TECHNICAL REPORT

Atlas-Based Multichannel Monitoring of Functional MRI Signals in Real-Time: Automated Approach

Jong-Hwan Lee,¹ Heather M. O'Leary,¹ Hyunwook Park,² Ferenc A. Jolesz,¹
and Seung-Schik Yoo^{1,3*}

¹Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Massachusetts

²Brain Science Research Center, Department of Electrical Engineering and Computer Science, Korea
Advanced Institute of Science and Technology, Daejeon, Korea

³Department of BioSystems, Korea Advanced Institute of Science and Technology, Daejeon, Korea

Abstract: We report an automated method to simultaneously monitor blood-oxygenation-level-dependent (BOLD) MR signals from multiple cortical areas in real-time. Individual brain anatomy was normalized and registered to a pre-segmented atlas in standardized anatomical space. Subsequently, using real-time fMRI (rtfMRI) data acquisition, localized BOLD signals were measured and displayed from user-selected areas labeled with anatomical and Brodmann's Area (BA) nomenclature. The method was tested on healthy volunteers during the performance of hand motor and internal speech generation tasks employing a trial-based design. Our data normalization and registration algorithm, along with image reconstruction, movement correction and a data display routine were executed with enough processing and communication bandwidth necessary for real-time operation. Task-specific BOLD signals were observed from the hand motor and language areas. One of the study participants was allowed to freely engage in hand clenching tasks, and associated brain activities were detected from the motor-related neural substrates without prior knowledge of the task onset time. The proposed method may be applied to various applications such as neurofeedback, brain-computer-interface, and functional mapping for surgical planning where real-time monitoring of region-specific brain activity is needed. *Hum Brain Mapp* 29:157–166, 2008. © 2007 Wiley-Liss, Inc.

Key words: neurofeedback; evoked-potential; EEG; fMRI; brain-computer-interface; surgical planning

INTRODUCTION

Multi-channel electroencephalograph (EEG) detects the electrical signal associated with neural activation. Since the EEG data is recorded from a finite number of surface electrodes, the localization of the source is only estimated by solving inverse problems with the introduction of a priori constraints in terms of the dipole size, detector location, and conducting media (i.e. head anatomy). Using three-dimensional digitizers or direct visualization under MRI [Yoo et al., 1997], the location of the surface electrodes can be reliably identified. However, the electrical properties (such as conductance and resistance) accounting for the shape of tissues in the head are extremely difficult to esti-

Contract grant sponsor: NIH; Contract grant numbers: R01-NS048242, U41RR019703; Contract grant sponsor: Korean Ministry of Commerce, Industry, and Energy; Contract grant number: 2004-02012; Contract grant sponsor: Gachon Neuroscience Research Institute.

*Correspondence to: Seung-Schik Yoo, Ph.D. MBA, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St., Boston, MA 02115.
E-mail: yoo@bwh.harvard.edu

Received for publication 30 May 2006; Revision 4 November 2006; Accepted 2 January 2007

DOI: 10.1002/hbm.20377

Published online 16 March 2007 in Wiley InterScience (www.interscience.wiley.com).

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mate, thus introducing error in the source localization process [Chauveau et al., 2004; Koles, 1998]. In addition, the choice of a source model for estimation (for example, as to the number of dipole currents) is still under the subject of debate [Michel et al., 2004; Vitacco et al., 2002]. Therefore, EEG-based brain mapping typically has a low spatial resolution blurred beyond that of functional magnetic resonance imaging (fMRI) [Vitacco et al. 2002], which is based on the detection of blood-oxygenation-level-dependent (BOLD) signal contrast, directly measured from the MR image space.

Recently, real-time processing of fMRI data (which includes processing of data in a near real-time basis enabling the analysis of data on-site) has lead to the emergence of a new breed of imaging applications. For example, real-time fMRI (rtfMRI) has been applied for adaptive multi-resolution data acquisition schemes whereby the specific areas of brain can be interactively zoomed in/out to increase efficiency and flexibility in cognitive neuroscience imaging experiments [Yoo et al., 1999]. Clinical applications of rtfMRI include non-invasive pre-operative functional mapping for neurosurgical intervention [Fernandez et al., 2001; Hennig et al., 2003]. Intra-operative rtfMRI is especially valuable for the identification of functional areas in the presence of brain volume shift during surgery [Gasser et al., 2005a]. In spite of these advantages, dedicated data processing and communication hardware are typically required for the computationally-intensive, real-time updates of image reconstruction and voxel-wise statistics [Bagarinao et al., 2005; Cox et al., 1995]. Advancement in data processing capability and communication bandwidth has rendered real-time generation and updates of functional activation map more readily available. However, the utility for tracing the temporal dynamics of BOLD signals rising from specific brain regions has been largely overlooked. Most of the available methods only make it possible to monitor the dynamic BOLD signals from a limited number of regions-of-interest (ROIs), often delineated manually.

Simultaneous real-time monitoring of the BOLD signal from multiple brain regions will cast new opportunities in existing brain mapping experiments that emphasize the utilization of the dynamic BOLD signal itself rather than the functional map. These new breeds of applications include neurofeedback [Posse et al., 2003; Weiskopf et al., 2003] and brain-computer-interfaces (BCI) [Weiskopf et al., 2004; Yoo et al., 2004b] whereby the region-specific (for example, sensorimotor areas during the motor imagery tasks) BOLD signal is fed back to the subject in real-time to guide the degree of brain activation. One of the crucial technical elements in implementing such real-time monitoring is that the brain anatomy needs to be segmented/labeled automatically at a processing speed that facilitates real-time operation. By registering and normalizing an individual's anatomy to a pre-segmented template brain atlas (i.e., stereotactic normalization procedure), the variation in each individual's brain anatomy can be accounted

for and subsequently parcellated. Combined with real-time image reconstruction, we have developed an automated method to measure functional MRI signals from the atlas-based ROIs, and display them through multiple channels. Unlike EEG signal measurement from surface electrodes, dynamic and real-time recordings of BOLD signals from parcellated brain areas reflect the underlying cortical activity directly arising from the various locations within the brain.

METHODS AND MATERIALS

Overview of the Data Flow

Figure 1 shows the overall schematics of the workflow indicating the time necessary for each processing step. The 'Off-line' stage is necessary for the normalization and registration of the individual brain image data to the standardized pre-segmented template image space. The individual's brain anatomy was segmented and labeled by this process, and saved for the subsequent 'On-line' stage. During the 'On-line' stage, subject's functional EPI (Echo Planar Imaging) data was reconstructed and motion-corrected in real-time. After passing through the motion-screening process, the ROI-specific MR signal was displayed in real-time based on the registered anatomical indices obtained during the 'Off-line' stage. The Matlab (version 6.5, Mathworks, Natick, MA) computing environment was used for the entire processing scheme including data transfer, reconstruction, normalization, registration, realignment, and display.

Scanning Parameters and Algorithm Implementation

The study was conducted in a 3 Tesla clinical scanner (Signa VH, GE Medical Systems) using a standard bird-cage head coil for RF transmission and detection. A head cushion was applied to passively restrain head movement during scans. Prior to the fMRI scan, a T1-weighted 3-plane localizer was acquired to identify the location of the motor and auditory regions for the EPI scan prescription. An EPI sequence was then used to image most of the brain volume (13 axial slices, flip angle of 80°, TE/TR = 40/1000 ms at a resolution of 64 frequency and 64 phase encodes, 5 mm thickness with a 1-mm gap, 240-mm square field-of-view: FOV) for detection of the BOLD signal associated with neural activity. We employed an EPI Nyquist ghost-removal method [Buonocore and Zhu, 2001] to correct for k-space aliasing in the EPI data during image reconstruction.

To enable tracking of the BOLD signal activities in real-time from the desired anatomical ROIs, automated segmentation of the brain anatomy was needed. Two pre-segmented anatomical templates, i.e., the Brodmann's Area (BA) and the Automated Anatomical Labeling (AAL) images [Tzourio-Mazoyer et al., 2002] were downloaded from

Figure 1.

A workflow and processing time of the implementation. Off-line processing (left panel in green) includes image normalization and segmentation (less than 20 s). The segmented ROIs were used as masks for BOLD signal display during on-line processing (right panel in blue). The time necessary from raw EPI data acquisition to BOLD signal display was less than 2 s. If head motion of more than 1 mm of translation or 1° of rotation in any direction is detected during real-time fMRI, the scan is reinitiated and subsequent normalization/segmentation process is repeated. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

MRICro (www.mricro.com version 1.39). These template images ($X:Y:Z = 181:217:181$, 1 mm^3 isotropic voxel) were labeled with different numerical indices for identification. By utilizing anatomical templates other than those used in our implementation, a tailor-made anatomical definition is also possible. Then, the normalization and registration algorithms provided by the SPM2 MATLAB codes (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) were modified to segment the EPI data for later user-interaction.

First, the anatomical templates were registered to the normalized EPI data (Fig. 2A), which we used as a reference (ICBM₁₅₂ Space: International Consortium for Brain Mapping; $X:Y:Z = 91:109:91$, 2 mm^3 isotropic voxel, as provided by SPM2). Before the initiation of functional scanning and real-time processing, an individual's EPI anatomy ($X:Y:Z = 64:64:13$, $3.75 \times 3.75 \times 5.5 \text{ mm}^3$ voxel size) with heavy T_2 -weighting was also normalized to this reference EPI data (Fig. 2B). This part of the normalization was conducted using the data normalization routine used in SPM2, which is typically adopted to facilitate inter-subject averaging and group processing in neuroimaging studies [Ashburner et al., 1997]. The first step of this normalization procedure determined the optimum 12-parameter affine transformation matrix to match an individual's EPI data to the template. A more detailed registration (non-linear

warping) followed to maximize the likelihood of similarities between the two image volumes, operating under the Bayesian framework [Ashburner and Friston, 1999; Kiebel et al., 1997]. Consequently, the anatomical segmentation template was registered to individual anatomy (EPI data) via a spatial transformation matrix (Fig. 2C).

Using this normalization transformation matrix, the segmented templates were warped to the subject's EPI space [resolution, $64 \times 64 \times 13$], and formed a binary mask with the appropriate labeling information. Nearest neighbor interpolation was used to spatially down-sample the segmented templates to the lower spatial resolution of an individual's EPI data. Computationally, this approach is less demanding than transforming every (low-resolution) EPI data set in the time sequence to the (higher-resolution) template at every TR period. This step, which is the most time-consuming and computationally intensive, took less than 20 s.

Real-time EPI then proceeded while subjects performed hand motor and internal speech generation tasks (as marked as 'On-line' processing in Fig. 1). All the EPI data was saved as a raw data file (without reconstruction) every 2 s (corresponding to 2 EPI volume acquisitions), and transmitted to the computational platform (Personal computer, operating on an Intel 2 GHz CPU) automatically upon data acquisition via an Ethernet connection (2 Giga bit/second bandwidth) using an FTP (file transfer proto-

Figure 2.

An illustration of the procedure for anatomical template registration and ROI definition. **A:** First, AAL and Brodmann's area template maps ($X:Y:Z = 181:217:181$, 1 mm^3 isotropic voxel) are registered with a standardized template EPI data in MNI coordinate space ($X:Y:Z = 91:109:91$, 2 mm^3 isotropic voxel). **B:** An individual's EPI space ($X:Y:Z = 64:64:13$, $3.75 \times 3.75 \times 5.5 \text{ mm}^3$ voxel size) is then normalized to the MNI space. **C:** After finding the transformation matrices to relate AAL and BA templates to the individual EPI data, anatomical templates can be overlaid on individual EPI images, and **D:** can undergo spatial operations to define regions-of-interest (ROIs) for real-time monitoring of the BOLD signal. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

col). The raw EPI data sets were then reconstructed and realigned (motion-corrected) to the first image volume set.

We used a least-squares approach to estimate the head motion between each data acquisition time window [Friston et al., 1996]. A spatial filtering with a 6 mm FWHM (Full-Width-at-Half-Maximum) three-dimensional Gaussian kernel was applied before estimating the realignment parameter as implemented in the SPM2 platform. This realignment procedure generates a six-parameter affine spatial transformation matrix, which consists of translational parameters in the x , y , and z coordinates (x_t , y_t , z_t) as well as rotational parameters such as pitch (θ° of rotation around x axis; right-left), roll (ϕ° of rotation around y axis; anterior-posterior), and yaw (ψ° of rotation around z axis; superior-inferior) with respect to the first image volume in the time series. Therefore, a pixel whose coordinates are in (x_o, y_o, z_o) at each time point can be transformed into the new coordinates (x', y', z') by the following equation:

$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos \theta & \sin \theta \\ 0 & -\sin \theta & \cos \theta \end{bmatrix} \begin{bmatrix} \cos \phi & 0 & \sin \phi \\ 0 & 1 & 0 \\ -\sin \phi & 0 & \cos \phi \end{bmatrix} \begin{bmatrix} \cos \psi & \sin \psi & 0 \\ -\sin \psi & \cos \psi & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x_o \\ y_o \\ z_o \end{bmatrix} + \begin{bmatrix} x_t \\ y_t \\ z_t \end{bmatrix}$$

Using these movement parameters, we screened for excessive head motion. Head motion of more than 1 mm of translation or 1° of rotation in any direction prompted the re-initiation of the scan, and the normalization process was subsequently repeated (Fig. 1). We chose this criteria since it is known that temporal EPI signals associated with movement as small as 1 mm of translation or 1° of rotation of the head can change the magnetic field homogeneity to an extent beyond compensation by standard image realignment methods, producing time-dependent distortions in fMRI studies [Caparelli, 2005; Jezzard and Clare, 1999]. This strict motion-screening step is typically valuable when advanced motion detection and correction schemes such as the navigator-echo phase alignment technique [Welch et al., 2004] are not available.

The image data that passed motion screening was available for further real-time processing. Since there are more than 70 anatomical areas and more than 30 Brodmann's areas from which the BOLD signal activities are potentially extracted (analogous to the EEG recording channels), users selected multiple brain locations based on the list provided by the AAL or BA templates, and chose to display averaged BOLD signals from the voxels within the selected ROIs. Optionally, spatial operations, such as intersection, union, and complement operators, can be applied to further modify the selected ROIs. Because the goal of the study was to passively monitor the BOLD signals, the subjects' activation maps were not obtained.

Assessment of Reproducibility of Registration and Normalization Algorithms

The registration and normalization algorithms used in this technical implementation, adapted from the SPM software, have been extensively used by the neuroimaging community because of superb registration and normalization accuracy [Crivello et al., 2002]. Therefore, detailed validations of between-subject/between-session variability and reproducibility of the algorithms were not performed separately. Nonetheless, reproducibility with respect to head positioning (or motion) was assessed using simulated image data. Twelve different types of motion features (i.e. $[\pm 3^\circ]$ of rotation in terms of pitch, roll, and yaw) and $[\pm 2]$ voxels of displacement along right-left, anterior-posterior, and superior-inferior directions) were applied to a sample EPI data template (T2-weighted) in the same space as the pre-segmented atlas (also downloaded from MRIcro). Motion features significantly greater than our motion-screening procedure were used to examine the effectiveness of the normalization/registration algorithms. Transformed images were down-sampled to have the same voxel dimension of experimental EPI data. Subsequently, the implemented normalization/registration algorithms were applied to these 12 sets of motion-simulated EPI data to create registered AAL and BA maps. Reference AAL and BA maps were also prepared without spatial transformation. Upon registration, the size of overlap between each registered atlas map (after motion) and the reference atlas (without motion) was calculated for each of the anatomical regions and averaged as percent overlap with respect to the reference atlas.

Task Paradigm and Presentation

This study was approved by the local Institutional Review Board (IRB no. BWH 2004P-001980). A total of twelve (aged 24.7 ± 4.5 , five females) right-handed healthy volunteers, without a history of major medical, neurological or psychiatric illness, participated. Those with a history of head trauma and a corresponding loss of consciousness or those on medications of sedatives, analgesics or pharmaceutical agents (that affect brain functions) were excluded from the study. The data obtained from one additional subject was not reported for a technical reason (malfunction of a paradigm computer). The twelve subjects performed (1) right hand motor, (2) left hand motor, and (3) internal speech generation tasks to validate the implemented algorithm. Data obtained from more than six subjects are typically required in a fixed-effect, conjunction analysis to ensure general population effect ($P < 0.05$) [Friston et al., 1999]. Therefore, the group-averaged data obtained from 12 subjects is sufficient to show the time trend of the BOLD signal across the subjects. For two types of hand motor tasks, the subjects were asked to clench their right or left hand at a rate of about 2 Hz. For the internal speech generation task, they were asked to covertly

say familiar lyrics or sentences of choice, without actually moving their lips and tongue. The order and length of the each task paradigm was balanced and randomized throughout the study.

A total of 75 volumes were acquired in 75 s. The first 10 volume sets were discarded from further data processing to allow for the T1 signal equilibration. The timing of the task was started at the 25th time point, and lasted for only 3 s, thus achieving a trial-based paradigm. The start and end of the task were notified via a prerecorded voice of “go” and “stop”. These auditory cues were prepared using sound-generating software (Gold wave, Canada) and presented via an MR-compatible audio system (Model SS2100, Avotec, FL) from a personal digital assistance (PDA) device (iPAQ, Compaq, USA). The initiation of the MRI data acquisition and the task paradigm were synchronized.

The subject’s motor-related BOLD signal was measured from four ROIs that were defined as (1) BA4 $\cap$ (intersection) the left precentral gyrus (M1), (2) BA4 $\cap$ the right M1, (3) BA6 $\cap$; the supplementary motor area (SMA), and (4) basal ganglia (including the caudate, the putamen, and the thalamus) in the segmented atlas. For the internal speech-related activities, BOLD signals from (1) BA41-42 $\cap$ the left superior temporal gyrus; the left primary auditory cortices (AC), (2) BA41-42 $\cap$ the right superior temporal gyrus; the right primary AC, (3) the left BA44-45 (i.e. Broca’s area), and (4) the left BA22 (i.e. a part of the Wernicke’s area) were traced. In the mean time, other areas-of-interest could be optionally displayed.

To examine the subject-initiated fMRI task (in the absence of instruction on the timing of the task) and concurrent detection/monitoring of BOLD signals in real-time, a 35-year-old subject was asked to start the hand motor task (right or left) at any time, for a duration he wanted. To compare the MR recording with the timing and duration of the task, hand motion was detected using an MR-compatible motion sensor on the subject’s index finger (infrared pulse oximeter; GE Medical Systems). The subject’s motor-related activities were measured from four sets of bilateral ROIs—(1) BA4 $\cap$ the precentral gyrus (M1), (2) BA3-1-2 $\cap$ the postcentral gyrus (SI), (3) supplementary motor area, and (4) the thalamus.

RESULTS

All participants conducted the tasks without the need for reinitiating any portion of the scan due to head motion, thus suggesting the utility of the head cushion for passive head restraint. The computational time following the acquisition of each set of raw EPI data (2 EPI volumes; 2 s) was less than 2 s (On-line data processing shown in Fig. 1). The data processing bandwidth was sufficient enough to process the data flow of 106.5 Kbytes/s ($64 \times 64 \times 13$ image voxels, each occupying 2-bytes per TR period). This ensured the constant flow of the data stream without introducing any data accumulation/backlog. Regarding the

robustness of the implemented algorithm in regard to head motion, a paired *t*-test showed that there was no difference between the motion-added atlas map and the reference atlas in terms of the size of segmented areas ($P > 0.1$). The spatial reproducibility of the algorithm, as measured in terms of the degree of overlap between the motion-added atlas map and the reference atlas, was $(92.5 \pm 3.9)\%$ (in AAL map) and $(90.0 \pm 5.5)\%$ (in BA map) from the six simulated rotational motions, and $(99.9 \pm 0.1)\%$ (in AAL map) and $(99.9 \pm 0.2)\%$ (in BA map) from six simulated translational motions.

The BOLD signal traces from the different ROIs, averaged across the 12 subjects, are shown in Figures 3 and 4. The horizontal axis shows the time index (scan number) and the vertical axis shows the % BOLD signal enhancement compared with the baseline signal. From the hand clenching, task-related evoked-activations were clearly seen in the task-specific ROIs [Kobayashi et al., 2003]. The ROIs demarcated by the intersection of BA4 and precentral gyrus showed a distinct laterality in the BOLD activations based on the side of the hand tasks (Fig. 3A,B for the right hand task, and Fig. 3E,F for the left hand task) along with activations in the supplementary motor area and basal ganglia (Fig. 3C,D,G,H). For the internal speech generation task, the leftward laterality of BOLD activations was identified in the auditory cortices (Fig. 4A,B). This result is consistent with the predominant activations of left-hemispheric neural networks for speech sounds [Tervaniemi and Hugdahl, 2003]. Activations in Broca’s and Wernicke’s area (Fig. 4C,D) also showed task-correlated responses that are related to the creation of grammatically complex sentences and the understanding of spoken language [Damasio et al., 2004].

An example of single-subject BOLD signal recordings from a few representative regions is shown in Figure 5. The format of data display resembled multi-channel EEG recordings whereby simultaneous and real-time monitoring of cortical activity of multiple spatial origins was possible. Task-related signal modulation from these areas was evident. The left superior medial frontal gyrus (No. 8 in Fig. 5) is shown as an example of quiescent areas without task-related activity. It is noticeable that the BOLD signal traces from either AAL map or the BA map alone showed unclear laterality in the BOLD signal depending on the side of the hand tasks. However, when the trace was obtained from the intersection ($\cap$) of the BA4 and precentral areas (Nos. 13 and 14, Fig. 5), a distinctive contralateral dominance in BOLD signal activity was found.

Real-time monitoring of cortical activity from a subject-driven/initiated task was demonstrated in Figure 6. Retrospective analysis showed that the subject initiated right-hand clenching at the 12th scan for ~ 4 s. With a brief pause, the subject performed left hand clenching at the 32nd scan for ~ 6 s. The corresponding BOLD measurement showed the two-peak BOLD signal patterns with a greater signal magnitude at the second peak due to the accumulative effect of BOLD that are associated with longer task duration (6 s compared with 4 s). As expected, the

Figure 3.

BOLD signal traces averaged across 12 subjects for task-specific brain regions during the performance of the right-hand (A–D) and left-hand clenching tasks (E–H). The x-axis denotes the time index (scan number) while the y-axis indicates % BOLD signal enhancement compared to the baseline signal. Values are mean (blue solid

line) $\pm$ standard deviation (red bars) of BOLD activations. A thick black solid line (three scans starting from the 15th scan) indicates the task duration. BA: Brodmann's Area M1: Precentral Gyrus SMA: Supplementary Motor Area. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 4.

BOLD signal traces averaged across 12 subjects for internal speech generation (IS) task-specific brain regions. Values are mean (blue solid line) $\pm$ standard deviation (red bars) of BOLD activations. A thick black solid line (three scans starting from 15th scan) indicates the task duration. AC: Auditory Cortex; Sup. Temp.: Superior Temporal Gyrus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

primary sensorimotor areas (represented BA4∩Left M1 and BA3-1-2∩Left SI in Fig. 6) showed task-specific laterality in activation whereby a greater increase in BOLD signal was observed in the areas contralateral to the side of the task. BOLD signal enhancement in the supplementary motor area (SMA) and the thalamus was also observed with apparently less laterality.

DISCUSSION

We have implemented a functional MRI method that enables real-time tracing of BOLD signal activity from automati-

cally segmented brain ROIs. The real-time data transfer, reconstruction, realignment, and display routine had enough processing and communication bandwidth over a conventional Ethernet connection without a dedicated means of data communication such as Direct Memory Access [Yoo et al., 1999] or an operating-system dependent SAMBA connection [Weiskopf et al., 2004]. Although not tested, the situation that demands more computations, for example, processing of larger data size, can be effectively addressed by multi-processor based grid-computing [Bagarinao et al., 2005].

In this report, an activation map from the subject was not obtained in a real-time fashion since our study empha-

Figure 5.

The time plot (x-axis in scan number) of the BOLD signal responses (y-axis in % BOLD signal enhancement with respect to the baseline signal) from the different ROIs during the right hand (in red; gray line) and left hand (in blue; black line) tasks from one subject (21-year-old male). The top two rows are from the AAL, the third row from the

BA, and the fourth row is the intersection of the selected areas from both BA and AAL templates. A 3D rendering of AAL and BA is overlaid on a cortical activation map ($P < 0.0001$; example shown in the lower right hand corner). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 6.

The time plot (x-axis in scan number) of the BOLD signal responses (in terms of % BOLD signal from the baseline signal level) from the different ROIs (color-coded) during the performance of the subject-initiated motor task (data from a 35-year-old male). The timing of the motor task is shown (right hand: black solid line; left hand: gray solid line). BA: Brodmann's Area; M1: Precentral Gyrus; SMA: Supplementary Motor Area; SI: Postcentral Gyrus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

recursive calculation of the correlation coefficient with respect to the task-associated hemodynamic response function can be applied to the real-time assessment of statistical confidence of activated regions [Cox et al., 1995; Yoo et al., 1999], and readily integrated with the current implantation. This algorithm typically involves simple arithmetic computations and would not introduce any significant burden on data processing.

The reproducibility measures acquired from the simulated head motions showed that the implemented algorithm reliably segmented the cortical areas. Reduced reproducibility in rotational displacement compared with the translational one could be attributed to interpolation errors associated with down-sampling of normalized atlas images to fit (overlay on) the low-resolution EPI data (as described in the method section). The use of non-EPI (such as conventional Gradient Echo or Spin-Echo based) MRI data acquired in the same anatomical plane for normalization and registration procedures may help to reduce the errors associated with susceptibility-related spatial distortion in EPI [Yoo et al., 2004a].

We have demonstrated that the proposed algorithm detected the temporal dynamics of task-specific activations from multiple subjects (as shown in Figs. 3 and 4). This indicates that our data normalization and registration method, based on the algorithms adapted from the widely used SPM platform, adequately isolated the functional anatomies of interest and enabled the simultaneous monitoring of BOLD signals. The format of the data display shared multichannel features of the EEG recording. Although the temporal resolution of the method is much slower than that of a conventional EEG recording due to a low sampling frequency (1 Hz) and the slow hemodynamic nature of the BOLD signal, the technique can be used to detect event-related fMRI signal changes, an analogue to the evoked potential measurement of EEG. We did not correct for the difference in image acquisition time between slices due to a short TR period of 1 s used in this experiment. However, a study that demands a higher temporal resolution would benefit from the adoption of an additional slice-time correction scheme [Paradis et al., 2001].

High-spatial resolution of fMRI combined with a real-time processing capability and automated anatomical segmentation may offer greater flexibility and power over the conventional multichannel EEG studies with a new breed of potential clinical applications, such as experiments involving (1) Neurofeedback fMRI and (2) Brain-computer-interface (BCI).

Neurofeedback fMRI refers to an fMRI method capable of delivering information about anatomically localized brain activity to the subject as biofeedback. Guided by the fMRI information about their own cortical activity, subjects gain a level of voluntary control in modulating brain activity [Weiskopf et al., 2003; Yoo and Jolesz, 2002]. Recently, DeCharms and colleagues have shown that the perception of pain could be modulated by feeding the region-specific

BOLD signal (from rostral anterior cingulate cortex) back to the subjects [DeCharms et al., 2005]. An automated anatomical identification of the ROIs is crucial for the efficient quantification of functional activation in the neurofeedback environment. A BCI is a way of conveying an individual's thoughts to control a computer or electro-mechanical hardware [Wolpaw, 2004]. Real-time fMRI has been employed to interpret the spatial distribution of brain function or variations of regional BOLD signals as BCI commands. For example, four different imagery tasks and the associated cortical activation patterns have been translated into predetermined cursor commands [Yoo et al., 2004b]. In these BCI experiments, the expedited definition of ROI is important for the association of the regional BOLD signal with the corresponding computer-outputs. The reported method can provide the automatic means to define multiple ROIs with much-needed flexibility, and therefore, can be easily adapted to and used in conjunction with fMRI BCI experiments.

Real-time monitoring of regionally specific fMRI signals may also be clinically relevant in neurosurgical planning. The purpose of cortical mapping for neurosurgical planning is to delineate functionally viable cortical regions from adjacent tumors/lesions to be removed [Fandino et al., 1999; Hirsch et al., 2000; Yoo et al., 2004a]. A major imperfection of this preoperative functional mapping, however, is that gathered functional information may not be spatially accurate after the onset of surgery because of the shift in brain anatomy [Nabavi et al., 2001]. In addition, the patients may not be able to perform active tasks because of functional deficits and/or a lack of compliances. To improve these imperfections, intraoperative fMRI mapping, along with a passive paradigm based on electrical stimulation of the median and tibial nerves, was conducted to identify the primary somatosensory and motor cortices in anesthetized patients [Gasser et al., 2005a,b]. Our real-time fMRI data-monitoring scheme may provide added flexibility in monitoring BOLD signals from salvageable functional areas adjacent to a tumor. However, the validity of BOLD measurements near a brain tumor margin should be carefully addressed in the context of intra-operative mapping since a loss of autoregulation in tumor vasculature, especially in malignant glioblastomas, was reported to alter the BOLD signal responses [Holodny et al., 1999, 2000; Righini et al., 1996]. Very importantly, anesthesia also alters the time-course of BOLD signal response [Gasser et al., 2005a,b]. Further study is urgently needed to address the utility of fMRI for intraoperative surgical planning.

Another potential application could be found from the detection and monitoring of epileptic loci. Detection of epileptic activity and its spatial localization are important for surgical intervention and removal [Sullivan and Detre, 2005]. So far, simultaneous recordings of EEG signals in the MRI environment provide the temporal features of seizure-related brain activity [Salek-Haddadi et al., 2002]. The proposed technique, by enabling the display of real-time

cortical activity, can be readily adapted to detect the irregular and unpredictable BOLD signal signature associated with epileptic discharges. Combined with blind-source localization techniques such as ICA [Esposito et al., 2003], the temporal features of the detected BOLD signal can be used to locate the epileptic locus/loci.

The proposed method, we believe, can also be used as a valuable adjunct to magnetoencephalography (MEG) since both evaluate brain functions in an online fashion. MEG detects magnetic fields generated by neuronal activity inside the brain using direct-current superconducting quantum interference devices (SQUIDs) [Ahonen et al., 1993]. Similarly with EEG analysis, an inverse problem has to be solved with a limited number of estimators to find localized sources from surface MEG measurements. However, MEG reportedly provides localization results more accurately than EEG, because magnetic fields are less prone to be affected by the cranium and scalp structure [Hämäläinen et al., 1993]. Both EEG and MEG have a superior temporal resolution (on the order of milliseconds) over fMRI. Therefore, the proposed method of real-time monitoring of fMRI signals may serve as a complementary method to examine region-specific, “chrono-architecture” (time-based anatomy) of the human brain [Bartels and Zeki, 2004, 2005; Hasson et al., 2004].

CONCLUSION

In summary, the proposed method provides a simple means to monitor cortical activities across a distributed neural network in real-time, and is readily adoptable by many commercial MRI platforms. The automated delineation of cortical regions and concurrent monitoring of BOLD signals will support studies that require subject-initiated regulation of regionally specific cortical activity through neurofeedback. In addition, this technique may supplement the utility and function of multichannel EEG and MEG recordings while retaining the superb spatial resolution of fMRI. Exploration of future clinical applications constitutes further direction of our investigation.

ACKNOWLEDGMENTS

Authors thank Drs. Chen N.K. and Panych L.P. (Brigham and Women’s Hospital, Boston) and Dr. Park H.J. (Yonsei University College of Medicine, Seoul, Korea) for their technical support. Authors also thank editorial support of Mr. Matthew Marzelli (Boston University, Boston).

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