NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 30 (2006) 1133 – 1148

Linear aspects of transformation from interictal epileptic discharges to BOLD fMRI signals in an animal model of occipital epilepsy

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Received 17 January 2005; revised 29 October 2005; accepted 2 November 2005
Available online 18 January 2006

Epileptic disorders manifest with seizures and interictal epileptic discharges (IEDs). The hemodynamic changes that accompany IEDs are poorly understood and may be critical for understanding epileptogenesis. Despite a known linear coupling of the neurovascular elements in normal brain tissues, previous simultaneous electroencephalography (EEG)–functional magnetic resonance imaging (fMRI) studies have shown variable correlations between epileptic discharges and blood oxygenation level-dependent (BOLD) response, partly because most previous studies assumed particular hemodynamic properties in normal brain tissue.

The occurrence of IEDs in human subjects is unpredictable. Therefore, an animal model with reproducible stereotyped IEDs was developed by the focal injection of penicillin into the right occipital cortex of rats anesthetized with isoflurane. Simultaneous EEG–fMRI was used to study the hemodynamic changes during IEDs. A hybrid of temporal independent component analysis (ICA) of EEG and spatial ICA of fMRI data was used to correlate BOLD fMRI signals with IEDs. A linear autoregression with exogenous input (ARX) model was used to estimate the hemodynamic impulse response function (HIRF) based on the data from simultaneous EEG–fMRI measurement. Changes in the measured BOLD signal from the right primary visual cortex and bilateral visual association cortices were consistently coupled to IEDs. The linear ARX model was applied here to confirm that a linear transform can be used to study the correlation between BOLD signal and its corresponding neural activity in this animal model of occipital epilepsy.

Keywords: Experimental animal models; Electroencephalography; Epilepsy; Interictal epileptic discharges; Magnetic resonance imaging; Functional magnetic resonance imaging; Blood oxygenation level-dependent; Independent component analysis; General linear model; Hemodynamic impulse response function; Linear autoregression with exogenous input model

Introduction

Epilepsy is a chronic neurological disorder with recurrent spontaneous seizures, which are abnormal hypersynchronous electrical discharges of the brain accompanied by behavioral manifestations such as altered awareness, manual automatisms, and generalized tonic–clonic movements (Clark and Wilson, 1996). Despite the clear argument for combining electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) (Jacobs et al., 2001), simultaneous EEG–fMRI has had a limited role in the study of patients or animals with seizures, since seizures rarely occur 'on demand' in the magnet. However, subjects with epilepsy also exhibit focal epileptic spikes known as interictal epileptic discharges (IEDs), which are paroxysmal epileptic discharges of a population of neurons in a small region of the brain. These discharges have minimal or no propagation, generally resulting in no behavioral changes (Engel, 1992). While IEDs occur unpredictably in human subjects, they are generally more frequent and less disruptive than seizures and their morphology and amplitude may vary from patient to patient (Ebersole and Wade, 1991). As such, detection of IEDs presents an alternative approach to co-localizing potential seizure foci using fMRI and EEG. In this paper, we present such an approach using an animal model of epilepsy with simultaneous fMRI and EEG.

To investigate the relationship between IED and BOLD response, an animal model of IEDs was developed (Mirsattari et

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.neuroimage.2005.11.006

al., 2005b). This model involved the focal injection of penicillin into a small region of the cerebral cortex of rats anesthetized with inhalational isoflurane to induce stereotyped IEDs (Reichenthal and Hocherman, 1977) without seizures. Penicillin-induced IEDs are paroxysmal depolarization shifts in membrane potential of hyperexcited cortical neurons resulting from the blockade of post-synaptic type A γ-aminobutyric acid (GABA-A) receptors (Ajmone Marsan, 1969). Simultaneous acquisition of BOLD and EEG in this acute animal model of focal epilepsy provides a unique opportunity to explore BOLD-fMRI correlates of IEDs.

With the ability to acquire high-quality EEG inside an MRI scanner (Ives et al., 1993), simultaneous EEG–fMRI can be used to study the neural basis of BOLD changes in neurological disorders such as epilepsy. However, the relationship between BOLD and underlying neural activity (Logothetis and Wandell, 2004) may differ between normal and abnormal brains, manifesting as a different hemodynamic impulse response function (HIRF). Previous simultaneous EEG–fMRI studies have shown partial concordance between BOLD and neural activity in normal animals (Disbrow et al., 2000; Logothetis et al., 2001). EEG–triggered fMRI (Warach et al., 1996; Krakow et al., 2001) and continuous EEG–fMRI (Lemieux et al., 2001; Bénar et al., 2002; Nersesyan et al., 2004) have been used to study the relationship between epileptiform discharges and various properties of the BOLD response such as amplitude and duration. Using a linear transform model and assumed HIRF, the neurovascular coupling between normal neural activity and BOLD response has been mathematically modeled (Boynton et al., 1996; Heeger and Ress, 2002). The investigation on effects of an assumed HIRF in epilepsy has been explored by several studies (Bénar et al., 2002; Kang et al., 2003; Bagshaw et al., 2004; reviewed in Salek-Haddadi et al., 2003). Following their work, we have explored the use of the Independent Component Analysis (ICA) method in our study to decrease the reliance of purely hypothesis-driven methods. A major advantage of ICA is its applicability to paradigms for which detailed a priori models of brain activity are not known, making it a suitable technique for the analysis of transient random neural events such as IEDs. ICA has been applied to other areas in neuroscience (Gu et al., 2001), and has been used to analyze the EEG data (Mirsattari et al., 2005b; reviewed in Makeig et al., 2004) and fMRI data (reviewed in McKeown et al., 2003) but data-driven analysis has not been applied to simultaneous EEG/fMRI (Salek-Haddadi et al., 2003). In the current study, we use spatial ICA to analyze the echo planar imaging (EPI) data and incorporate simultaneously acquired temporal ICA of EEG data as a novel approach to analyze simultaneous EEG–fMRI data.

The objective of this study was to use a novel method for analyzing simultaneous EEG–fMRI data by combining temporal ICA on the EEG data and spatial ICA on the fMRI data to investigate the relationship between IED and BOLD response in an animal model. Temporal ICA was used to detect the occurrence of IEDs in the EEG data. Then, using a hybrid ICA and standard General Linear Model (GLM) approach (McKeown, 2000), IED-related components of BOLD signal were identified to analyze the fMRI components. We applied this hybrid framework to fully exploit the advantages of data-driven simultaneous EEG–fMRI measurements over purely hypothesis-driven methods for detecting IEDs and reliable statistical tests. The relationship between IEDs and BOLD responses were investigated by creating an HIRF model using autoregression with exogenous input (ARX) model derived from the results obtained by the above hybrid ICA and GLM approach (Goutte et al., 2000). The HIRF model derived from the experimental data was then convolved with the IEDs to calculate the corresponding BOLD response and compare to the measured BOLD signal. We examine the relationship between the measured BOLD and estimated BOLD signal from IED and data-derived HIRF model which is the fundamental basis of most current fMRI studies.

Materials and methods

Animal preparations

This study was approved by the University of Western Ontario's Institutional Animal Care and Use Committee. Three adult male Sprague–Dawley rats (body weight = 300 ± 30 g) were housed in a 12 h dark and 12 h light cycle and fed ad lib. Rats were anesthetized with 1.25–2% isoflurane USP delivered with a mixture of O_2:N_2 (30%:70%) gas and mechanically ventilated after oral intubation. The anesthetized rats were then placed in an MRI-compatible stereotactic frame. The animal head was shaved and scalp excised in order to expose the skull. One burr hole measuring 0.8–1.0 mm in diameter was made in the homotopic regions of the cortex overlying the occipital cortex (−7.0 mm from Bregma, Lateral ± 4.0 mm) (Paxinos and Watson, 1998). The animals were injected with 0.2 μl of 100 units sodium penicillin G (Sigma–Aldrich, Switzerland) dissolved in an artificial CSF devoid of sodium chloride at 0.8 mm below the cortical surface in the right occipital cortex. Vital physiologic parameters including heart rate, blood oxygen saturation, end-tidal CO_2, temperature, and electrocardiogram (ECG) were monitored simultaneously throughout the experiments with high-field MRI compatible instrumentation. Body temperature was maintained between 36.5 and 37.5°C. Details of the surgical set-up have previously been published (Mirsattari et al., 2005a).

EEG and fMRI data acquisitions

Two carbon fiber EEG electrodes were placed directly over the cortex in the burr holes and one additional carbon electrode was placed on the skull 5 mm anterior to each burr hole. Ag/AgCl electrodes placed subcutaneously under the armpits were used for ECG recordings and those from the head and neck regions served as reference and ground electrodes. The ground and reference electrodes were inserted adjacent to the active occipital EEG electrodes on either side of the head. Details of the EEG recording set-up have previously been published (Mirsattari et al., 2005b).

Anatomical and fMRI images were acquired on a Varian Unity INOVA 4.0 T whole-body research system equipped with a Siemens Sonata gradient coil and amplifiers. A surface coil measuring 1.8 cm in diameter was placed directly against the animal head and secured to the stereotactic frame. Before collecting fMRI data, inversion prepared 3D T_1-weighted coronal anatomical images (TI/TE/TR = 500/10/1600 ms) were obtained over a 5.0 cm × 5.0 cm × 1.6 cm field of view (FOV) (matrix size 256 × 256 × 16) producing a 1.0 mm slice thickness. During fMRI experiments, one T_2*-weighted MR image was acquired per animal in 8 center-out segments over the same FOV with a 2 mm slice thickness using a gradient-recalled EPI pulse sequence (TE/TR = 10/200 ms, flip angle ∼30°). Matrix size was 128 × 128 with an in-plane resolution of 390 μm. Simultaneous EEG–EPI data