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EEG-fMRI Reciprocal Functional Neuroimaging

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Abstract

Objective—Integration of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) has been pursued in an effort to achieve greater spatio-temporal resolution of imaging dynamic brain activity. We report a data-driven approach to image spatio-temporal features of neural oscillatory activity and event-related activity from continuously recorded EEG and fMRI signals.

Methods—This approach starts with using the independent component analysis (ICA) to decompose the spatio-temporal EEG data into a linear combination of scalp potential maps and time courses. The time course of each independent component (IC) is used to construct a regressor to fit the fMRI time series. The resultant fMRI map then feeds back as a spatial constraint to the estimation of the source distribution underlying the corresponding IC's scalp map. The estimated source distributions multiplied by the corresponding IC time courses are summed across all ICs, giving rise to the reconstructed spatio-temporal brain activity. Functional connectivity between cortical areas can be further revealed from the imaged source signals using phase synchrony measures. We tested the method using both simulated oscillatory activity and event-related neural activity at various cortical regions. We also used this method to study the alpha-band EEG modulations in an eyes-open-eyes-closed human experiment.

Results—In the simulation study, reliable reconstruction of the localization, time-frequency feature and cortical functional connection were achieved for the simulated oscillatory and event-related activities. In the experimental study, the alpha rhythmic modulation was localized mainly in the occipital visual area and the parieto-occipital sulcus. Within these regions, time-frequency analysis and phase-synchronization analysis indicated increased alpha power and alpha-band phase-synchronization in eyes closed condition versus eyes-open condition.

Conclusion—Our results suggest that the proposed approach is well suited to image continuously oscillatory activities and their functional connectivity.

Significance—Such ability promises to facilitate the investigation of the long-term neural behaviors and large-scale cortical interactions involved in spontaneous brain activity and cognitive tasks.

Keywords

spatio-temporal functional neuroimaging; EEG; fMRI; ICA; source imaging; connectivity

Introduction

Numerous efforts have been made in an attempt to develop high resolution spatio-temporal functional neuroimaging methods in order to better understand brain functions and dysfunctions. EEG (Nunez and Srinivasan, 2005) and magnetoencephalography (MEG)

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(Cohen, 1968; Hämäläinen et al., 1993) respectively measure the scalp electrical potential and magnetic field, generated by neuronal currents. fMRI detects hemodynamic changes accompanying neural activity, most typically through measuring blood oxygen level dependent (BOLD) contrast MR signals (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). It has been widely recognized that EEG/MEG and fMRI are featured with complementary advantages and limitations: high temporal resolution but low spatial resolution for EEG and MEG, in direct opposition to high spatial resolution but low temporal resolution for fMRI (for reviews, see Dale and Halgren, 2001; He and Lian, 2002; He and Liu, 2008).

These complementary features of EEG/MEG and fMRI have motivated the recent attempts of combining EEG/MEG and fMRI to achieve higher spatio-temporal resolution than each individual modality alone. Two methodological strategies have been commonly taken. The first is the fMRI-constrained EEG/MEG source imaging (Liu et al., 1998; Dale et al., 2000; Liu and He, 2008), which uses the fMRI activation map in correlation with tasks as a spatial weighting in the EEG/MEG source analysis carried out at each time instance. However, EEG/MEG and fMRI are generated and measured at significantly different temporal scales. The sluggish fMRI signal may be blind to transient EEG/MEG phenomena and instantaneous EEG/MEG signals may not necessarily arise from all regions highlighted in fMRI (Liu et al., 1998; Liu et al., 2006; Liu and He, 2008). The mismatches between a static fMRI activation map and dynamic EEG/MEG source distributions represent a challenge to constraining EEG/MEG source imaging according to fMRI spatial information. The second strategy is EEG (or MEG)-informed fMRI analysis (Goldman et al., 2002; Laufs et al., 2003; Gotman et al., 2006; Vulliemmoz et al., 2009), which uses EEG to derive temporal regressors applied to obtaining fMRI activation maps in correlation with specific electrophysiological signatures. In most of the previous studies, the temporal regressors are calculated from either a single channel or the global field power of EEG, either of which represents mass response of the underlying brain activation not necessarily well correlated with the temporal behavior of neural activity at a given location where the BOLD signal is being measured. An improved strategy has been developed to use regressors specific to an independent time series derived by applying ICA to EEG signals (Feige et al., 2005; Debener et al., 2006), although such method may fail to differentiate brain regions with signals similar in hemodynamics but different in electrophysiology.

In the present study, we have developed a data-driven method for the integrative analysis of EEG (or MEG) and fMRI, by combining both the EEG (or MEG)-informed fMRI analysis and the fMRI-constrained EEG (or MEG) source imaging. While our proposed method is applicable to either EEG-fMRI or MEG-fMRI integrative analysis, we focus on EEG-fMRI integrative analysis in the present study to illustrate the merits of the proposed method, and shall call the proposed approach the EEG-fMRI reciprocal neuroimaging. The performance of the proposed method is evaluated by a series of computer simulations and in a human study using an eyes-open-eyes-closed paradigm.

Methods and Materials

The key concept of the EEG-fMRI reciprocal neuroimaging is illustrated in Fig. 1. It contains five steps: 1) ICA is applied to multi-channel EEG data to obtain a number of temporally independent ICs. Each IC is represented as a scalp potential map multiplied by a time course. 2) The time course of each IC is used to derive a temporal regressor to obtain an fMRI activation map highlighting the regions in which the hemodynamic time series are in correlation with the regressor. 3) The fMRI activation map, corresponding to each IC, is further used as a spatial prior to constrain the estimation of the source pattern underlying the IC spatial map. 4) The estimated source patterns multiplied by the corresponding IC time courses are summed across all ICs, giving rise to the whole-brain spatio-temporal source reconstruction. 5) Functional

connectivity patterns and event-related source activity can be estimated or extracted from the reconstructed spatio-temporal source imaging.

EEG-fMRI reciprocal neuroimaging algorithm

EEG measurements $\mathbf{Y}$ are modeled by a linear time-invariant system, and linked with neural current density distribution $\mathbf{X}$ as follows

$$\mathbf{Y} = \mathbf{L}\mathbf{X} + \mathbf{B} \quad (1)$$

where $\mathbf{Y}$ is an $N_E \times N_T$ matrix (N_E is the number of scalp electrodes and N_T is the number of temporal sampling points), $\mathbf{X}$ is an $N_X \times N_T$ source matrix (N_X is the number of equivalent current dipoles in an EEG source model), $\mathbf{B}$ is a $N_E \times N_T$ noise matrix, and $\mathbf{L}$ is an $N_E \times N_X$ lead field matrix. The lead field matrix $\mathbf{L}$ can be obtained with the aid of the boundary element method (BEM) (He et al, 1987; Hämäläinen and Sarvas, 1989) and structure MRI. Each column in the lead field matrix represents the scalp potentials generated by a unitary current source at a specific brain location.

ICA is a data-driven technique to divide spatio-temporal signals into groups with maximal temporal independence among the groups. When applied to multi-channel EEG data, it allows for a blind separation of neural activities with independent temporal behaviors (Makeig et al., 2002; Feige et al., 2005; Calhoun et al., 2008). In the present study, the infomax ICA algorithm is employed (Bell and Sejnowski, 1995; Delorme and Makeig, 2004) to decompose the spatio-temporal EEG data into a time-by-space formulation:

$$\mathbf{Y} = \mathbf{Q}\mathbf{W}\mathbf{T} \quad (2)$$

where $\mathbf{Q}$ is an $N_E \times N_E$ matrix, $\mathbf{W}$ is an $N_E \times N_E$ diagonal scaling matrix, and $\mathbf{T}$ is an $N_E \times N_T$ matrix. Equation (2) can be expanded as:

$$\mathbf{Y} = \sum_{i=1}^{N_E} \mathbf{Q}_i w_i \mathbf{T}_i \quad (3)$$

where $\mathbf{Q}_i$ is the i^{th} column i of $\mathbf{Q}$, $\mathbf{T}_i$ is the i^{th} row of $\mathbf{T}$, and w_i is the i^{th} diagonal element of $\mathbf{W}$. Equation (3) suggests that the EEG data $\mathbf{Y}$ can be formulated as a weighted superposition of a series of scalp potential maps $\mathbf{Q}_i$ multiplied by associated time courses $\mathbf{T}_i$. The temporal component $\mathbf{T}_i$, in principle, is statistically independent with each other. The temporal, spectral and spatial characteristics of the components have been widely used to identify and remove artifactual components corresponding to eye, muscle and recording artifacts in EEG (Jung et al., 2000; Iriarte et al., 2003; Urrestarazu, et al., 2004). In addition of artifact deduction, we can further separate brain electrophysiological sources by selecting ICs with spatial or time-frequency features associated with certain aspects of neural activities (Makeig et al., 2002; Nam et al., 2002; Debener et al., 2005, 2006). Assuming N out of N_E ICs are selected as source components, the EEG measurement generated by brain source activities can be rewritten as

$$\mathbf{Y} = \sum_{i=1}^N \mathbf{Q}_i w_i \mathbf{T}_i$$

Detailed component selection will be discussed in the simulation and experiment section.

In the present study, we assume a linear neurovascular coupling relationship, where the BOLD fMRI response is modeled by the power of local synaptic current convolved with a canonical hemodynamic response function (HRF) (Liu and He, 2008). From $\mathbf{T}_i$ of each IC, an fMRI regressor $\mathbf{F}_i$ can be derived as:

$$\mathbf{F}_i = g(\mathbf{T}_i) \otimes \text{HRF} \quad (4)$$

where $g(\mathbf{T}_i)$ is a function of $\mathbf{T}_i$, representing the functional linkage between the neural signal and fMRI signal. In this study, the power of neural activity ($g(\mathbf{T}_i) = \mathbf{T}_i^2$) and band-pass filtered

activity ($g(\mathbf{T}_i) = \sum_{f=\min}^{\max} \mathbf{P}_i(f, t)$, where $\mathbf{P}_i(f, t)$ spectral power at frequency f and time t) were used in analysis, although various linear or nonlinear neurovascular coupling models (Büchel et al., 1998; Kilner et al., 2005; Mukamel et al., 2005) can be easily incorporated by defining the function $g(\mathbf{T}_i)$.

Fitting each $\mathbf{F}_i$ to fMRI time series at every cortical voxel using general linear model (GLM) analysis gives rise to a map $\mathbf{R}_i$ that highlights the regions, in which the hemodynamic response (or modulation) is temporally consistent with the electrophysiological response (or modulation) of the i -th IC of EEG (Bandettini et al., 1992; Friston et al., 1995; Friston et al., 1998). The IC-specific fMRI map $\mathbf{R}_i$ can be represented by a $N_X \times 1$ vector, and integrated with IC scalp map $\mathbf{Q}_i$ through an fMRI-weighted EEG inverse calculation. The absolute value of each element in $\mathbf{R}_i$ represents the fMRI weighting assigned to an equivalent dipole according to the voxel it belongs to. Knowing lead field matrix $\mathbf{L}$, EEG topography $\mathbf{Q}_i$ and fMRI weighting $\mathbf{R}_i$, we can derive an IC-specific source estimation $\hat{\mathbf{S}}_i$ ($i = 1 \sim N$) by solving an optimization problem:

$$\begin{aligned} \min \quad & \|\mathbf{L}\hat{\mathbf{S}}_i - \mathbf{Q}_i\|^2 + \lambda^2 \|\mathbf{C}_s^{-1}\hat{\mathbf{S}}_i\|^2 \\ \hat{\mathbf{S}}_i = & (\mathbf{L}^T \mathbf{L} + \lambda^2 \mathbf{C}^T \mathbf{C})^{-1} \mathbf{L}^T \mathbf{Q}_i \\ \mathbf{C} = & \frac{1}{C_s} \text{diag}\left(\frac{1}{|R_i|}\right) \end{aligned} \quad (5)$$

where λ is a regularization parameter estimated using L-curve function (Hansen and O'Leary, 1993), and $\mathbf{C}_s$ is an $N_X \times N_X$ source covariance matrix, where the i -th diagonal element incorporates the fMRI weighting (Dale and Sereno, 1993; Liu et al., 1998; Liu and He, 2008). $\mathbf{Q}_i$ as an IC topography, because of the linear relationship between the scalp measurement and underlying neural activities described in Eq. (1), can be formulated by the product of lead field matrix $\mathbf{L}$ and estimated IC source distribution $\hat{\mathbf{S}}_i$. Thus, Eq. (3) can be written as:

$$\mathbf{Y} = \sum_{i=1}^N (\mathbf{L}\hat{\mathbf{S}}_i) w_i \mathbf{T}_i = \mathbf{L} \left(\sum_{i=1}^N \hat{\mathbf{S}}_i w_i \mathbf{T}_i \right) \quad (6)$$

Combining Eq. (1) and (6), the spatio-temporal source activity $\hat{\mathbf{X}}$ can be derived as:

$$\hat{\mathbf{X}} = \sum_{i=1}^N \hat{\mathbf{S}}_i \mathbf{W}_i \mathbf{T}_i \quad (7)$$

Equation (7) suggests that the reconstruction of the spatio-temporal neural activity can be equivalently formulated as a weighted summation of the estimated source spatial distributions $\hat{\mathbf{S}}_i$ multiplied with the corresponding IC time courses $\mathbf{T}_i$.

The reconstructed spatio-temporal source activity $\hat{\mathbf{X}}$ is a $N_X \times N_T$ matrix, which covers every brain voxels and every recording time point. It can be further utilized to investigate large-scale and long-term neural communications. We employed the calculation of the phase synchronization value (PSV) to estimate brain functional connectivity between different regions (Lachaux et al., 1999, 2000; Rodriguez et al., 1999). Assuming time courses $\hat{\mathbf{X}}_a$ (row a of the matrix $\hat{\mathbf{X}}$) and $\hat{\mathbf{X}}_b$ (row b of $\hat{\mathbf{X}}$) are extracted from two cortical regions, the PSV analysis starts with filtering the time courses with Morlet wavelets (Lachaux et al., 1999; Lin et al., 2004), and the outcomes of which are time-frequency complex $W_a(t, f)$ and $W_b(t, f)$. The phase difference $\theta_{a-b}(t, f)$ between the cortical regions a and b can be calculated by (Lachaux et al., 1999):

$$\begin{aligned} \theta_{a-b}(t, f) &= \varphi_a(t, f) - \varphi_b(t, f) \\ \varphi_i(t, f) &= \tan^{-1} [\text{Im}(W_i(t, f)) / \text{Re}(W_i(t, f))] \end{aligned} \quad (8)$$

where $\varphi_i(t, f)$ is the estimated phase value at a cortical voxel, Im indicates the imaginary part of the complex number, and Re indicates the real part of the complex number. In continuous data, PSV has been proposed as a numerical indicator of functional connectivity, which calculates the variability of phase difference between two time series across successive time-window δ (Lachaux et al., 2000). PSV can be defined as a function of time t and frequency f as:

$$PSV(t, f) = \frac{1}{\delta} \int_{t-\frac{\delta}{2}}^{t+\frac{\delta}{2}} \exp(j\theta_{a-b}(\tau, f)) d\tau = \frac{1}{\delta} \sum_{t-\frac{\delta}{2}}^{t+\frac{\delta}{2}} \exp(j\theta_{a-b}(\tau, f)) \quad (9)$$

The significance test can be conducted by randomly generating a group of new time series and calculating the PSV between the new series and the original signal (Lachaux et al., 1999, 2000). The proportion of these PSVs higher than the original PSV at time t indicates the chance of false positive for a significance level (Lachaux et al., 1999, 2000).

Computer Simulations

Computer simulations were conducted to evaluate the performance of the proposed method in two aspects: (1) mapping continuously oscillatory neural activity, and evaluating the long-term and large-scale inter-cortical functional connectivity, and (2) imaging event-related neural responses.

In the computer simulations, we used a realistically shaped BEM model constructed from a human high resolution anatomical T1 images ($1 \times 1 \times 1 \text{ mm}^3$). The head volume was separated into three compartments: the brain, the skull and the scalp. Their conductivity values were set to be 0.33 S/m, 0.0165 S/m and 0.33 S/m, respectively (Lai et al., 2005; Zhang et al., 2006).

To model the neuronal distribution, a cortical current density source model was used. Several thousand equivalent current dipoles were positioned evenly on the folded cortical surface (Dale and Sereno, 1993). The orientations of the dipoles were fixed to be perpendicular to local cortical surface.

In the first simulation, nine sources belonging to three functional networks were generated (Fig. 2A). These simulated source locations have been reported to be largely involved in neural oscillatory activities (Laufs et al., 2003; Mantini et al., 2007). Ninety-second waveforms with dominant alpha or beta oscillations were assigned to the nine sources (see Fig. 2 for details). As illustrated in Fig. 2B, sources had synchronized temporal oscillations within the same network, but were temporally de-synchronized across different networks. The 9th source was simulated as a confounding source. It was assigned a waveform with same dominant oscillatory frequency and modulation pattern with the sources in network 1. But it was de-synchronized with any other sources during the entire time period. From the simulated source locations and waveforms, scalp EEG signals were simulated and sampled every 1 millisecond. Gaussian white noise with maximum signal-to-noise-ratio (SNR) of 3 (mean SNR of 0.5) was added to the simulated EEG signals (Fig. 2C). The BOLD fMRI signal was generated at every brain voxel by convolving the simulated source power with an HRF function. Gaussian white noise with maximum SNR of 10 (mean SNR of 3) was added to the simulated fMRI signal as well as other brain voxels where there are no neural activities. ICA was applied to decompose the simulated EEG data. Those ICs with topographies not satisfying the discrete Picard condition (Hansen 1990) were assumed to be dominated by recording noise and thereby were removed. Visual inspection was conducted to assist the component selection. The total power ($f(\mathbf{T}_i) = \mathbf{T}_i^2$) of each source IC was fitted into a GLM fMRI analysis. A statistical threshold with $p < 0.005$ was used. After the stepwise source reconstruction, the spatial locations, time-frequency features and connectivity patterns were compared with the simulation setting.

In the second simulation, three current dipoles (Fig. 2D) were placed at discrete cortical regions along the right hemisphere visual pathway. Typical waveforms were assigned to these dipoles to simulate event-related responses. The source waveforms were repeated twice per second during 30-second task blocks (Fig. 2E) interleaved with 30-second control blocks during which alpha band oscillations (8 – 12 Hz) were randomly generated. Scalp EEG was simulated based on the source configuration and Gaussian white noise was added the same way as described in the 1st simulation (Fig. 2F). Event-related source activities were estimated from the simulated fMRI and EEG data by using the proposed method, in comparison with the simulation setting.

Eyes-open-eyes-closed experiment

To further assess the performance of the proposed approach in imaging continuously oscillatory activity, we conducted a pilot human experiment using an eyes-open-eyes-closed paradigm. A healthy subject (male, age 27) was recruited to participate in the human experiment under the approval of the Institutional Review Board at the University of Minnesota. Written informed consent was obtained before the experiment. During a period of 3.5 minutes, the subject laid quietly in the dark MR scanner. EEG recording and fMRI scanning started with the subject's eyes closed. Every 30 seconds, the subject was given an aural signal to open or close his eyes. In the eyes-open conditions, the subject was instructed to gaze at a central fixation point.

During the experiment, EEG and fMRI data were simultaneously acquired. The MRI and fMRI data were collected on a 3-T MRI system (Siemens TrioTim, Siemens, Germany). The high resolution anatomical MRI dataset was acquired using the following parameters: TR/TE = 2530ms/4ms, voxel size = $1 \times 1 \times 1 \text{ mm}^3$. The T2*-weighted functional images were acquired from 24 slices covering the whole brain using the following parameters: TR/TE = 1200ms/

30ms, voxel size = $3 \times 3 \times 4\text{mm}^3$, flip angle = 45. The fMRI images were sequentially subjected to the slice scan time correction, motion correction, spatial smoothing (FWHM = 4) and high-pass temporal filtering (BrainVoyager QX, Brain Innovation, Netherlands). EEG signals were collected using a 64-channel MR-compatible system (BrainAmp MR 64 plus, BrainProducts, Germany) and referenced at FCZ. The data sampling rate was 1000 Hz. Gradient artifact and cardiac ballistic artifact were removed from the raw EEG data by means of template subtraction (Vision Analyzer, Brain Products, Germany). The EEG data were then down-sampled (250 Hz) and band-pass filtered (1 ~ 30 Hz).

It is well known that alpha-band EEG signal changes most predominantly in eyes-closed condition versus eyes-open condition. This study design thereby experimentally generates a modulation of oscillatory activity. To image the spatial and temporal patterns of this rhythmic modulation, we selected ICs showing alpha-band spectral power modulation with above-average correlation with the experimental paradigm. The power of each 8-12-Hz-band-pass filtered IC time course was used to calculate the fMRI regressor. fMRI data was preprocessed for the volume time correction, motion correction, spatial smoothing (FWHM=4mm), and high-pass filtering using BrainVoyager QX (Brain Innovation, Netherlands). The regressor derived from each IC was fitted into a GLM fMRI analysis. A statistical threshold with $p < 0.005$ was used. The spatial and temporal patterns of the oscillatory activity modulated by the alternation of the eyes-open and eyes-closed conditions were reconstructed. The cortical synchrony between different voxels was estimated.

Results

Continuously oscillatory activity

In the first simulation, five source ICs were derived after noisy components were excluded. Each IC was represented by a spatial map (Fig. 3A, right) and a time course, from which the spectrogram (the signal power as a function of time and frequency) was calculated by a wavelet-based time-frequency analysis (Fig. 3A, left). The spatial map of each IC was consistent with a certain combination of the scalp potential maps generated by individual sources. As such, an IC scalp potential map was a superposition of a subset of the simulated sources. The oscillatory signal modulations were revealed by the spectrograms: alpha-band oscillations from posterior and medial frontal channels; beta-band oscillations from central parietal channels. These rhythmic signal modulations were in agreement with the simulation setting (illustrated in Fig. 2B).

fMRI regressors (Fig. 3B) were derived from the IC time courses. The regressors corresponding to the first three ICs (Fig. 3B orange box) and the 4th and 5th ICs (Fig. 3B blue box) showed similar patterns, regardless of their temporal independence captured by EEG in a fine time scale. As a result, the fMRI maps in correlation with similar regressors derived from distinct ICs showed almost identical populations of neural sources. For instance, the fMRI map corresponding to the 1st IC (Fig. 3C, red-to-yellow color bar) showed a spatial pattern covering the posterior and frontal cortical regions, which was similar with the fMRI maps specific to the 2nd and 3rd ICs (not shown). The fMRI maps corresponding to the 5th (Fig. 3C dark-blue-to-light-blue color bar) and 4th (not shown) ICs identified the same central parietal cortical regions. These results indicate that the IC-related fMRI maps lack the ability to distinguish sources with independent neuronal temporal features but similar hemodynamic temporal dynamics. The lack of temporal specificity of fMRI signals resulted in the lack of spatial specificity of the IC-related fMRI maps.

Each above mentioned fMRI map related to each IC was applied as a spatial constraint to the reconstruction of the cortical current density distribution that generated the associated IC scalp potential map. The estimated source distributions (Fig. 3D) inherited high spatial resolution

from fMRI signal. Furthermore, it was possible to distinguish neural activity generated by distinct ICs (color coded in Fig. 3D), which failed to be clarified by IC-informed fMRI analysis (Fig. 3C).

A spatio-temporal brain imaging was achieved by combining the spatial and temporal estimates derived from EEG and fMRI. A fast Fourier transformation (FFT) implemented in Matlab (Mathworks, Natick, USA) was used to transform the estimated time series at each cortical voxel to a frequency spectrum. The magnitudes of 8-12 Hz and 12-28 Hz components were summed, giving rise to the cortical distributions of the alpha-band (Fig. 4A, red-to-yellow color bar) and beta-band power (Fig. 4A, dark-blue-to-light-blue color bar), respectively. Spectrograms extracted at simulated source locations (Fig. 4A) successfully reveal the rhythmic modulation patterns consistent with the simulation settings.

We further evaluated the inter-cortical synchronization by extracting the time course from a seed region (region 1 as illustrated in Fig. 2A; red line circled in Fig. 4A) and then computing the phase relations between this time course and those from other regions of interest (ROIs) (regions 2-9 as illustrated in Fig. 2A). The phase plot (Fig. 4B, left) indicates -0.3π phase difference between the seed region and the 6th ROI within the alpha band. The PSV curve at 11 Hz (Fig. 4B, bottom) passed the 1% significant test (Fig. 4B, red dotted line), which demonstrates a significant phase-synchronization between these two regions during periods of 5s~35s and 55s~85s. De-synchronization between the seed point and the 7th (Fig. 4C) and 9th ROIs (Fig. 4D) were also reflected in the corresponding PSV estimates, which were both under the significance level. Collectively, these results render a functional connectivity pattern (Fig. 4A, middle panel): ROIs 2-6 (Fig. 4A connected with the seed region by solid lines) were synchronized with the seed region during the simulated “Sync” blocks, and the ROIs 7-9 (Fig. 4A, connected with the seed region by dotted lines) were de-synchronized with the seed region over time. The results reconstruct the functional synchronization pattern between sources in agreement with the simulation settings. Particularly, the 9th ROI was simulated as a confounding source. It was designed with same oscillatory frequency and modulation pattern with the seed region and ROIs 2-6, but was de-synchronised with any other sources. Our results were able to reconstruct the similar time-frequency features of this confounding source and other sources (seed region and ROIs 2-6). Furthermore, the results successfully distinguished the functional independence between the confounding source and all the other sources.

Event-related neural responses

In the second simulation, temporally uncorrelated source waveforms (Fig. 5B cross lines) were assigned to the three cortical locations as illustrated in Fig. 2D. Time delays between these event-related waveforms were used to model their different responding times. Event-related source waveforms and distributions were derived by averaging the estimated spatio-temporal activities with respect to the event onsets. Fig. 5A shows the event-related cortical source distributions at three peak latencies. The cortical voxels with maximal amplitudes in these spatial source distributions at the peak latencies were defined as estimated source locations. Fig. 5B plots the event-related waveforms (solid lines) at the estimated source locations in comparison with the real source waveforms (cross lines). The spatial patterns, as well as the temporal morphology of the real sources, were well retained in the estimated event-related source activity. The localization errors (i.e. the distance between the estimated source locations and the simulated locations) were 2.69, 1.75 and 0.90 mm for the three sources, respectively. These results suggest high spatial specificity and high temporal precision of the proposed approach in imaging the event-related source activity.

To further evaluate the proposed approach in various conditions, we assigned a variety of other waveforms to the three simulated dipoles, as used in (Liu and He, 2008). We derived 1.82 ± 0.77 mm localization errors for these conditions. Event-related waveforms were reconstructed at

estimated source locations for temporally correlated sources (Fig. 5C), transient neural activity (Fig. 5D), rhythmic oscillations (Fig. 5E and 5F), and waveforms gained from real human data (Fig. 5G). For all these source configurations, the results indicate tight correlations between the estimated temporal dynamics and the real source waveforms. Temporal information, including the shape, timing, phase and frequency, were reconstructed with high precision.

Furthermore, these results imply high robustness of the proposed approach against white noise. Temporal fluctuations existed in estimated waveforms caused by noise in a previous study (Liu and He, 2008) did not exist in the reconstructed results in this simulation.

Experimental results

As shown in Fig. 6A, six ICs drawn from EEG data showed alpha spectral power modulated by the eyes-open-eyes-closed experimental paradigm. These selected ICs and the simultaneously recorded fMRI data were used to image the spatio-temporal pattern of the task-induced alpha modulation. In order to display the alpha spectral power distribution, we calculated FFT on the estimated time course at each voxel, and plotted the resultant alpha band spectral power on the inflated cortical surface (Fig. 6B). The alpha activity was mainly originated from the occipital visual area, the parieto-occipital sulcus and in part from the precentral gyrus of the right hemisphere. The estimated cortical location of the alpha modulation is consistent with previously reported fMRI and EEG/MEG studies (Gross et al., 2001; Goldman et al., 2002; Laufs et al., 2003; Feige et al., 2005;). Detailed 3.5-minute long temporal information can be drawn from arbitrary cortical voxels. For instance, spectrograms were plotted for two ROIs (Fig. 6B, green circled) located on the left hemisphere (Fig. 6C) and right hemisphere (Fig. 6D). Both of the highlighted ROIs show alpha activity increased in eyes-closed conditions versus eyes-open conditions. The time-frequency phase relation (Fig. 6E) and the 8-12 Hz PSV curves (Fig. 6F) show increased phase-synchronization in the alpha-band between the two ROIs in the eyes closed conditions. The increased synchronization was also observed between other imaged regions, but was not shown here.

Discussion

EEG-fMRI “reciprocal” imaging

In the present study, we have proposed the EEG-fMRI reciprocal neuroimaging approach. The “reciprocal” procedure here indicates the sequential use of EEG-informed fMRI imaging and fMRI-constrained EEG source imaging to integrate EEG and fMRI. Our pilot simulation and experimental results have demonstrated that the present method is well suited for analyzing electrophysiological oscillatory activities and their modulation patterns. The high resolution spatio-temporal imaging of the continuous neural activity will allow us to further investigate long-term neural activities and large-scale neural interactions underlying various brain conditions.

The integration of EEG and fMRI signals lies in the coupling between electrophysiological response and hemodynamic response. To examine this, recent studies have conducted parallel (or simultaneous) measurements of intracranial EEG and BOLD fMRI. Their results revealed significant correlation between BOLD signal and local field potential (LFP) in different brain areas (Arthurs et al., 2000; Logthetis et al., 2001; Mukamel et al., 2005). Studies have also been conducted to demonstrate that a spatially localized BOLD increase (or decrease) can be accompanied by the regional modulation of oscillatory activities measured in LFP (Mukamel et al., 2005). In line with these studies, a tight coupling relationship with BOLD has also been suggested in EEG recordings (Singh et al., 2003; Oakes et al., 2004), which are believed to share the common electrophysiological sources with LFP signals. As such, it is reasonable to assume the temporal and spatial correspondence between the EEG source and fMRI source.

According to this assumption, the present method is based upon a biophysical model, which assumes (1) the temporal independence between groups of neural sources, based on which ICA is applied to un-mix sources; (2) the temporal coupling between the neural electrophysiological signal and BOLD signal, based on which EEG-informed fMRI analysis is conducted to define IC-related hemodynamic response; and (3) the spatial correspondence between EEG and fMRI sources, based on which fMRI-constrained EEG source imaging is used to reconstruct the IC-specific source distribution.

Source separation and space-time separation

ICA used in the present study has been considered as a tool to divide activated neural regions into groups, with temporal behaviors coherent within each group but independent across groups (Makeig et al., 2002). Importantly, it also serves to decompose spatio-temporal signals into representations in a time-by-space format, which allows for a separation of the temporal and spatial aspects of neural activity (Calhoun et al., 2006; Mantini et al., 2007). Previous studies imply that the linear neurovascular coupling can be applied to the interpretation of the temporal relationship between EEG IC time series and BOLD fMRI response (Feige et al., 2005; Debener et al., 2006; Calhoun et al., 2008; Eichele et al., 2009). Spatial correspondence has also been reported between the EEG IC spatial features and fMRI maps (Debener et al., 2005). Taking advantage of ICA, the proposed approach can target a single group of sources at a time. A time-space-separated strategy can be utilized, through which EEG and fMRI signals are related in the time domain and in the spatial domain separately. The present method is also computationally efficient. Traditional spatiotemporal imaging methods usually conduct an inverse calculation at each time instant (Liu et al., 1998; Lin et al., 2004) or at each brain voxel (Gross et al., 2001), which may need a large number of inverse calculations to derive a continuous spatiotemporal imaging. The present method, in contrast, allows the imaging of long-term neural activity with very limited number, which equals to the number of selected ICs, of inverse calculations.

The interpretation of components derived from ICA analysis remains an important problem in many ICA related studies. Studies have used ICA to identify components related to recording artifacts and physiological noise (Jung et al., 2000; Iriarte et al., 2003; Urrestarazu, et al., 2004), and more importantly, components corresponding to physiological sources, such as the modulation of rhythmic activities (Feige et al., 2005; Nam et al., 2002) and single-trial neural activities (Makeig et al., 2002; Debener et al., 2005, 2006). In the current study, we selected components according to their spatial and time-frequency features. Artifactual components were rejected and physiological-meaningful components associated to the modulation of rhythmic activities and event related activities were identified and used for source analysis. The IC selection criterion can be changed according to different experimental designs and different aspects of neural activities. The criterion should be carefully designed and further investigation is needed to establish criteria for interpreting physiologically meaningful ICs.

EEG-informed fMRI analysis

The EEG-informed fMRI analysis used in the present method allows us to selectively localize hemodynamic correlates to certain EEG temporal features. It is capable of identifying the spatial patterns of long-term oscillatory modulations as well as transient neural responses (Makeig et al., 2002; Feige et al., 2005; Debener et al., 2006). A linear neurovascular coupling is assumed in the present study to relate the IC time course to fMRI signals. However, the present method is not limited to a single neurovascular coupling assumption. It could be generalized to any linear or non-linear neurovascular coupling models by deriving fMRI regressors from various mathematical models (Büchel et al., 1998; Kilner et al., 2005; Mukamel et al., 2005). Similarly, although a canonical HRF is assumed in the present study, this method

can incorporate different location- or frequency- (de Munck, et al., 2007) or pathology-dependent (Gotman, et al., 2006) HRFs.

EEG-informed fMRI analysis is an important tool to investigate neural activities in task-free conditions, such as spontaneous neural activities in the resting brain (Laufs et al., 2008). Recent studies have pointed out the significance of spontaneous neural activity. It consumes a large portion of the brain's energy, and may contribute to or be suspended by goal-directed tasks (Raichle et al., 2001; Fox and Raichle, 2007). Spontaneous oscillations have been known as one of the most prominent EEG phenomena in the resting brain. They have been found to be correlated with large-scale resting state brain networks (Laufs et al., 2003; Mantini et al., 2007). The present approach, taking advantage of the EEG-informed fMRI analysis, is suited to study this critical spontaneous neural activity. In our experiment, we experimentally generated the alpha oscillatory modulation. The results demonstrated that this method is capable of imaging the oscillatory activities and their temporal modulation patterns. The spatial distribution, temporal dynamics, and modulation of cortical synchronization of the oscillatory activity were successfully reconstructed.

However, it is argued that EEG-informed fMRI analysis alone may impose insufficient spatial constraints on physically plausible source locations (Bledowski et al., 2007). This limitation originates from the inherent difference in the temporal resolutions between the two modalities. As our results suggest (Fig. 3C), fMRI signals lack of temporal specificity to differentiate neural regions, of which the temporal patterns are similar in hemodynamics but different in electrophysiology.

fMRI-constrained EEG source imaging

In the present approach, we incorporate the spatial information from EEG to achieve higher spatial specificity than that can be derived by fMRI alone. Our results demonstrate that brain regions indistinguishable through EEG-informed fMRI analysis can be differentiated through the subsequent step of the fMRI-constrained source imaging (Fig. 3D).

It is important to note that the fMRI constraint is used in a different way from most previous fMRI-constrained EEG source imaging methods. In the majority of other studies, the task- or stimulus-related fMRI spatial prior remains static, and is related to the EEG scalp potential pattern, which varies during the continuous recording time or event-related period (Liu et al., 1998; Lin et al., 2004). Constraining the solutions to a dynamic estimation problem by a static spatial prior faces the challenge of the lack of correspondence (or mismatch) between the constraint and the solution (Liu et al., 2006; Liu and He, 2008). In contrast, in the present study, a static fMRI map is used to constrain the source estimation for a static EEG map. For each IC, the EEG-informed fMRI map and the associated IC scalp map reflect and only reflect the static spatial distribution of the source. The fMRI time course and EEG IC time course carry and only carry the temporal information. This time-space-separated strategy is able to model the integration between EEG and fMRI in the time domain and in the spatial domain separately. It better resolves the temporal mismatch problem between the two signals.

The proposed imaging framework further allows the integration of a different fMRI-weighted EEG imaging algorithm. Various fMRI-weighted EEG source imaging techniques have been developed based on the findings in both animal and human experimental studies that the EEG and fMRI signals are closely associated with each other (Logothetis et al., 2001; Debener et al., 2005; Arthurs et al., 2000; Mukamel et al., 2005). However, EEG and fMRI measure different aspects of neural activities. EEG sources can be invisible in fMRI and fMRI sources can be invisible in EEG (Liu et al., 2006; He and Liu, 2008; Liu and He, 2008). To enhance robustness of the source imaging against EEG-fMRI mismatch, recent studies have developed fMRI-constrained source imaging algorithms using partial fMRI weighting (Liu et al., 1998;

Dale, et al., 2000), or EEG-fMRI-combined weighting (Liu and He, 2008). This issue of mismatch could also possibly happen between corresponding IC topography and IC-informed fMRI map, and can be solved by incorporating a mismatch-robust fMRI-constrained EEG source imaging technique (Liu et al., 1998; Liu and He, 2008) in the step of fMRI-constrained IC source localization.

Spatio-temporal imaging in long-term and event-related time scales

The combination of the spatial and temporal estimates gives a whole-brain spatio-temporal map. If ICA is considered a process of separation in the sensor level, the proposed approach can be considered an inverse process of combination in the source level. ICA has been known for its capability of blind source separation. However, ICA decomposes signals to achieve maximal independence but not absolute independence. As such, one component may contain multiple sources with similar modulation patterns, and one source may be separated into two components as what have been shown in the results section. Assuming one IC represents the activity of a single source may not be valid. That is why the proposed method with a step of source re-combination and time-space recombination is particularly important. By means of the re-combination, a source, which may be separated into two ICs, can be combined in the source space into one source again.

This step of re-mixing makes the proposed method particularly suited to study whole-brain continuously oscillatory activity and the functional linkage between distant cortical regions. Source distributions in millimeter spatial scale can be plotted at each time instant, and the time series in millisecond temporal scale can be drawn from arbitrary cortical voxels. This high-resolution spatio-temporal whole-brain mapping is especially desired for long-term brain connectivity analysis. Recently, fMRI signals have been used to investigate neural networks (Buchel and Friston, 1997; Fox et al., 2005). However, the slow evolvement of hemodynamic signal is incapable of capturing neural communication happening at a millisecond time scale. EEG/MEG signals and EEG/MEG source imaging techniques have also been used to estimate the neural communication in various conditions (Gross et al., 2001, 2004; Astolfi et al., 2004; Babiloni et al., 2005; Ding et al., 2007). However, EEG/MEG based connectivity studies suffer from the low spatial resolution of the non-invasive electromagnetic measurements. The present method, in contrast, provides high resolution in both time and space. Using this method, we were able to reconstruct the cortical rhythmic oscillations and their phase relations from simulated data and real human data. This ability of the proposed technique can be further applied to various neuroscience studies, which focus on continuous or single-trial neural activity.

More significantly, the present method allows us to focus the source imaging on certain modulation patterns of oscillatory activity, instead of the oscillatory activity itself as in some spectral imaging algorithms (e.g. Gross et al., 2001; Lin et al. 2004; Yuan et al., 2008). This distinguishing feature is achieved by only selecting ICs with modulation patterns of interest into the source reconstruction. For example, in the present study, we selectively estimated the source activity generating the ICs that showed alpha-band modulation in correlation with the experimental paradigm, whereas other background alpha signals independent of the task were excluded. This capability of extracting and imaging neural rhythmic modulation may be used to investigate the correspondence between the neural modulation and the performance of cognitive task (Vanni et al., 1997), the change of attentional load (Gross et al., 2004), and the variation of behavior states (Harris-Warrick and Marder, 1991; Feige et al., 2005) etc. It may also be used to separate the modulations of alpha rhythm, beta rhythm, and gamma rhythm, which may reflect different neural process in cognitive tasks or in resting states.

The present approach could also be generalized to study event-related neural responses. Our results indicate (Fig. 5) that event-related activity can be derived at an arbitrary brain voxel by

averaging the continuously estimated source time course. It differs from the conventional event related potential analysis by conducting temporal averaging in the source space rather than in the sensor space. As such, we can visualize phase-locked source ERP, and at the same time preserve non-phase-locked single-trial variation in the source space. In addition, the noise robustness of the present method was also demonstrated by the present promising results. ICA, although mainly used for the source separation and space-time separation, also serves as a spatio-temporal “filter” for the noise reduction.

Cortical alpha modulation

In our human experiment, we found the eyes-open-eyes-closed-modulated alpha rhythm mainly originated from the parieto-occipital cortex. This spatial distribution generally agrees with some previous EEG-fMRI (Goldman et al., 2002; Laufs et al., 2003; Feige et al., 2005) and EEG/MEG studies (He and Musha, 1992; Hari et al., 1997; Gross et al., 2001). At these cortical regions, the alpha amplitude and phase-synchronization increases in the eyes-closed conditions relative to the eyes-open conditions. It is important to point out that the amplitude and phase-synchronization are two separate measures of the alpha activity. In the calculation of the phase-synchronization between two ROIs, the amplitude difference does not influence the computation of phase-synchronization.

Previous studies have suggested that visual attention network communicates by neural phase-synchronization (Gross et al., 2004; Womelsdorf et al., 2007). In accompany with the visual attentional variation, alpha modulation has been consistently observed in parieto-occipital brain (Foxe et al., 1998; Worden et al., 2000). In line with these studies, the modulation of the alpha phase-synchronization observed in this study may suggest a significant change of visual attentional demands in the parieto-occipital network. The eyes-closed resting state requires minimum demand of visual attention, and the parieto-occipital network is characterized by high synchrony across hemispheres. Such inter-hemispherical synchrony may be suppressed with eyes open, as neurons responsible to different visual fields may compete for attentional resources even in the absence of visual stimuli (Smith et al., 2000). This hypothesis, although being speculative, does provide a plausible interpretation on our data that alpha amplitudes and phase-synchronization were larger during eye-closed periods than during eye-open periods.

Conclusion

In the present study, we have developed an EEG-fMRI “reciprocal” integrated imaging method, which utilizes the techniques of ICA, EEG-informed fMRI analysis, and fMRI-constrained EEG source imaging. The present approach offers a principled framework to integrate fMRI and EEG, and promises to provide high resolution and precision in both time and space. A unique contribution of the present approach lies in its capability of imaging continuously oscillatory activities and their functional connectivity. This technique is especially suited to study long-term and large-scale coherent neural behaviors in cognitive tasks or in resting states. It allows us to study various neuroscience problems, such as the localization of spontaneous or task-induced neural oscillations and their modulation patterns; the investigation of temporal dynamics at arbitrary cortical ROIs; and the characterization of inter-cortical functional connectivity and networks. The present method can also be applied to study event-related neural activity.

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Fig.1.

Diagram of the proposed EEG-fMRI reciprocal neuroimaging. (1) ICA; (2) IC informed fMRI analysis; (3) fMRI-constrained IC source imaging; (4) Source combination; (5) Functional connectivity and event-related analysis.

Fig. 2.

Illustration of the settings in the 1st (A, B, C) and 2nd (D, E, F) simulations. (A) Nine sources (number labeled) with three networks (color coded). (B) Synchronization patterns within and across of these three networks: sources within each network were synchronized during the “Sync” blocks and de-synchronized in the control blocks. In the 1st network (red), 11-Hz EEG signal extracted from a resting eyes-closed experiment was assigned to source 1. It was further shifted for certain phase delays and assigned to the sources 2-6. Sources in network 2 (green) were synchronized at 17 Hz. The source 9 in network 3 (blue) was designed as a confounding source. It was assigned an 11-Hz signal notch-pass filtered from a Gaussian white noise. (C) An example of source and EEG waveforms during 10~12s. To show the waveforms clearly, only source waveforms from 4 ROIs and EEG waveforms from randomly selected 16 channels were plotted. (D) Cortical locations of three current dipole sources. (E) Simulated paradigm including three 30-s task blocks interleaved by four 30-s control blocks. During a task block, the stimulus (red arrow) was repeated every 500 ms to induce repeated single-trial responses. (F) An example of source and EEG waveforms during 30-32s. EEG waveforms from randomly selected 16 posterior channels were plotted.

Fig. 3.

Intermediate results of simulation 1. (A) IC scalp potential maps (right column) and spectrograms of the IC time courses (left column). The first three ICs show alpha-band oscillation, and the other two ICs show beta-band oscillation. (B) fMRI regressors derived from IC time courses. The regressors in the orange box and blue box share similar temporal patterns. (C) IC informed fMRI maps corresponding to the 1st (red color bar) and 5th ICs (blue color bar). The fMRI map in correlation with the 1st IC highlights posterior and medial frontal brain regions. The fMRI map in correlation with the 5th IC shows central parietal response. (D) fMRI-constrained EEG source imaging of the selected ICs. The source distributions corresponding to the five ICs are illustrated in different colors according to the color bar shown on the left.

(A) Spatiotemporal imaging & Functional connectivity pattern

Fig. 4.

Spatio-temporal imaging and estimation of phase relations. (A) Alpha (red-to-yellow color bar) and beta (dark-blue-to-light-blue color bar) power distribution visualized on the inflated cortical surface. Estimated source spectrograms are shown close to the simulated source locations. The central panel depicts the functional networks estimated through phase synchronization analysis. ROIs 2-6 were synchronized (pink solid lines) with the seed region (red solid line circled) and ROIs 7-9 were de-synchronized (dotted lines) with the seed region. (B-D) Phase plots (upper) and PSV curves (lower) estimated between the seed region and ROIs 6, 7 and 9, respectively. Only the 6th ROI shows synchronization with the seed region at a 0.3π phase delay. 1% statistical significance value was marked by the red dotted lines.

Fig. 5.

Event-related spatio-temporal source estimates. We first assign temporally uncorrelated waveforms to the simulated dipoles. (A) Cortical current distributions at three peak latencies. (B) Estimated event-related waveforms at three estimated source locations (solid lines) in comparison with the real source wave forms (cross lines). We then tested various complex source configurations, and showed the estimated event-related waveforms for (C) correlated Gaussian shaped wave forms, (D) correlated wave forms and transient neural response, (E) rhythmic activity with the same phase but different frequencies, (F) rhythmic activity with same frequency but different phase (G) waveforms extracted from real human data. The labels on the left of the graphs are the amplitude of the simulated source waveforms while the labels on the right are the amplitude of the estimated waveforms.

Fig. 6. Experimental results in a human subject. Six ICs (A) show correlated alpha band activity with the eyes-open-eyes-closed paradigm. The box marked with “O” denotes the eyes-open conditions. The cross correlation (CC) values between the alpha spectral power and the experimental paradigm were calculated for each IC. Based on the EEG-fMRI reciprocal spatio-temporal imaging, (B) alpha spectral power distribution was plotted on the inflated cortical surface. Time courses were extracted from two ROIs (green circled) and spectrograms were calculated for the left hemisphere ROI (C) and right hemisphere ROI (D). Phase differences (E) and the 8-12 Hz PSV curve (F) between the two ROIs were calculated. Both suggest increased synchronization in eyes-closed conditions versus eyes-open conditions.