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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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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 ten 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) spatial-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 ten 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.

Keywords

High-density EEG; Ictal activities; EEG source imaging; FINE; Epilepsy; directed transfer function

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 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., 2010; 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 spatial-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 et al., 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

spatial-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. Fig. 1 illustrates the schematic diagram of the procedures in the present study. See below for details.

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 presurgical 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 one year follow up of the surgical operation by skilled epileptologists. Table 1 summarized the patients' characteristics.

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 4 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: $0.9375 \times 0.9375 \times 1.0 \text{ mm}^3$, 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 spatial-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

$$\Phi(t) = A(R, Q)S(t) \quad (1)$$

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 model, and the source space was set as the whole three dimensional brain. The subspace correlation (SC) between the source dipolar topographies and noise-only scalp EEG subspace were defined as

$$SC_{FINE}(r) = \max_{\bar{q}} \left(\frac{A(\bar{r}, \bar{q})^T F_{\theta} F_{\theta} A(\bar{r}, \bar{q})}{A(\bar{r}, \bar{q})^T A(\bar{r}, \bar{q})} \right) \quad (2)$$

where $\bar{r}$ is the possible source location at three dimensional source space, $SC_{FINE}(r)$ is the source correlation value at location $\bar{r}$, $A(\bar{r}, \bar{q})$ is the transfer matrix at source location $\bar{r}$ with source orientation $\bar{q}$, F_{θ} is the FINE vector projected to the noise subspace. The sources are obtained by scanning the locations with local minimum of subspace correlation. Subspace correlation threshold is set at 5% and only subspace correlation values below it are considered as possible sources. Source waveforms of the identified sources are then estimated by solving the over determined inverse problem.

2.3 Functional connectivity analysis

The functional connectivity analysis utilizing DTF (Kaminski and Blinowska, 1991; Kaminski et al., 2001) is an extension of Granger causality theory (Granger, 1969). Instead of being only suitable for paired-wise directional causality as in Granger theory, the DTF can be applied to analyze connectivity among multi-channel signals (Astolfi et al., 2004, 2005; Babiloni et al., 2005; Wilke et al., 2009, 2010; He et al., in press). Multivariate autoregressive (MVAR) modeling was firstly applied to estimate the model parameters of signals as

$$X(t) = \sum_{i=1}^p \Lambda(i)X(t-i) + E(t) \quad (3)$$

where $X(t)$ is the signal data at time t , $\Lambda(i)$ are the matrices of multivariate model coefficients, p is the model order, and $E(t)$ is a vector of multivariate white noise. After transforming MVAR model parameters into frequency domain,

$$\Lambda(f)X(f)=E(f) \quad (4)$$

$$X(f)=\Lambda^{-1}(f)E(f)=H(f)E(f) \quad (5)$$

where $\Lambda(f)=\sum_{k=1}^P \Lambda_k e^{-j2\pi f \Delta t k}$, and $H(f)$ is the transfer function matrix of the system. The DTF value $\gamma_{ij}^2(f)$ from signal j to signal i can be obtained by normalizing the system transfer function matrix

$$\gamma_{ij}^2(f)=\frac{|H_{ij}(f)|^2}{\sum_{m=1}^n |H_{im}(f)|^2} \quad (6)$$

Signals which have significant directional DTF value to other signals were considered to have directional causality to other signals. Nonparametric surrogate testing was conducted to test the significance. The shuffling procedure destroying the phase information of the original signals was repeated 5000 times and the DTF values with the significance level $p<0.05$ were considered as directional significant. Spatial-temporal localized sources having significant directional DTF values to other sources were considered as the primary sources.

2.4 Evaluation of source imaging results

The source imaging results were evaluated with the surgically resected areas of the patients. Structural MRI images were acquired from these patients a few months after their surgical operation (General Electric Medical Systems, Milwaukee, WI). The surgically resected areas were evidenced by post-operative magnetic resonance studies. Since all the patients were seizure free after the surgical operation following one year follow-up, the resected areas of the patients were used as our reference to validate the EEG source imaging results. More specifically, localization error of clinical data, which was defined as the distance between the estimated source to the boundary of surgical resection, was applied to evaluate the source imaging results in patients. The localization error was considered zero if the estimated source was located inside the surgical resection.

2.5 Effect of high-density EEG for source imaging

Computer simulation of ictal source analysis was performed using configurations of different electrode numbers and noise levels. Dipolar sources with random location and orientation were simulated in the 3D brain, and the time course of the source was generated from a damped sinusoidal waveform. A realistic geometric BEM head model was utilized to compute lead-field matrix and simulate 76-channel scalp EEG. Gaussian white noise with different signal-to-noise ratios (SNRs) was added to the generated scalp EEG. The simulated 76-channel EEG was spatially downsampled into uniformly distributed 64, 48, 32, and 21 electrode configurations. At each electrode setting and noise level, FINE was applied to estimate the sources in the 3D brain. Localization error of computer simulation, which was defined as the distance between estimated source and truly simulated source, was incorporated to quantitatively compare the performance of source imaging with different numbers of electrodes.

We then tested the effect of electrode numbers on EEG source imaging results in patient data. As in computer simulation, patient EEG with different electrode configurations (76,

64, 48, 32, and 21 electrodes) was used for ictal source analysis. The sources were localized using the same procedure for all electrode configurations. Localization error of clinical data represents the distance between the estimated source to the boundary of surgical resection. Statistical analysis was performed to test the significance between low density configurations and high density configurations. Dependent t-test was applied to test the significant paired difference between any two electrode configurations. One-way analysis of variance (ANOVA) was also used to test the significant group difference among all the electrode configurations.

3. Results

Ten patients with medically intractable epilepsy were analyzed in this study. High-density EEG was recorded in these patients during the long-term video monitoring at Mayo Clinic. All of the patients had resective surgery and were seizure-free after one-year follow up of the operation.

Patient 1 was a 32-year-old male epilepsy patient suffering from left temporal lobe seizures. Four seizures were captured from this patient during the pre-operative long-term video EEG recording. The scalp EEG waveform (Fig. 2) of one seizure in this patient showed rhythmic delta activities that were initially observed in left temporal electrodes and then remained prominently during the rest of the ictal period. The rising of such rhythmic activities were also found in right temporal electrodes, but in a temporally delayed and attenuated manner.

The source imaging results for Patient 1 is shown in Fig. 3. Two sources (S1, S2) are identified after applying FINE. Fig. 3a, the source locations and extent are superimposed and displayed with the pre-operative structural MRI of the patient. The waveforms of the two sources are also displayed next to the sources in Fig. 3a. The arrow between the sources indicates the connectivity analysis results, directing from primary source to propagated source. Fig. 3b shows the significance level of DTF information flow between S1 and S2 as a function of frequency. DTF results above the red line indicate the significant information flow ($p < 0.05$) from this source to the other source. In this patient, S1 had significant information flow to S2 while no such significance can be observed from S2 to S1. S1 was thus identified as the primary source, which is located in the left temporal lobe. Fig. 3c shows the post-operative MR image with red circle marking out the surgically resected area that is located in the left temporal lobe.

Patient 2 was a 50-year-old female with right temporal lobe seizures. One ictal period was captured from this patient during the long-term video monitoring. Rhythmic activities can be observed over the right hemisphere channels of the patient's scalp EEG during the seizure onset period. This patient underwent right temporal lobe lobectomy. The EEG source imaging results of Patient 2 are shown in Fig. 4. The two sources identified in this patient are located in right frontal lobe (S1) and right temporal lobe (S2). The location and extent of these two sources are displayed in Fig. 4a along with the pre-operative structural MRI of the patient. The waveform of the source activity is also shown next to the two source locations in Fig. 4a. The connectivity analysis results in Fig. 4b show significant information flow from S2 to S1. Accordingly, the primary source identified in this patient was identified as S2, which is localized in the right temporal lobe. Fig. 4c shows the post-operative MR image with surgically resected area circled in the right temporal lobe.

Patient 3 was a 22-year-old female suffering from left frontal lobe seizures. Three seizures were captured from this patient during pre-operative long-term video EEG monitoring. This patient completed a left frontal cortectomy. Rhythmic activities can be observed in the frontal EEG channels during ictal period of the patient. The EEG source imaging results of Patient 3 are shown in Fig. 5. FINE identified two sources (S1, S2) in the frontal lobe. S1 is

in the left frontal lobe and S2 in the right frontal lobe close to the midline. Source locations and activities are shown together with the pre-operative MRI in Fig. 5a. Significant information flow from S1 to S2 is found over the 6–13 Hz frequency band in results of Fig. 5b. The results indicated that S1 is the primary source and is located in the left front lobe, which is in the same area as the surgical resection area (Fig. 5c).

The results in all the 23 seizures of the ten patients were shown in the Table 2. Source imaging results in the rest of the patients were also concordant with the surgically resected areas shown in post-operative MRI images. To quantitatively evaluate the source imaging results, group level analysis of localization error was performed on all the patients by calculating the distance between the estimated source and surgically resected boundary. To study the effect of electrode number in source imaging, we compared the results of different electrode configurations from both computer simulation and patient data.

Fig. 6 shows the localization error of the computer simulation using different electrode configurations and noise levels. Localization errors in the computer simulation were defined as the distance between estimated source and simulated source. Significant group difference (ANOVA, $p < 0.01$) of localization error exists among all the different electrode configurations (76, 64, 48, 32, and 21 electrodes). In low noise level condition (SNR=10 dB), a significant paired difference (t-test, $p < 0.05$) of localization error is observed between any pairs of 64, 48, 32, and 21 electrodes. A significant paired difference can also be observed between 76 electrodes and other configurations (48, 32, and 21 electrodes). When SNR is 0 dB, a significant paired difference ($p < 0.05$) is found between pairs of 76, 64, 48, and 32 electrodes. Significant paired difference can also be found between high density configurations (76, 64, and 48 electrodes) and 21 electrodes. In intermediate noise level condition (SNR=-10 dB), a significant paired difference ($p < 0.01$) is observed between pairs of 64, 48, 32, and 21 electrodes. Significant paired difference can also be observed between 76 electrodes and other configurations (48, 32, and 21 electrodes). In high noise level condition (SNR=-15 dB), significant paired difference ($p < 0.01$) exists between any two pairs of all the electrode configurations. These computer simulation results suggest that localization error increases as the number of electrodes is reduced. Under higher noise level, the localization errors are larger and more significantly distinguishable between different electrode configurations. This indicates the importance of using dense-array configurations in real conditions.

Fig. 7 shows the group level analysis of localization error in all the patient ictal data. Localization errors in clinical data represent the distance between the estimated source and surgically resected boundary. In patient results, larger localization error is also observed in fewer electrode configurations. Statistical t-test shows that the localization error is significantly smaller ($p < 0.01$) in higher density configurations compared to configuration with 21 electrodes. The high density electrode configurations (76, 64, and 48 electrodes) show a significant paired difference ($p < 0.05$) compared to configuration with 32 electrodes. An improving trend for localization can be observed by changing electrode configurations from 48 to 64 channels and from 64 to 76 channels. A significant paired difference ($p < 0.1$) can also be observed between configurations with 76 and 48 electrodes. The ANOVA test shows a significant group difference ($p < 0.05$) of localization error among all electrode configurations. Clinical data analysis presents the significant improvement of EEG source localization by increasing EEG signal channels from low density to high density electrode configurations. The most significantly improved source imaging result is observed in configurations with 76 electrodes. These results demonstrate the importance of applying high-density EEG in source imaging and suggest that it is necessary to use dense array EEG for high resolution source imaging.

4. Discussion

Despite the development and clinical application of various imaging techniques, accurately localizing epileptogenic zones in pre-surgical workup of medically intractable epilepsy remains to be vitally important. Intracranial recordings utilizing subdural grids and depth electrodes are currently the gold standards of identifying the position and extent of epileptogenic zones. Due to the limited spatial coverage and invasive nature of intracranial grids, many noninvasive functional neuroimaging techniques (PET, SPECT, fMRI) have been developed to enhance pre-surgical planning. Each of these functional neuroimaging techniques enables the capture of additional useful information for pre-surgical workup and, ultimately, enhanced outcomes of epilepsy patients. However, these extant techniques have poor temporal resolution and may not indicate the precise epileptogenic zone, but rather regions of seizure propagation. On the other hand, EEG represents a direct measurement of brain electrophysiological activities and has a high temporal resolution (at millisecond scale), which makes it possible to study the initiation and propagation of epileptiform discharges and seizure activities. Long-term video EEG monitoring is now available as a routine procedure in most clinical centers, and could be a more useful pre-surgical evaluation tool when coupled with source analysis techniques.

Many attempts have been made to study the application of noninvasive EEG source imaging techniques for localizing epileptic sources. Cortical potential imaging techniques was applied in epilepsy patients and found the consistency between epileptic cortical areas and surgical resections (Zhang et al., 2003; Lai et al., 2011). Good performance of equivalent current dipole modeling was demonstrated in source analysis of temporal and frontal lobe epilepsy (Gavaret et al., 2004, 2006). Parameterization of ictal data in time domain or frequency domain was also applied to study ictal source analysis (Worrell et al., 2000; Morlet and Gotman, 2001; Lantz et al., 2001; Boon et al., 2002). The approach applied in this study combines spatio-temporal source localization and source connectivity analysis for seizures. This integrative approach is capable of characterizing causal information flow between different sources and discriminating the primary ictal source from propagated sources.

An important issue in EEG source imaging is modeling source configurations and choosing inverse algorithms. Dipolar source model and distributed source model are the most commonly used source models in EEG source imaging (He et al., 2002; Michel et al., 2004). The assumption for dipolar source model is that a few discrete sources are adequate to explain the scalp potential. Studies have shown that equivalent current dipolar source model can be successfully applied in localizing focal epileptiform activities (Assaf and Ebersole, 1997; Gavarat et al., 2004). However, *a priori* knowledge of the source number is usually hard to determine and dipolar models cannot adequately represent the extent of the sources, despite efforts on estimation of the number of dipoles (Bai and He, 2005, 2006). In distributed source models, current sources are located in the whole source space such as 3D brain volume or 2D cortical surface. Various inverse methods were successfully employed to image the electrical sources of epilepsy patients (Assaf and Ebersole, 1997; Gavarat et al., 2004; Michel et al., 2004; Holmes, 2008). To utilize EEG source analysis as a pre-surgical evaluation tool in clinical procedure, more studies are needed to investigate the feasibility of source imaging approaches in localizing epileptogenic foci of epilepsy patients.

Due to the availability and feasibility of dense array EEG recording systems, high-density EEG source imaging has been attracting more and more attention from epilepsy researchers and clinicians. Studies have shown that more recording electrodes allow for accurate epileptic source localization results (Lantz, et al., 2003). A great precision in localizing interictal epileptic activity was reported by applying high-density EEG source imaging in

epilepsy patients (Michel et al., 2004). Dense array EEG has also proved useful in noninvasive ictal localization for both generalized and localization-related seizures (Holmes, 2008). In contrast to routine scalp EEG recordings in current clinical settings, which only use 19–21 recording electrodes, in this study we utilized high-density EEG with 76 channels to localize ictal onset zones with high resolution. We also compared the source imaging results in different electrode configurations by downsampling 76 channels into 64, 48, 32, and 21 channels. Our results demonstrated the significant improvement of EEG source localization by increasing the electrode numbers. That is, the most significantly improved result was observed in configurations with 76 electrodes. The potential application of high-density EEG may provide more information than the traditional scalp EEG recordings and help lateralizing or localizing epileptogenic zones.

Epilepsy patients with partial seizures usually limit their seizure activities in a few focal regions of the brain. In this study, seizure source imaging was successfully applied to ten partial epilepsy patients in localizing their epileptogenic zones. In extratemporal patients or other epilepsy patients, seizure activities may start from more brain regions and involve with larger brain networks. Studies in different epilepsy types in the future may be interesting and meaningful to extend the seizure imaging in more complex epilepsy types. While the nature of the present study involves a substantial amount of work including high density EEG recordings, seizure source imaging and comparison with surgical resection outcomes, the study is limited in its patient population. Future studies in larger patient groups may still be needed to assess the high-density EEG recording and seizure imaging in localizing epileptogenic zones.

In summary, we applied the FINE approach to noninvasively localize the seizure activities of medical intractable partial epilepsy patients. High-density EEG recordings together with patient specific BEM head models were utilized to improve the spatial resolution of the source imaging. Furthermore, Granger causality analysis using DTF was used to further define the primary seizure sources. Our source imaging results in the ten epilepsy patients showed high co-localization with their surgical resections. We further compared the performance of source imaging from different numbers of electrodes. Computer simulation and clinical data analysis showed the improvement of EEG source imaging as a result of increasing the number of electrodes. Overall, the present study demonstrates the feasibility of high-density EEG recordings and high resolution ictal source analysis in localizing ictal onset zones and indicates its potential usage in pre-surgical planning of epilepsy patients.

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Highlights

- FINE spatial-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.

Fig. 1.
Diagram of procedural steps in the present seizure source imaging.

Fig. 2.

The waveform and time-frequency representation of the ictal scalp EEG data with 76-channel recordings. The red vertical line marked on the EEG waveform is the seizure onset time recognized by experienced epileptologists. EEG channels near left temporal lobe (LT) and right temporal lobe (RT) of the patient were marked on the right side of the EEG waveform.

Fig. 3. Source imaging results of Patient 1. (a) Waveforms (green curves), locations (highlights on grey MRI images), and directional causality (blue arrow) of two sources (S1, S2). (b) Significance level of directional DTF values between S1 and S2. Statistical DTF value above the red line is significant with p -value < 0.05 . (c) Surgical resection marked by red circle on post-operative MR image. Patient 1 had left temporal lobe epilepsy.

Fig. 4. Source imaging results of Patient 2. (a) Waveforms, locations, and directional causality of two sources (S1, S2). (b) Significance level of directional DTF values between S1 and S2. (c) Surgically resected area on post-operative MR image. Patient 2 had right temporal lobe epilepsy.

Fig. 5. Source imaging results of Patient 3. (a) Waveforms, locations, and directional causality of two sources (S1, S2). (b) Significance level of directional DTF values between S1 and S2. (c) Surgical resection on post-operative MR image. Patient 3 had left frontal lobe epilepsy.

Fig. 6. Mean and standard deviation of localization errors in computer simulation. Localization errors of different electrode configurations (76, 64, 48, 32, and 21 electrodes) are coded in colors (from white to black). Simulation results in different noise levels are separated in groups.

Fig. 7.
Mean and standard deviation of localization errors in clinical data analysis.

Table 1

Clinical information of the patients in this study.

Patient	Gender	Age	Ictal symptoms	Pathology	MRI lesion	Depth electrode/Surgery	Outcome
1	Male	32	Behavioral arrest, oral automatisms, and right arm posturing	Left hippocampus: mesial temporal sclerosis	Left HC atrophy and T2 signal	Left anterior temporal lobectomy	ILAE-1
2	Female	50	Sense of impending doom, oral automatisms	Right hippocampus: mesial temporal sclerosis	Right HC atrophy	Right temporal lobectomy	ILAE-1
3	Female	22	Left hand nose wiping, and oral automatisms	Subcortical and subpial gliosis	Left frontal polar encephalomalacia	Left frontal cortectomy	ILAE-1
4	Male	58	Swallowing and oral automatisms; non-forced head turning to left	Right temporal subpial gliosis	Normal	Right temporal depth electrode/Right anterior temporal lobectomy	ILAE-1
5	Female	28	Right hand automatisms, oral automatisms, ictal scream, and hypermotor activity	Gliosis, subpia, subcortical, entorhinal cortex	Normal	Left temporal depth electrode/Left temporal lobectomy	ILAE-1
6	Female	45	Behavioral arrest, oral automatisms, and right arm posturing	Severe subpial gliosis consistent with chronic seizure disorder	Mild generalized cerebellar atrophy	Right temporal lobectomy	ILAE-2
7	Male	49	Behavior arrest followed by oral automatisms	Cortex and white matter with non-specific mild gliosis	Focal mass anterior left temporal lobe	Left temporal lobectomy	ILAE-1
8	Female	33	Behavioral arrest, staring, chewing type oral automatisms	Right hippocampus: mesial temporal sclerosis	Bilateral increased T2 signal in HC without evidence of	Right temporal lobectomy	ILAE-1
9	Female	25	Oral automatisms and right hand more often than left hand automatisms	Right hippocampus: mesial temporal sclerosis	Normal	Right temporal lobectomy	ILAE-1
10	Female	51	Lip smacking movements, tightness of the left face, head turn to the left	Gliosis, subpia, subcortical, entorhinal cortex	T2 hyperintensity in the right inferior temporal cortex	Right anterior temporal lobectomy	ILAE-1

ILAE: International league against epilepsy. ILAE-1: Completely seizure free; no auras. ILAE-2: Only aura, no other seizures.

Table 2

Summary of source image results in all 23 seizures of the ten patients. The estimated sources are compared with surgical resection of the patients.

	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6	PT 7	PT 8	PT 9	PT 10
+	4	1	2	1	1	1	0	1	2	3
++	0	0	1	1	0	2	1	0	1	0
+++	0	0	0	0	0	1	0	0	0	0
Total	4	1	3	2	1	4	1	1	3	3

+: within 10 mm distance to the surgical resection boundary. ++: within 20 mm distance to the boundary. +++: within 25 mm distance to the boundary.