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NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 37 (2007) 834–843

Spatial filters and automated spike detection based on brain topographies improve sensitivity of EEG–fMRI studies in focal epilepsy

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Received 22 December 2006; revised 3 May 2007; accepted 7 May 2007
Available online 7 June 2007

The ballistocardiogram (BCG) represents one of the most prominent sources of artifacts that contaminate the electroencephalogram (EEG) during functional MRI. The BCG artifacts may affect the detection of interictal epileptiform discharges (IED) in patients with epilepsy, reducing the sensitivity of the combined EEG–fMRI method. In this study we improved the BCG artifact correction using a multiple source correction (MSC) approach. On the one hand, a source analysis of the IEDs was applied to the EEG data obtained outside the MRI scanner to prevent the distortion of EEG signals of interest during the correction of BCG artifacts. On the other hand, the topographies of the BCG artifacts were defined based on the EEG recorded inside the scanner. The topographies of the BCG artifacts were then added to the surrogate model of IED sources and a combined source model was applied to the data obtained inside the scanner. The artifact signal was then subtracted without considerable distortion of the IED topography. The MSC approach was compared with the traditional averaged artifact subtraction (AAS) method. Both methods reduced the spectral power of BCG-related harmonics and enabled better detection of IEDs. Compared with the conventional AAS method, the MSC approach increased the sensitivity of IED detection because the IED signal was less attenuated when subtracting the BCG artifacts. The proposed MSC method is particularly useful in situations in which the BCG artifact is spatially correlated and time-locked with the EEG signal produced by the focal brain activity of interest.

Keywords: Simultaneous EEG–fMRI; Ballistocardiogram artifact; Multiple source correction; Spike detection; Principle components analysis

Introduction

EEG-correlated fMRI (EEG–fMRI) can be used to non-invasively map blood-oxygen-level dependent (BOLD) signal changes linked to spontaneous EEG activity (Gotman et al., 2006). This technique has been applied in numerous studies to characterize hemodynamic correlates of interictal epileptiform discharges (IED) (Benar et al., 2006; Federico et al., 2005; Kobayashi et al., 2006; Salek-Haddadi et al., 2006). Despite great success in the last 5 years, the sensitivity of EEG–fMRI experiments in epilepsy is still limited. Significant BOLD changes have been observed in about 40–80% of patients suffering from focal epilepsies (Gotman et al., 2006). Several factors may influence the sensitivity of the simultaneous EEG–fMRI measurements used to detect IED-related BOLD responses. Diagnostic sensitivity may be improved by applying individual hemodynamic response functions in the fMRI analysis (Kang et al., 2003; Aghakhani et al., 2004; Lu et al., 2006), reducing cardiac noise in the BOLD signal by cardiac cycle modeling (Liston et al., 2006a), and faster data acquisition with a larger magnetic field (Briellmann et al., 2003). However, the most important factor that determines the sensitivity is the reliable identification of each IED. A failure to reliably detect all IEDs that occur during the EEG–fMRI session results in suboptimal statistical models and reduces the sensitivity of the method (Diehl et al., 2003; Liston et al., 2006b; Salek-Haddadi et al., 2006). Therefore, approaches which improve the detection of IEDs constitute an important step towards a clinically useful application of EEG–fMRI investigations in the field of epilepsy.

In the majority of previous EEG–fMRI studies designed for epilepsy, the identification and selection of IEDs were based on visual inspection with respect to scalp topography and morphology of the IEDs. The efficacy of visual inspection depends on the experience of the observer and on the quality of the EEG.

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

1053-8119/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2007.05.049

However, EEG recordings are usually contaminated by artifacts caused by the rapidly changing electromagnetic gradients and the ballistocardiogram (BCG). Since the end of the 1990s, several algorithms have been developed to reduce artifact contamination. Whereas the time-stable and highly reproducible gradient artifact can be effectively eliminated using either the averaged artifact subtraction (AAS) method (Allen et al., 1998) or Fourier transformation (Hoffmann et al., 2000), the BCG artifact resulting from a physiological signal is more difficult to eliminate. This is because the spatial and temporal features of the BCG artifact are more variable than the gradient artifact (Allen et al., 1998, 2000; Goldman et al., 2000; Benar et al., 2003). Different methods have been developed to remove the BCG artifact: the averaged artifact subtraction (AAS) method (Allen et al., 1998; Goldman et al., 2000), spatial and adaptive filtering techniques (Bonmassar et al., 1999, 2002; Ellingson et al., 2004), procedures based on principle component analysis (Benar et al., 2003; Niazy et al., 2005) and independent components analysis (Benar et al., 2003; Srivastava et al., 2005; Nakamura et al., 2006; Debener et al., 2007). However, despite some progress, the quality of correction varies between subjects, and a residual BCG artifact often persists in the EEG data (Allen et al., 2000; Benar et al., 2003). Since the residual BCG artifact sometimes has a morphology similar to the IEDs and the accuracy of IED identification from the scalp EEG is quite limited (Kobayashi et al., 2001; Nayak et al., 2004), the contamination of the EEG with a BCG artifact may increase false-negative and false-positive IED detections. Especially in patients with a great number of IEDs, the probability of spatial and temporal correlations between artifact and brain topographies can be high. This may reduce the success rate of IED detection because the artifact correction algorithm attenuates or distorts the intrinsic IED signal.

In this paper we applied a *multiple source correction (MSC)* method to subtract the BCG artifact from the EEG data that had been recorded in patients with epilepsy during fMRI examinations. The aim was to increase the reliability of IED detection in those patients and thereby strengthen the sensitivity of the combined EEG–fMRI to detect regional changes in the blood-oxygen-level dependent (BOLD) signal elicited by IEDs. In a previous study, the MSC approach has been successfully used to remove eye movement artifacts in EEG recordings (Ille et al., 2002). As shown in a recent study by Liston et al. (2006b), an automated spike detection and classification based on IED topography may enhance the sensitivity of EEG–fMRI recordings as well. In this study, we also used an automated detection method for IEDs based on a spatio-temporal pattern search (Scherg et al., 2002). The efficacy of the MSC method was compared with the AAS correction (Allen et al., 1998, 2000).

Materials and methods

Subjects

Seven children (6 boys and 1 girl, mean age of 7.1 ± 1.4 years) with IEDs originating in the centro-temporal region underwent a 20-minute EEG recording outside the MR scanner and a 20-minute continuous EEG–fMRI recording in the same week. The children were selected from the databank of the Department of Neuropediatrics, University of Kiel. This databank of EEG–fMRI recordings contains more than 100 children with different forms of epilepsy. The selection criteria were (1) focal IEDs with a uniform and well-localized EEG signature (centro-temporal spikes, one type of IED), (2) age 6–9 yeas, (3) sufficient number of IEDs (>100). Clinical data of the children are given in Table 1. The children were sedated (oral chloral hydrate in a maximal dose of 50 mg/kg) 30 min prior to EEG acquisition; both EEG investigations outside and inside the MR scanner were performed while the children were asleep. The study was performed in accordance with the declaration of Helsinki and was approved by the local ethical committee. The parents had given their written informed consent.

EEG–fMRI acquisition

The EEGs outside and inside the scanner were continuously recorded from 30 scalp sites. Twenty electrodes were placed according to the international 10–20 system for EEG-electrode placement. Additional electrodes were placed over FC1, FC2, CP1, CP2, FC5, FC6, CP5, CP6, TP9 and TP10. The reference electrode was between Fz and Cz. Sintered Ag/AgCl ring electrodes were attached using the "EasyCap" (Falk-Minow Services, Herrsching-Breitbrunn, Germany). Electrode impedance was kept below 7 kΩ. Two additional electrodes were placed on the infraorbital ridge of the right eye for recordings of the vertical EOG and on the left perivertebral part of the lower back for acquisition of the electrocardiogram (ECG) in order to monitor ballistocardiogram artifacts. The EEGs outside the scanner were recorded using a Nihon Kohden amplifier (Nihon Kohden Co., Tokyo, Japan; 500 Hz sampling rate, 250 Hz low-pass and 0.005 Hz high-pass filters). The EEG inside the scanner was recorded using an MR-compatible EEG recording device (BrainAmp-MR, Brainproducts Co., Munich, Germany). EEG signals were sampled at a sampling rate of 5 kHz using a band-pass filter (low-pass: 250 Hz; high-pass: 0.03 Hz).

MRI was performed at 3 T (Philips Achieva scanner) using an eight-channel SENSE head coil. For functional MRI we used a single-shot, T2*-weighted gradient-echo planar imaging sequence (TR = 2250 ms, TE = 45 ms, 30 slices, 64 × 64 matrix, slice thickness = 3.5 mm, FOV = 200 mm, flip angle = 90°, 540 scans per 20 min). Structural MRI was acquired using a T1-weighted, three-dimensional MPR sequence (1 mm slice thickness, 208 × 208 matrix, 150 slices, FOV = 208 mm, TE = 3.6 ms, TR = 7.8 ms, flip angle = 8°, NSA = 2).

Processing of the EEG obtained outside the scanner

EEG was analyzed offline using the Brain Electrical Source Analysis software, Version 5.1 (BESA, MEGIS Software GmbH, Graefelfing, Germany). For visual detection of IEDs, data were

Table 1
Clinical characteristics of patients

Patients	1	2	3	4	5	6	7
Age (years)	6	7	7	6	8	7	6
Seizures [a]	SFS	SFS	SFS	TCS	CFS	CFS	CFS
MRI abnormalities [b]					+	+	+
AEDs [c]	STM	STM	CBZ	STM	STM, OCX	STM	LEV
EEG focus	right	left	right	right	right	right	right
Number of IEDs	379	483	223	402	238	191	233

[a] SKS = simple focal seizures; TCS = tonic–clonic seizures; CFS = complex focal seizures.
[b] Periventricular leucomalacia being the only MRI abnormality found.
[c] CBZ = carbamazepine, LEV = levetiracetam, OXC = oxcarbazepine, STM = sulthiame.