Complex Relationship Between BOLD Signal and Synchronization/Desynchronization of Human Brain MEG Oscillations

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Abstract: Functional magnetic resonance imaging (fMRI) depends on the coupling of cerebral blood flow, energy demand, and neural activity. The precise nature of this interaction, however, is poorly understood. A positive correlation between BOLD-response and cortically generated local field potentials, which reflect the weighted average of synchronized dendrosomatic components of pyramidal synaptic signals, has been demonstrated. Likewise, positive BOLD-responses have been reported in conjunction with scalp-recorded synchronized electromagnetic activity by a number of groups. However, it is not yet clear how the opposite electromagnetic pattern, i.e. cortical desynchronization, is related to the BOLD signal. To address this question, we conducted a combined event-related fMRI and 275 sensor whole-head MEG study during identical visual two-choice reaction time task conditions in 10 human subjects. We found complex sequences of MEG-synchronization and desynchronization across a wide frequency range in the visual and motor area in close correspondence with “locales” of positive BOLD-responses. These results indicate that a correspondence of positive BOLD-responses is not exclusively found for cortical synchronization but also for desynchronization, suggesting that the relationship between BOLD signals and electromagnetic activity might be more complex than previously thought. *Hum Brain Mapp* 28:805–816, 2007. © 2006 Wiley-Liss, Inc.

Key words: MEG; BOLD; synchronization; desynchronization

INTRODUCTION

The precise nature of the coupling between BOLD- (blood-oxygen-level-dependent) response and neural sig-

nals is currently a topic of intense research [Logothetis, 2003]. Rees et al. [2000] compared human fMRI (functional magnetic resonance imaging) measurements with single unit recordings in monkeys and suggested a proportional relationship between BOLD-response and the average neuronal firing rate. A relationship between neuronal spiking rate and BOLD-response was then shown directly by Hyder et al. [2002] and Smith et al. [2002] who demonstrated a linear correlation between oxygen metabolism and neuronal firing rate in rats. A linear correlation was also reported by Logothetis et al. [2001] who simultaneously acquired intracortical electrophysiological and fMRI data in monkey visual cortex. However, the same study also suggested that

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synaptically generated local field potentials (LFPs) are a substantially more reliable predictor of the BOLD-response than neuronal spiking activity whereby LFPs and spiking rate were found to covary only moderately with each other. This finding that synaptic activity may correlate more closely with blood flow than spiking rate has been described in a comparable way for Pukinje cell activity in rat cerebellum [Mathiesen et al., 1998/2000]. Recently, Attwell and Iadecola [2002] offered an explanation for why the BOLD-response may correlate more closely with synaptic activity than with neuronal firing rate under certain conditions—an explanation, which is based on estimations of the cortical gray matter energy budget. In rodents, 47% of the energy used on signaling is predicted to support action potentials and 34% to support postsynaptic potentials. However, in primates the developmentally acquired greater number of synapses reverses this relationship and postsynaptic currents account for ~74% of the total energy used on signaling while action potentials are thought to consume only about 10% of the signaling energy.

The work of Logothetis et al. [2001] has spurred efforts to obtain a better understanding of the relationship between BOLD-response and LFPs or EEG/MEG oscillations in humans. Cortically generated LFPs are thought to reflect the weighted average of synchronized dendrosomatic components of pyramidal synaptic signals and they are the physiological basis of synchronized electromagnetic oscillations as obtained from scalp recordings through electroencephalography (EEG) or magnetoencephalography (MEG) [Buchwald et al., 1965; Creutzfeldt et al., 1996a,b; Fromm and Bond, 1964; Juergens et al., 1999; Mitzdorf, 1987]. The oscillatory EEG- or MEG-activity can be further subdivided into frequency bands, which correspond to certain states and operations of the brain [Başar, 1988; Lopes da Silva and van Leeuwen, 1969]. Correlations of positive BOLD-responses could be demonstrated with scalp-recorded and intracranial low frequency oscillations, including epileptic spike activity [Aghakhani et al., 2004; Benar et al., 2002; Salek-Haddadi et al., 2002], surface-negative slow cortical potentials [Hinterberger et al., 2003; Nagai et al., 2004], and event-related potentials across different task conditions [Henning et al., 2005; Huettel et al., 2004; Matsumoto et al., 2005; Mulert et al., 2004; Schulz et al., 2004]—all of which are generated by synchronized activity of cortical neuronal populations. However, recently, another MEG/fMRI-study by Singh et al. [2002] conducted in humans provided indirect evidence that the opposite relationship may also be found, i.e., a positive BOLD-response correlating with cortical non-phase-locked desynchronization of electromagnetic field oscillations. Investigating two different groups of subjects under the same task conditions, the authors described a left-hemispheric lateral prefrontal decrease in signal power, i.e., event-related desynchronization (ERD) while a positive BOLD-response was observed in the same cortical area during a letter fluency task. Several brain areas showing ERD in correspondence to positive BOLD-responses were

also seen during a visual discrimination task—in particular in the visual area (V1) where an event-related decrease of signal power was found within the 7–12 Hz α -frequency range. In addition, the authors also report an increase of power, i.e., event-related synchronization (ERS) in the hand motor area. Discussing their results, the authors acknowledge the contradiction between their findings and the observations of Logothetis et al. [2001] since the latter study would have predicted a relationship between positive BOLD-responses and ERS. It is therefore of interest that the same group recently reported that ERD in the α band is accompanied by an ERS in the γ band and that both oscillatory phenomena covary with the BOLD-response in the visual cortex during a simple visual paradigm [Brookes et al., 2005]. In agreement with this finding, Mukamel et al. [2005] lately demonstrated a similar correspondence in the auditory cortex between BOLD-response and LFPs as measured by implanted electrodes, i.e., a negative correlation was shown for low-frequency LFPs in the α/β (5–15 Hz) frequency range whereas a high positive correlation was obtained in the 40–130 Hz high-frequency range.

In the present study, we addressed the question on the biophysical relationship between BOLD-response on one side and ERS and ERD on the other side by investigating one single group of subjects both with fMRI and whole-head MEG during identical visual two-choice reaction task conditions. Comparable motor response tasks are known to elicit α -frequency ERD in the occipital area, which is thought to reflect visual information processing and mechanisms of attention [Klimesch et al., 1998; Pfurtscheller et al., 1994]. Also, an action preparation β -frequency ERD that precedes the motor response is expected to be seen [Pfurtscheller and Lopes da Silva, 1999; Toro et al., 1994] and a motor response-related θ -frequency ERS [Caplan et al., 2003; De Araujo et al., 2002; Luu and Tucker, 2001] which has been suggested to coordinate and integrate sensory and motor brain activity [Bland and Oddie, 2001].

SUBJECTS AND METHODS

Subjects

A total of 10 healthy subjects (mean age: 25.7 ± 10.1 years, four females) participated in the study. The study was approved by the Institutional Review Board of the National Institute of Mental Health and conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from each participant.

Behavioral Task

We employed a mixed “event-related and blocked design” in order to maximize the task-related BOLD-response [Donaldson and Buckner, 2001; Winterer et al., 2002]. 108 visual static, i.e., non-flickering checkerboard stimuli were presented in an identical way during the MEG and the fMRI session either on the left or right side

of the visual hemifield by means of a back-projection system onto a translucent screen using the “Presentation” software package (Neurobehavioral Systems Inc.[®]). While fixating a red dot in the center of the screen, subjects were instructed to respond as fast and accurate as possible to each stimulus by pressing either the left or the right button depending on the side of appearance of the checkerboard. Stimuli were presented with a duration of 400 ms in counter-balanced and pseudorandomized order at inter-stimulus intervals (ISIs) of 2–4–6 s between stimulus onsets such that each ISI was present in one third of all ISIs. In addition, seven longer ISIs of 12 s were interspersed at regular intervals of 12 consecutive stimuli in order to allow the BOLD-response to fully recover (i.e., event-related and blocked design). The relatively short and pseudorandomized ISIs were chosen because a similar stochastic design is generally employed in electrophysiological studies to maximize the electromagnetic brain response and because we have successfully used a similar task design in previous topographic electrophysiological studies [Gallinat et al., 2002; Mulert et al., 2001; Winterer et al., 1999]. Moreover, our earlier systematic fMRI pilot work with longer ISIs up to 12–18 s did not result in stronger BOLD-responses. This observation has been essentially confirmed by a recent simulation study that has suggested that the detectability of the BOLD-response actually increases with relatively short and randomized ISIs [Birn et al., 2002]. Motor responses (latencies, errors, and missing button presses) were recorded through a fiber optic response box with buttons arranged in the same configuration as the stimuli presented on the screen. The total duration of the task was 500 s.

Data Acquisition

MEG-data were collected with a whole-head MEG system (CTF Systems Inc., Vancouver, Canada[®], <http://www.ctf.com>), which is located in a magnetically shielded room (Vacuumschmelze). Data were recorded continuously at 600 Hz during the visual choice reaction task with the subjects positioned at 15° from vertical. The SQUID sensor array consisted of 275 radial first-order gradiometers (5 cm baseline) uniformly distributed over both hemispheres (Fig. 1), giving an average interchannel spacing of 2.2 cm. The MEG data were digitized along with the behavioral response data (reaction latencies, errors). Markers were set in the MEG-data at the onset of each visual stimulus and button response. Nasion and preauricular points of each subject were marked, photographed, and the head coils applied for localization of the head within the sensor array. The coils, which can be detected by the MEG system itself, form a coordinate system that is used to register the MEG and MRI data.

fMRI imaging was conducted using a 3T General Electric MRI scanner with a real-time functional imaging upgrade and a standard quadrature head coil (Milwaukee, WI). To facilitate localization and coregistration of functional data, structural scans were acquired using T1-

weighted MRI sequences (Magnetization prepared rapid gradient echo (MP-RAGE)): TR/TE = 8.2/3.3 ms; flip angle = 6°; 96 slices; slice thickness = 1.5 mm; matrix, 256 × 192. Whole-brain BOLD-responses (excluding the lateral aspects of the temporal lobe region) were obtained with a gradient echo planar imaging sequence (24 sagittal 6-mm thick interleaved slices without gap, relaxation time/echo time (TR/TE = 2,000/30 ms; flip angle = 90°; 24 slices; matrix = 64 × 64 resulting in voxel dimensions of 3.75 × 3.75 × 6 mm) while subjects performed the visual choice reaction task. Stimulus presentation was triggered automatically by the first slice acquisition of functional images.

Data Analysis

MEG raw data was filtered in 3rd gradient mode for noise reduction using a system of reference coils with fixed weights along with DC offset removal, minimal highpass filter (0.61 Hz), and powerline (60 Hz) filtering using Digital Signal Processing (DSP) firmware (DSP Research, Inc., Sunnyvale, CA[®]). MRIs of each subject were converted into CTF format. The original fiducial points were marked on the images within MRIVIEWER for the purpose of registration of the MR images with the MEG-data. Electromagnetic source analysis was conducted with SAM (Synthetic Aperture Magnetometry) beamformer technique (CTF Systems Inc., Vancouver, Canada). By using a spatial filter, SAM resolves the linear superposition of wanted signal covariance and unwanted noise variance of brain activity using the entire array of MEG sensors. It uses the recorded magnetic field at each sensor and a specific set of weighting factors for each location within the cortex, producing a 3D representation of brain activity. SAM finds an optimal spatial filter for estimating source power within specific time windows and frequency bands. The task-related power (fT²) of the averaged data was analyzed in the θ (4.0–7.0 Hz), α (8.0–12.0 Hz), β (14.0–30.0 Hz), and γ (30.0–50.0 Hz) frequency bands. We employed SAM beamformer technique for MEG source analysis, which is a newly introduced nonlinear minimum variance beamformer technique for estimating the source distribution in the brain [Ishii et al., 1999; Robinson and Vrba, 1999; Taniuchi et al., 2000]. Empirical data suggest good spatial accuracy and validity, for instance, as obtained through a direct comparison of the MEG source solution and the BOLD-response in fMRI experiments [Singh et al., 2002; Schulz et al., 2004]. Generally, beamformers construct a spatial filter for a selected target point (voxel) in space and the filter output is a linear combination of the measurements over time. SAM requires—unlike equivalent dipole source models—no a priori specification of the number of active sources and provides current source density (CSD) images in 3D space within specific frequency bands. For each subject, a pseudo F-ratio source image was created by comparing the power estimates from pre- and post-stimulus or pre- and post-response intervals on the basis of a sliding window analysis for combined left and right stim-

(SAMerf) was employed to determine sources of average stimulus evoked activity [Robinson, 2004]. SAM analysis was performed on a 1–30 Hz frequency band for a stimulus-related time window of –300 to 700 ms. Virtual channels were then created for each voxel location by applying the SAM spatial filters. The virtual channel time series for each stimulus were averaged and a sliding window ratio of post- to pre-stimulus power was used to generate functional images. Separate 100 ms post-stimulus windows with 50 ms steps were compared to a fixed 100 ms pre-stimulus window, with log power ratios calculated for each voxel. Individual volumes were normalized to Z-scores and a *t*-statistic was calculated for group averages ($P < 0.05$).

Voxel-by-voxel fMRI-analysis was performed with FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Visual inspection of motion-correction estimates confirmed that no participant's head moved >1.5 mm in any dimension from one volume acquisition to the next. The following pre-statistics processing was applied: Employing different modules of FSL-software package, we conducted motion correction using MCFLIRT [Jenkinson et al., 2002], non-brain removal using BET [Smith, 2002], spatial smoothing using a Gaussian kernel of FWHM = 6 mm, mean-based intensity normalization of all volumes by the same factor, and high-pass temporal filtering (Gaussian-weighted LSF straight line fitting, with $\sigma = 9.0$ s). General linear model (GLM) time-series statistical analysis of individual data sets was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction [Woolrich et al., 2001]. We used one explanatory variable (i.e., left and right visual stimulus/motor response) convolved with a Double-Gamma hemodynamic response function (phase shift = 6 s) [convolving the hemodynamic response function with stimuli and responses gave identical results]. *Z* (Gaussianized *T*) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.01$ [Forman et al., 1995; Friston et al., 1994; Worsley et al., 1992]. Registration to high resolution images was carried out using FLIRT [Jenkinson and Smith, 2001; Jenkinson et al., 2002]. GLM group-level analysis (mixed effect analysis) was performed with FLAME (FMRIB's Local Analysis of Mixed Effects). *Z* (Gaussianized *T*) statistic images were thresholded using again clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.01$ [Forman et al., 1995; Friston et al., 1994; Worsley et al., 1992] or as specified in the figure legends. The group-maps were then used to create masks (thresholded on the basis of *P*-values) in order to determine for each individual subject the mean and maximum activity change for a given BOLD-response and location.

Statistics

Paired *t*-tests and Spearman's *R* were used for within-group comparisons of behavioral as well as fMRI and MEG imaging data.

Figure 2.

Time-frequency spectrogram across the entire group of subjects ($n = 10$), i.e., the time-frequency analysis was done on the separate time series of each study subject (raw data) and the time-frequency representations were then averaged. The plots are an average of all sensors across all subjects. Top: time-frequency analysis is referenced to the visual stimuli. Bottom: time-frequency analysis referenced to the motor reaction.

RESULTS

Reaction Time and Error Rate

The group mean reaction time was 481.9 ms (SD 167.0). Mean error rate was less than 1%. During the fMRI session, the group mean reaction time was 401.5 ms (SD 49.9) and mean error rate was 1.7%. No significant difference of mean reaction time was found between the MEG and fMRI-session (paired $t = 2.0$; $df = 9$; $P > 0.05$).

Figure 3.

Time-frequency spectrogram before and after averaging of data across the entire group of subjects ($n = 10$). Top: time-frequency plots in occipital (visual) cortex (green in Fig. 1) are referenced to the visual stimuli. Bottom: time-frequency plots in

central (motor) cortex area (purple in Fig. 1) referenced to the motor reaction (also see Fig. 1). Left side: time-frequency plots of raw data (before averaging). Right side: time-frequency plots of averaging data (i.e., averaged event-related magnetic fields).

MEG/fMRI-Analysis

All analyses were made with the combined left and right stimulus/motor-response vectors. A left-right separation of stimuli/motor-responses did not yield meaningful results as of a lack of power.

Figure 2 shows two time-frequency spectrograms across all sensors referenced to the stimulus onset and running from -200 to $1,200$ ms (top) and referenced to the onset of the motor reaction and running from -800 to 800 ms (bottom). There are several time-frequency features of interest. First of all, little differences are seen between the two plots because spectrum analysis has been conducted on the raw data of each subject with no prior (event-

related) averaging of the single evoked responses. In essence, what is seen is a ERD around 500 ms after stimulus onset with two frequency maxima in the α and β frequency range with extension into the γ frequency range. This ERD is followed by a “rebound” ERS around $1,000$ ms after stimulus onset with a maximum in the low β frequency range extending into the high β and γ frequency range. Moreover, a power increase (ERS) in the very low θ and δ frequencies is observed, which is maximal around 800 ms after stimulus onset. Figure 3 (left side) provides similar information as depicted in Figure 2; however, the time frequency plots were not conducted across all sensors but separately for those sensors in the occipital cortical area (top) and the central cortical area (bottom) in order to

Figure 4.

A surface-rendered group-averaged ($n = 10$) overview is provided on the task-related BOLD-response (upper left and lower left). Note that convolving the hemodynamic response function with stimuli and responses gave identical results. The motor response-related θ -ERS (upper right) and the stimulus-related α -ERD (lower right) are also depicted.

Figure 5.

Group MEG SAM analysis and event-related fMRI analysis ($n = 10$ subjects). In the SAM analysis, post-stimulus activity (sliding time-window searching for maximum activity change) is compared to 300 ms prestimulus in the α frequency band (combined analysis for left and right stimulus). Blue indicates a significant decrease in power ($P < 0.05$) associated with desynchronization (ERD). In the fMRI group analysis, the BOLD-response is thresholded at a Z value of 2.8 ($P = 0.05$, two-tailed). α -Desynchronization is seen in the left and right visual cortex area and in the parietal area where the MEG-activity change is stronger on the right side whereas the BOLD-response is stronger on the left side.

Figure 6.

Group MEG SAM analysis and event-related fMRI analysis ($n = 10$ subjects). In the SAM analysis, post-stimulus activity (sliding time-window searching for maximum activity change) is compared to 300 ms pre-stimulus in the β (left) and γ (right) frequency bands (combined analysis for left and right stimulus). Blue indicates a significant decrease in power ($P < 0.05$) associated with event-related desynchronization (ERD). In the fMRI group analysis, the BOLD-response is thresholded at a Z value of 2.8 ($P = 0.05$, two-tailed). β -ERD and γ -ERD are both seen in the left and right motor area. The MEG-activity change are relatively symmetrical in both hemispheres whereas the BOLD-response is stronger on the left side.

Figure 7.

Group MEG SAM analysis and event-related fMRI analysis ($n = 10$ subjects). In the SAM analysis, response-locked activity (sliding time-window searching for maximum activity change) is compared to 300 ms prereponse in the θ -frequency band (combined analysis for left and right stimulus). Red indicates a significant increase in power ($P < 0.05$) associated with synchronization (ERS). θ -ERS is seen in the motor area and ACC. In the fMRI group analysis, the BOLD-response in the motor area is thresholded at a Z value of 2.0 ($P = 0.05$, two-tailed). The BOLD-response in the ACC is thresholded at a Z value of 1.7 ($P = 0.05$, one-tailed). The MEG-activity changes are relatively asymmetrical with θ in the right motor area and right ACC being stronger than on the left side.

TABLE I. Corresponding activity changes (maxima) in fMRI and MEG

Region	fMRI			MEG (SAM)		Latency (ms)	Euclidian distance (mm)
	X,Y,Z	Z _{Max}		X,Y,Z	Pseudo-F _{Max} (SE)		
ERD							
Visual-L	4, 90, 20	3.90	Alpha	8, 83, 6	−1.26 (0.35)	500	16.2
Parietal-R	−27, 62, 47	2.60	Alpha	−23, 53, 44	−1.62 (0.53)	500	10.3
Motor-L	48, 34, 43	3.85	Beta	38, 23, 59	−3.33 (0.80)	400	21.8
			Gamma	38, 23, 51	−2.80 (0.79)	450	16.9
ERS							
Motor-R	−33, 38, 46	3.04	Theta	−38, 15, 51	1.81 (0.64)	0	24.1
ACC-R	−7, −51, 1	−2.10	Theta	−23, −38, 21	1.15 (0.41)	100	28.7

provide information on the time–frequency characteristics as a function of cortical location (visual vs. motor areas). It is obvious that the ERD with “rebound” ERS in the α/β high frequency range is somewhat stronger in the motor as compared to the visual area. Vice versa, low frequency ERS in the θ/δ frequency range appears to be stronger in the visual area. When comparing these features with the time–frequency plots that have been obtained after averaging of the (event-related) single evoked responses (left side), one obtains the impression that the low frequency component constitutes the evoked responses that are either locked to the stimulus (top)—and which was expected from literature on the occurrence of visually evoked magnetic fields (P100m, N145m) and their frequency composition [Fawcett et al., 2004; Hashimoto et al., 1999; Schürmann et al., 1997]—or to the motor response (bottom) with the additional feature that the averaged stimulus-evoked response encompasses a broader frequency spectrum as compared to the averaged motor-evoked response.

Figure 4 provides a first surface-rendered overview of task-related BOLD-signal changes (left) and MEG-signal changes (right) (for more details see Figs. 5–9). In Figure 4, MEG-activity ERDs are depicted in the visual and parietal cortex in the α frequency band (right bottom) and in the motor cortex in the β and γ frequency bands (right top). The MEG θ -activity change (ERS), which shows a maximum in the motor area, is also presented. The latter is apparently motor-response locked (compare Fig. 3).

Figure 5 shows a group image SAM analysis of α -ERD in the visual cortex and parietal cortex. No significant ERDs were observed in these cortical areas in other frequency bands (e.g. θ , β , γ). Figure 2 also depicts BOLD-responses that are observed in the proximity of these two cortical areas (also see Table I). The time courses of the maximum α -ERD in the visual and parietal cortex both occur in the range between 450–500 ms after stimulus presentation. Despite the proximity of BOLD-responses and α -ERDs as observed in the group-averaged images (see Euclidian distances in Table I), no statistically significant or trend correlations were found across the entire group between individual BOLD-responses (maximum BOLD-response (max. Z-score) or number of activated voxels

within the masked area) and individual α -ERDs (maximum or mean ERD within the mask) with $P > 0.05$ in each correlation analysis. Notably, we observed a large variability in changes of the MEG and fMRI signal across subjects with a factor of up to 3–5 between the smallest and largest values for both signals. Also, no significant correlations were found between reaction time and α -ERDs or BOLD-responses ($P > 0.05$).

Figure 6 presents group image β - and γ -ERD in the motor cortex together with the BOLD-response in this cortical region (in these two frequency bands, the strongest ERDs have been found in the SAM analysis in the motor area, see Table I). Again, there is good spatial agreement between the BOLD- and the MEG-activity change (see Table I). Analysis of the time course of the two ERDs shows maxima in the range between 400 and 450 ms post-stimulus. Similar to the α -ERD, no significant correlations across group were found between individual BOLD-responses (maximum BOLD-response or number of activated voxels within the mask) and individual α -ERDs (maximum or mean ERD within the mask) with $P > 0.05$ in each correlation analysis. Again, a large variability in changes of the MEG and fMRI signal was observed across subjects with a factor of up to 3–5 between the smallest and largest values for both signals. Also, no significant correlations were found between reaction time on one hand and β -ERD, γ -ERD, or BOLD-responses on the other hand ($P > 0.05$).

Figure 7 shows a group image of ERS in the θ frequency band in the area of the hand motor cortex in the proximity to the positive BOLD-response (left). Another area of θ -ERS is found in the anterior cingulate cortex (ACC) (right). In this area, there is no corresponding positive BOLD-response, rather a negative BOLD-signal is seen which is, however, relatively weak. The maximum of the θ -ERD in the motor cortex occurs at the time of the button press (see Table I) and the maximum of the θ -ERD in the ACC appears around 100 ms later—possibly reflecting response monitoring [Gehring and Fencsik, 2001; Luu et al., 2003]. In the motor cortex as well as ACC, there was again good agreement between MEG-activity changes and BOLD-responses (Table I). However, again we did not find any statistically significant correlations across the entire group

between individual BOLD-responses (maximum BOLD-response or number of activated voxels within the mask) and individual -ERSs (maximum or mean ERS within the mask) with $P > 0.05$ in each correlation analysis. As with the ERDs, we observed again a large variability in changes of the MEG and fMRI signal across subjects with a factor between 3 and 5.

For completeness, we also tested the question whether averaged MEG-activity, i.e., the early transient evoked MEG responses (see Fig. 8) in the visual area or “rebound” ERS in this area are more closely related to the BOLD-signal. However, no significant correlations were found ($P > 0.05$).

Finally, we observed significant correlations between reaction time and -ERSs (see Fig. 9) while again no correlation was between reaction time and BOLD-responses ($P > 0.05$) or ERD ($P > 0.05$). Apart from suggesting that -ERS in the motor area might be more relevant with regard to task performance than ERD in the occipital and parietal cortex, this finding may also indicate that the relationship between brain function and behavior is stronger for direct measures of brain activity (like MEG-measures) as compared to indirect measures of brain activity (like BOLD-measures).

DISCUSSION

The primary aim of this study was to enhance our understanding of the biophysical relationship between the

Figure 8.

MEG event-related SAM (SAMerf) analysis of stimulus-related activity (1–30 Hz) changes ($n = 10$ subjects). The virtual channel time series for each stimulus were averaged (i.e., averaging across single trials) and a sliding window ratio of post- to pre-stimulus power was used to generate functional images. 300 ms sliding time window (center peak at 150 ms post-stimulus) was compared to a fixed 300 ms pre-stimulus window, with log power ratios calculated for each voxel. Individual volumes were normalized to Z-scores and a t-statistic was calculated for group averages ($P < 0.05$, two-tailed).

Figure 9.

Correlation of activity (ERS) and motor response time thresholded at Spearman's $R = -0.7$.

BOLD-response on one hand and ERS and ERD on the other hand. Overall, we found that both ERD and ERS in different frequency ranges are seen in those cortical regions where they were expected from literature [Caplan et al., 2003; De Araujo et al., 2002; Luu and Tucker, 2001; Pfurtscheller and Lopes da Silva, 1999; Toro et al., 1994]. ERD and ERS were found in close proximity to areas where a BOLD-response is seen. The distance between the maxima of group MEG and fMRI changes varied between 15 and 30 mm, which is in the range of the spatial resolution of SAM current source analysis when using an array of 275 sensors. Accordingly, these findings would suggest that there is a measurable correlation between the magnitude of the electromagnetic and BOLD-response in these areas across subjects, which, however, was not found. This negative finding was not entirely unexpected. While several recent studies reported a direct correlation between scalp-recorded EEG or MEG-activity and BOLD-signal [Hinterberger et al., 2003; Horovitz et al., 2004; Laufs et al., 2003; Liebenthal et al., 2003; Nagai et al., 2004], several other studies either failed to detect a correlation or only reported the group-averaged spatial relationship between the activation maxima of the two imaging modalities [Benar et al., 2002; Mulert et al., 2004; Parkes et al., 2004; Salek-Haddadi et al., 2002; Schulz et al., 2004; Tuunanen et al., 2003]. Our results suggest that one major reason for the lack of a direct correlation across subject might be the relatively transient character and high interindividual variability of brain responses as assessed by MEG and fMRI, which for instance, was reported in a similar way by Benar et al. [2002] for interictal spikes. They concluded that improved signal detection strategies may be required. In this context, however, one interesting observation in our study was that reaction time correlated with the MEG-response (θ -ERS) while no comparable correlation was seen with the BOLD-response. This may indicate that

direct measures of brain function, i.e., MEG signals, are more suitable for quantification of brain activity than indirect measures, i.e., BOLD-response signals, which, however, are generally thought to be superior in localizing brain activity.

Given this limitation of a correlation between signal amplitudes of BOLD- and MEG-responses, it is nevertheless interesting to note that apparently corresponding BOLD-signal and MEG-signal changes—as far as localization is concerned—are characterized by complex relationships. Both ERD and ERS (across different frequency bands) can be accompanied by a positive BOLD-response (with the exception that the θ -corresponding BOLD-response in the ACC was negative). Accordingly, our findings point into the same direction as the previously reported findings of Singh et al. [2002] who also described a relationship between positive BOLD-responses on one hand and ERDs on the other hand. Beyond those findings of Singh et al., our results moreover suggest that positive BOLD-responses apparently can be accompanied by a complex sequence of ERSs and ERDs in the very same location. By extension, these findings could suggest that a positive BOLD-signal change may not necessarily require activity synchronization in dentrosomatic components of pyramidal neurons with concomitant generation of LFPs. This means that under conditions of selective attention thalamic input to the cortex may have a sufficient magnitude to induce a BOLD-response (and perhaps increased metabolic demand) that is outpacing the BOLD-response, which exists in the occipital cortex during spontaneously occurring α -frequency oscillations [Laufs et al., 2003]. In this context, we also want to point out that we did not give any indication for high-frequency γ synchronization concomitant with low-frequency α desynchronization as recently reported by Brookes et al. [2005] in the visual cortex or in an analogous way by Mukamel et al. [2005] in the auditory cortex. In fact, in the motor area we even found a parallel desynchronization of low-frequency β activity and high-frequency γ activity. This discrepancy is currently difficult to explain and needs to be further addressed in the future. One possible explanation, however, can largely be excluded, i.e., that the discrepancy between findings is the result of the stimulus modality in our task conditions (flickering versus static stimulus presentation). Those previous studies [Adjamian et al., 2004; Brookes et al., 2005; Hall et al., 2005], which have observed stimulus-induced γ activity in the visual cortex, used static stimuli as we did in our study. One study, which used flickering stimuli [Fawcett et al., 2004], also failed to show induced γ activity. Possibly, one very simple explanation for the discrepancy could be that MEG/SAM is not able to reliably detect γ frequency synchronization because higher frequency oscillations are supported by tighter networks of fewer neurons and therefore may not give a strong enough signal [Pfurtscheller and Lopes da Silva, 1999].

Taken together, our findings indicate that (sequences of) qualitatively different electromagnetic oscillation patterns

correspond to a relatively uniform BOLD-responses, suggesting a more complex relationship between neuronal activity and blood flow than previously thought—a relationship which is not simply grasped by naively using terms like “activation” or “deactivation,” “excitation” or “inhibition” when interpreting task-related BOLD-responses.

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