an electromagnetically shielded room (Euroshield, Eura, Finland) and to keep their eyes closed for 5 min and open for 5 min, looking straight and avoiding unnecessary eye movements. Because of the potential sedative effects of lorazepam, subjects' vigilance was controlled by the presence of sleep spindles which naturally appear during drowsiness or may be induced by sleep-inducing drugs. MEG epochs containing sleep spindles (increase at 12–15 Hz and decrease at 0.75–4 Hz) were excluded from the signal analyses. The locations of the marker coils in relation to the head cardinal points (nasion, left and right pre-auricular points) were determined (Polhemus, Colchester, VT) for measuring the subject's head position in MEG. In a separate session, high-resolution 3D T1-weighted MRI was obtained (1.5T Siemens Magnetom Vision, Erlagen, Germany; MPRAGE, sagittal slice thickness 1 mm, TR/TE = 9.7/4.0 ms) for cortical surface reconstruction, for determination of the conductor geometry for the boundary element model (BEM) of the head (Hämäläinen and Sarvas, 1989), and for registering the MEG sensors' locations with the individual subject's anatomy (Dale et al., 1999, 2000; Fischl et al., 1999a; Sereno et al., 1995).

To analyze MEG spectral power, a Morlet wavelet with a central frequency of 10 Hz was applied to MEG raw data, extracted from a 30 s epoch 2–2½ min after closing/opening the eyes (Lin et al., 2004). All epochs with changes exceeding 150 μV in an electro-oculogram (EOG) or 3000 fT/cm at any or MEG channel, respectively, were automatically discarded from this analysis. Using the complex time-frequency representation $TF_i(t, f)$ for trial I, the spontaneous power was calculated as $\|TF_i(t, f)\|^2$, where $\|\cdot\|^2$ indicates the square of a complex number. An inverse technique was utilized to map the instantaneous MEG power over the cortex by $\|\mathbf{W}TF_i(t, f)\|^2$, where $\mathbf{W}$ is the inverse operator. Information of the MEG sensors' locations and the structural MRI segmentation were used to compute the forward solutions for all source locations using a single-compartment BEM (Hämäläinen and Sarvas, 1989). The individual forward solutions constituted the rows of the gain (lead-field) matrix ($\mathbf{A}$). For inverse computations, the cortical surface was decimated to ~5000 vertices per hemisphere. The noise covariance matrix ($\mathbf{C}$) was computed from the raw MEG data during the baseline period (eyes open condition). These two matrices, along with the gain matrix $\mathbf{A}$ and a diagonal source-covariance matrix $\mathbf{R}$, were used to calculate the inverse operator $\mathbf{W}=\mathbf{R}\mathbf{A}^{\mathrm{T}}(\mathbf{A}\mathbf{R}\mathbf{A}^{\mathrm{T}}+\mathbf{C})^{-1}$. The MEG at each time point was multiplied by $\mathbf{W}$ to yield the estimated source activity, as a function of time, on the cortical surface: $\mathbf{s}(\mathbf{t})=\mathbf{W}\mathbf{x}(\mathbf{t})$ (Dale et al., 2000; Liu et al., 1998, 2002). The bias toward superficial source locations was counterbalanced by depth weighting, incorporated to the source-covariance matrix $\mathbf{R}$ (Lin et al., 2006b). Noise normalization was utilized to further reduce the point-spread function, and to display alpha activations in *F*-statistics (Dale et al., 2000; Liu et al., 1998, 2002). Additionally, the median power of each 5 min epoch was calculated to examine the power ratio (eyes closed vs. eyes open) in 16 parieto-occipital gradiometer channels, separately for the lorazepam and placebo conditions.

For group analyses, individual source estimates were normalized by morphing each brain into a canonical averaged spherical brain representation (Fischl et al., 1999b). A grand-average statistical parametric map was then calculated based on a general linear model (GLM). For the GLM, we regressed out the mean of the MEG source time series in individual subjects. The construction of the contrast matrix included (1) eye-open/eye-closed contrast, (2) drug/placebo contrast, and (3) the interaction between (1) and (2). We calculated the *t*-statistics for all three contrasts assuming the noise is temporally uncorrelated. The resulting group statistical parametric maps were finally morphed onto the inflated cortical surfaces of a representative subject.

In an additional region-of-interest (ROI) analysis, we identified two ROIs per hemisphere, the calcarine sulcus and the parieto-occipital sulcus, in one subject based on anatomical criteria. The ROI identification was based on an automatic cortical parcellation algorithm, assigning a neuroanatomical label to each location on a cortical surface (Fischl et al., 2004). These ROI labels were co-registered to the cortical surface representations of rest of the subjects through the common spherical standard space (Fischl et al., 1999b). We then calculated the eyes closed/open ratio of the median power within each ROI in each subject and tested the group effects of lorazepam within each hemisphere by using a two-way Friedman ANOVA model. Finally, the drug effects on the eyes closed/open power ratio in the set of parieto-occipital gradiometers were analyzed using the Wilcoxon test.

Results

Lorazepam administration significantly reduced the signal power at 10 Hz in the parieto-occipital gradiometer channels ($Z=-2.2$, $P<0.05$; Wilcoxon test). This effect is clearly demonstrated in Fig. 1, which also suggests that the alpha attenuation is more evident in the eyes closed than eyes open condition. Furthermore, our spectral spatiotemporal imaging allowed us to reveal the cortical changes in alpha generation caused by lorazepam in the *source space*. Figs. 2 and 3 demonstrate that, without the drug manipulation, the 10-Hz alpha activity has distributed cortical sources, activated most significantly in the occipital visual

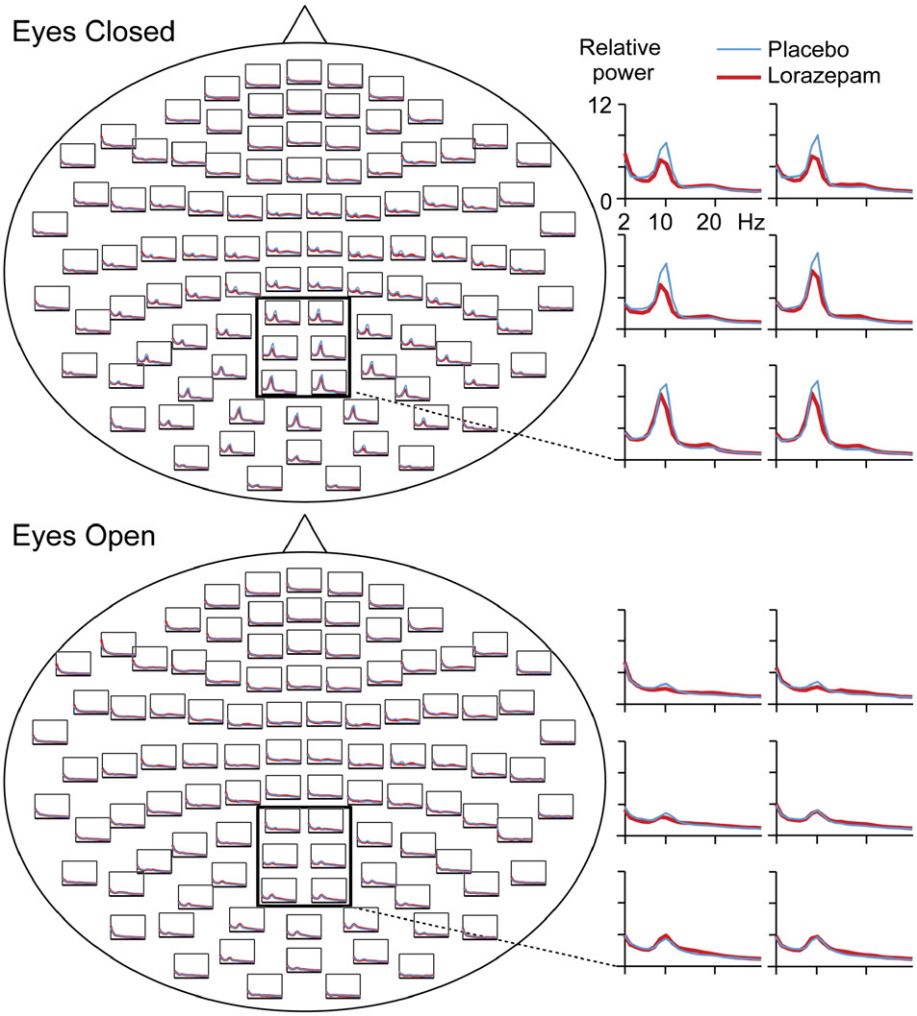

Fig. 1. Grand average MEG power spectra, showing the attenuation of alpha power by lorazepam. The *y*-axis represents the relative power, which has been normalized based on the total power (mean power at 0–150 Hz) in each sensor within each subject before group averaging. At each sensor location, the Figure shows the average of the two associated gradiometer power spectra. The inserts show the signal in a selection of parieto-occipital gradiometer pairs. As expected, the alpha peak, and its attenuation by lorazepam, is more prominent in the eyes closed condition. Note that the alpha activity appears to be slightly decreased by lorazepam in sensors located above the sensorimotor cortices as well.

cortex, around the calcarine sulcus (in or near the primary visual cortex) and in the medial surfaces near parieto-occipital junction (the parieto-occipital sulcus, gyrus precuneus, and gyrus cuneus). As shown in by the drug by task–condition interaction in Fig. 2, the most significant decreases of alpha activity by lorazepam administration are observed in the vicinity of these parieto-occipital sources. The group-average statistical parametric maps, further, show that the decreased alpha synchronization (eyes closed vs. open) by lorazepam was most prominent in and near the parieto-occipital sulcus. The surface-based group statistics were supported by the ROI analysis (two-way Friedman ANOVA), suggesting that lorazepam reduced the alpha ratio (closed/open) in the right ($\chi^2=8.3$, $P<0.05$) and left hemispheres ($\chi^2=9.5$, $P<0.05$).

Discussion

Lorazepam effects on generation of spontaneous neuromagnetic alpha were studied using a wavelet-based, anatomically constrained method (Lin et al., 2004). The decrease of alpha activity by lorazepam, a $GABA_A$ agonist benzodiazepine, is consistent with previous EEG and MEG observations (Fingelkurts et al., 2004; Link et al., 1991). However, few prior studies have modeled human pharmacodynamics utilizing cortically constrained MEG source localization, guided by the subjects' individual head and brain anatomy. Moreover, we analyzed the cortical alpha distribution in a spherically registered standard space, allowing the evaluation the cortical localization of drug effects at a group level. The results indicate that the alpha attenuation was strongest in and around the parieto-occipital sulcus, and in the calcarine sulcus. Finally, our results concerning the source localization of cortical alpha activity per se are principally in agreement with previous MEG source modeling studies, suggesting that the cortical alpha is mainly generated in the parieto-occipital sulcus (Hari et al., 1997; Osipova et al., 2005), and to a lesser extent, also in the calcarine sulcus (Hari et al., 1997).

In the present study, we applied our source modeling approach to localize lorazepam-related changes in the 10-Hz

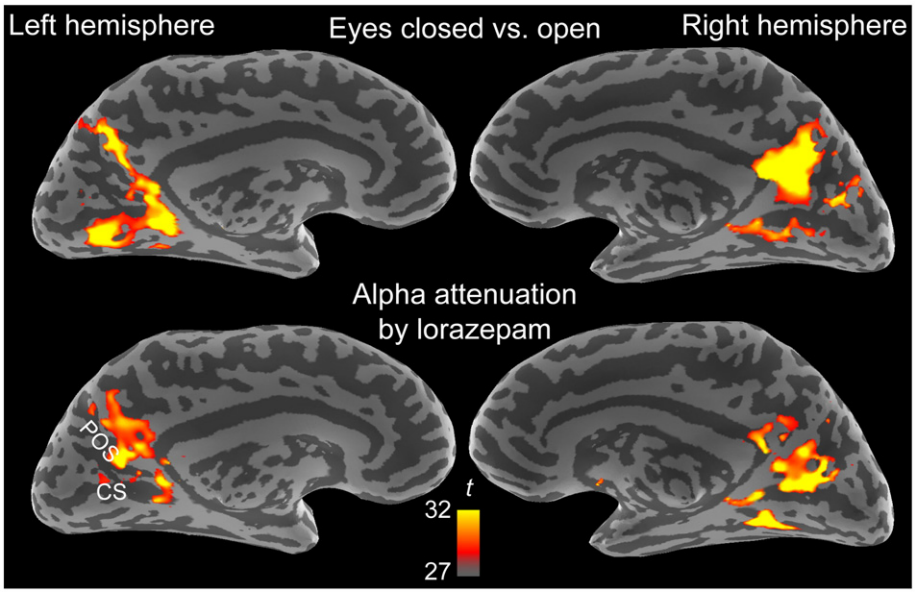

Fig. 2. (Top) Group statistical parametric maps (SPM) of alpha sources in the medial cortical surfaces. The activity maps show the contrast between eyes closed vs. open in all conditions. In other words, the activation pattern shows the brain regions where alpha activity was most significantly higher in the eyes closed vs. open conditions. (Bottom) Group SPMs of the cortical sources of maximal alpha attenuation by lorazepam. The color scale thus represents regions where alpha oscillations were most significantly deactivated in lorazepam vs. placebo conditions. Abbreviations: CS, the calcarine sulcus; POS, the parieto-occipital sulcus.

alpha range of resting MEG, typically associated with a prominent spectral peak in the posterior brain regions. This frequency range was chosen to optimize the signal-to-noise ratio in our source modeling procedure (Jensen and Vanni, 2002). However, previous studies have identified changes with benzodiazepines in other frequency bands as well. In particular, a well-documented pharmacodynamic feature of benzodiazepine drugs such as lorazepam is the increase of EEG and MEG activity in the beta frequency range. For example, Jensen et al. (2005) recently showed that the beta effects of the benzodiazepine diazepam originate in the primary sensorimotor cortex, near the hand area, which was interpreted to indicate that this region is the primary cortical effector site of benzodiazepines. However, our results are in agreement with previous human benzodiazepine receptor binding studies, based on positron emission tomography (PET) (Frey et al., 1991; Wang et al., 1996), which have indicated high density of GABA-benzodiazepine receptor binding sites in the occipital lobes.

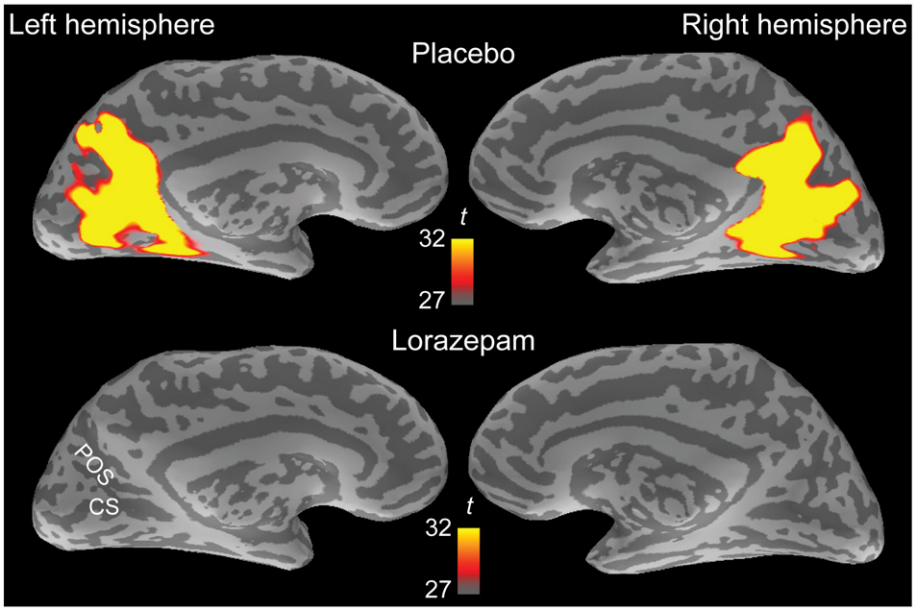

Fig. 3. Group statistical parametric maps (SPM) of the eyes closed vs. eyes open contrasts with and without lorazepam administration in the medial cortical surfaces. The parieto-occipital alpha activity, which is evident in the placebo condition, is strongly attenuated by lorazepam. Abbreviations: CS, the calcarine sulcus; POS, the parieto-occipital sulcus.

The inverse problem associated with MEG source localization is inherently ill-posed: the data can be explained by an infinite number of solutions and the computed source estimates may be very sensitive to noise. The standard approach to alleviate these problems is to employ anatomically and physiologically motivated constraints and to apply regularization methods in the computation of the estimates. The idea of the cortical anatomical constraint that we employed stems from the fact MEG signals most likely reflect activity of pyramidal cells of the cortical gray matter, oriented perpendicularly to the cortical sheet (Hämäläinen et al., 1993; Nunez, 1981). This allows us to utilize the information of the individual shape of the cortical surface to restrict the MEG or EEG solution space (Dale and Sereno, 1993). Cortical surface-based anatomical constraints in MEG source modeling have been successfully applied in multiple studies of evoked brain activity (Ahveninen et al., 2006; Dale and Sereno, 1993; Dale et al., 2000; Jääskeläinen et al., 2004; Lin et al., 2006a,b; Liu et al., 1998, 2002). One might, nonetheless, argue that the benefits of anatomical constraints in source estimation of brain oscillatory activity are limited because of the inaccuracy of head position measurements, typically resulting from subject movement. However, in the present study, the data were obtained during a relatively short period of time, while the subject was carefully monitored. The probability of interference due to head movement during the frequency-analysis period was, further, reduced by the fact that the MNEs were based on a 30 s sample of spontaneous activity.

The present methodology has certain limitations, which are principally common to all existing MEG/EEG source localization algorithms. MEG source localization is, for example, prone to problems caused by the anatomical convolution of the cortex. Spatial localization resolution of MEG often leaves ambiguous the side of a sulcus or a gyrus on which the source is located, especially if source estimation approaches producing diffuse images of the currents like the MNE are employed. Furthermore, although the present method results in anatomically realistic SPM maps of oscillatory activity, it does not provide a unique measure of the spatial extent of the source activity. For example, the spatial extent of activation varies according to the chosen statistical threshold. Another limitation of our approach is that no deep gray nuclei activity is included in the source model, given the importance of thalamocortical interactions in the generation and maintenance of neocortical oscillatory activity.

Alternative approaches for source localization of MEG/EEG oscillations include the L1 minimum current estimate (MCE) (Jensen et al., 2005; Matsuura and Okabe, 1995; Uutela et al., 1999) with exponential probability distribution function, while the dynamic imaging of coherent sources (DICS) (Gross et al., 2001) utilizes beamformer techniques. MCE and DICS, however, require a relatively high SNR (and their poorer temporal resolution may hamper the localization of transient stimulus-related oscillations). MNE-based localizing of cortical oscillations, such as the present solution, has been utilized by others as well (David et al., 2002; Hauk et al., 2002; Lachaux et al., 2002), but these solutions did not use the individual subject's MRI for the BEM head model or clips of spontaneous activity, or single trial epochs, for creation of an averaged power spatiotemporal map comparable to the present results. Above all, apart from the abovementioned study employing MCE in the estimation of the sources of benzodiazepine effects on sensorimotor beta (Jensen et al., 2005), few studies applying abovementioned approaches to localize neuropharmacological modulation of spontaneous brain oscillatory activity have been published to date.

In conclusion, our results demonstrate pharmacological modulation of alpha activity using MRI-constrained spectral imaging of MEG sources. Previous neuroimaging studies utilizing PET have typically been based on larger ROIs such as the forebrain lobes. Statistical parametrical mapping has been also attempted (Wang et al., 1999), but the evidence has remained spatially inaccurate to localize subregional (e.g., gyri, sulci) differences in $GABA_A$ effects, suggested by post-mortem receptor mapping studies in humans (Zilles et al., 2004). Our MRI-constrained MEG-source modeling method (Lin et al., 2004), showing the significance of alpha attenuation in more specific cortical structures, might thus be an useful pharmacodynamic neuroimaging measure (e.g., in combined multichannel EEG/PET studies).

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