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Seizure source imaging by means of FINE spatio-temporal dipole localization and directed transfer function in partial epilepsy patients

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HIGHLIGHTS

- FINE spatio–temporal source localization and connectivity analysis were utilized to identify the seizure sources during seizure onset.
- High-density scalp EEG with 76 electrodes was used in long-term monitoring of epilepsy patients.
- High-density scalp EEG provides significantly better localization accuracy of seizure onset compared with 32 or fewer electrodes.

ABSTRACT

Objective: To investigate the usage of a high-density EEG recording system and source imaging technique for localizing seizure activity in patients with medically intractable partial epilepsy.
Methods: High-density, 76-channel scalp EEG signals were recorded in 10 patients with partial epilepsy. The patients underwent routine clinical pre-surgical evaluation and all had resective surgery with seizure free outcome. After applying a FINE (first principle vectors) spatio–temporal source localization and DTF (directed transfer function) connectivity analysis approach, ictal sources were imaged. Effects of number of scalp EEG electrodes on the seizure localization were also assessed using 76, 64, 48, 32, and 21 electrodes, respectively.
Results: Surgical resections were used to assess the source imaging results. Results from the 76-channel EEG in the 10 patients showed high correlation with the surgically resected brain regions. The localization of seizure onset zone from 76-channel EEG showed improved source detection accuracy compared to other EEG configurations with fewer electrodes.
Conclusions: FINE together with DTF was able to localize seizure onset zones of partial epilepsy patients. High-density EEG recording can help achieve improved seizure source imaging.
Significance: The present results suggest the promise of high-density EEG and electrical source imaging for noninvasively localizing seizure onset zones.

1. Introduction

Epilepsy represents a chronic neurological disease that affects roughly 50 million people worldwide. Epilepsy patients are often severely disabled by the unpredictable seizures that the disease manifests (Fisher et al., 2000, 2005). A panoply of pharmacological agents have been used for treating epilepsy. However, about 30% of patients do not respond effectively to currently available medication (Cascino, 1994). For those patients who experience frequent seizures and whose lives are greatly impacted, resective surgery that aims to remove epileptogenic foci remains one of the last viable treatment options (Palmini et al., 1991; Siegel et al., 2004; Engel, 2008). Yet, a successful surgical outcome can only be achieved if the epileptogenic foci are accurately and completely removed or disconnected. Accordingly, techniques that can accurately aid in localizing epileptogenic foci are of great importance for epilepsy surgery and a successful, seizure-free outcome.

Intracranial EEG has been used for detecting seizures (Ayala et al., 2011) and delineating epileptogenic foci (Wilke et al., 2010). Intracranial EEG recording from ECoG grid or depth electrodes is also considered as the gold standard for identifying the seizure onset zone (Engel, 1987). Although intracranial recordings can provide direct neural-electrical measurement from the cortex, they are highly invasive, expensive, and painful for patients (Engel, 1987). Intracranial EEG also has limited cortical coverage due to

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the restriction of surgical operation. Heretofore, noninvasive positron emission tomography (PET) and ictal subtraction single photon emission computed tomography (SPECT) have been utilized to extract metabolic and perfusion information from epilepsy patients (Van Paesschen et al., 2007). FMRI, yet another functional imaging technique, has been used to detect hemodynamic responses from the neural activities of epilepsy patients (Gotman, 2008; Vulliemoz et al., 2011; Moeller et al., 2011). Attempts have been made in order to image (and thus localize) epileptic foci from noninvasive measurements (Ebersole, 2000; Oishi et al., 2002; Plummer et al., 2008; Brodbeck et al., 2009). Previous studies have, in fact, demonstrated that EEG source imaging could be a useful tool for localizing epileptogenic zones because of its high temporal resolution at the millisecond scale as well as its noninvasive nature. However, EEG has a limited spatial resolution due to the smearing effect of the head volume conduction and the conductivity heterogeneity (Lai et al., 2005; Zhang et al., 2006). In order to image epileptogenic zones for aiding pre-surgical planning, there is a need to enhance the spatial resolution of EEG.

Many efforts have been devoted to studying noninvasive EEG source imaging approaches in medically intractable epilepsy patients. Studies have shown that electrical source imaging can be a useful tool in identifying epileptogenic foci in patients with normal or lesion-evident MRI results (Brodbeck et al., 2009, 2010). In a few studies, significant correlations were reported between estimated neural-electrical sources and surgical resections (Michel et al., 2004; Lai et al., 2011). Moreover, some investigators have combined EEG and functional MRI for these purposes (Gotman et al., 2006; Vulliemoz et al., 2011). However, source imaging performed with this technique relied mainly on interictal spikes. Considering the clinical importance of ictal events in lateralizing or localizing seizure onset zone, source analysis based on ictal activities remains to be studied (Assaf and Ebersole, 1997; Worrell et al., 2000). The spatio–temporal source localization approach (FINE) was previously developed and studied in systematic computer simulations and motor evoked potential experiments (Xu et al., 2004; Ding and He, 2006). It was also applied to image epileptic sources in patients with lesion-evident MRI studies (Ding et al., 2007). Additional studies have suggested that more accurate source imaging results could be obtained by increasing the number of scalp EEG signal channels (Lantz et al., 2003; Michel et al., 2004; Holmes, 2008).

The aim of this study is to investigate a high resolution electrical source imaging technique and high-density EEG recordings for the purpose of identifying seizure onset zones in patients with medically intractable partial epilepsy. We applied a patient-specific boundary element method (BEM) head model and the source localization approach to obtain high spatio–temporal resolution of sources that corresponded to scalp ictal activities. Functional connectivity analysis was then utilized to identify the primary ictal source from propagated sources. Further, we investigated the localization improvement that can be achieved using dense array EEG recording. Five configurations with 76, 64, 48, 32, and 21 electrodes were tested. The localization of seizure onset zone was performed for each configuration using downsampled data. Computer simulations were also conducted to study the effect of electrode numbers in EEG source imaging. The computer simulation results were compared with the simulated sources and the patient data analysis results were evaluated with surgical resections in these patients.

2. Methods

2.1. Patients and data acquisition

Ten patients with medically intractable partial epilepsy were studied using a protocol approved by the Institutional Review Boards of the University of Minnesota and Mayo Clinic. The patients are consecutive partial epilepsy patients selected according to the following criteria: (1) seizures were captured in the high-density EEG recording, (2) the patients underwent surgical resections after pre-surgical workup, (3) the patients were seizure free after the resective surgery, (4) high-resolution structural MRI were acquired before and after their surgical operation. The surgical resections were used to evaluate the performance of source imaging results, and this information was not used in the source analysis. All the patients had pre-surgical evaluation including high-resolution structural MRI, long-term video-EEG monitoring (5.6 days on average) using 76 channels at Mayo Clinic (Rochester, MN, USA). All the patients underwent surgery to remove epileptogenic zones, and were rendered seizure free after 1 year follow up of the surgical operation by skilled epileptologists. Table 1 summarized the patients' characteristics and Fig. 1 showed the procedural diagram of seizure source imaging.

During the long-term monitoring, scalp EEG was recorded from 76 electrodes according to the modified international 10–20 system, with 500 Hz sampling frequency and 1–70 Hz band-pass filtering. Standard electrode locations were utilized for the source analysis. The long-term video EEG was reviewed for seizure activities and seizure onset time was marked by experienced epileptologists. Band-pass filter of 1 and 30 Hz was used to reduce the high frequency noise and DC linear trend of EEG. Among the captured seizures (1–4 seizures per patient, 27 seizures in total) from the patients, the ictal data in four seizures were excluded due to the large moving artifacts and all the other seizures (23 seizures) were used in the study. Seizure segments with approximately 2–3 s were selected after seizure onset time. The quasi-stationary and artifact-free conditions of the selected segment can be examined by inspecting the waveforms and time–frequency representation (TFR) of the EEG signals. Fig. 2 shows the waveform and TFR of the 76-channel EEG signals in one seizure.

Structural MRI T1 images (voxel size: $0.9375 * 0.9375 * 1.0\,\text{mm}^3$, 166 slices on average) were obtained for each patient from a 1.5 Tesla or 3 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, WI). These MRI images were used to build realistic geometry BEM of the head, which consists of three layers: scalp, skull, and brain. The patient specific BEM was constructed from the segmentation results of the three layers using CURRY6 software (Compumedics, Charlotte, NC). The conductivity values of scalp, skull, and brain were set as 0.33 S/m, 0.0165 S/m, and 0.33 S/m, respectively (Oostendorp et al., 2000; Lai et al., 2005).

2.2. Electrical source imaging

The spatio–temporal source localization approach (FINE) was previously studied in both computer simulations and human subjects (Xu et al., 2004; Ding and He, 2006; Ding et al., 2007). The problem can be expressed as

$$\Phi(t) = A(R, Q)S(t) \tag{1}$$

where $\Phi(t)$ is the electrical potential measurement on the scalp at time t, $A(R, Q)$ is the transfer matrix from source locations R with source orientations Q, $S(t)$ is the source activity at time t. The equation is meant to find the source locations R and source orientations Q in three dimensional source spaces that best fit the signal subspace. Once the transfer matrix $A(R, Q)$ is determined, the source waveforms $S(t)$ can be estimated by solving the inverse problem.

Patient-specific realistic geometry BEM head models with three layers (scalp, skull, brain) were built from the structural MRI images. The lead field matrix $A(R, Q)$ was then computed from the BEM head model (He et al., 1987; Hämäläinen and Sarvas, 1989). We employed the equivalent current dipole as the source