Published in final edited form as:

Phys Med Biol. 2006 August 21; 51(16): 4047–4062.

3D Source Localization of Interictal Spikes in Epilepsy Patients with MRI Lesions

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Abstract

Objective—The present study aims to accurately localize epileptogenic regions which are responsible for epileptic activities in epilepsy patients by means of a new subspace source localization approach, i.e. First-principle-vectors (FINE), using scalp EEG recordings.

Methods—Computer simulations were first performed to assess source localization accuracy of FINE under the clinical electrode set-up. The source localization results from FINE were compared with the results from a classic subspace source localization approach, i.e. MUSIC, and their differences were tested statistically using the paired t-test. Other influence factors to source localization accuracy were assessed statistically by ANOVA. The interictal epileptiform spike data from three adult epilepsy patients with medically intractable partial epilepsy and well-defined symptomatic MRI lesions were then studied using both FINE and MUSIC. The comparison between the electrical sources estimated by the subspace source localization approaches and MRI lesions were made through the co-registration between the EEG recordings and MRI scans. The accuracy of estimations made by FINE and MUSIC was also evaluated and compared by R^2 statistic, which was used to indicate the goodness-of-fit of the estimated sources to the scalp EEG recordings. The 3-concentric-spheres head volume conductor model was build for each patient with different radii of three spheres which takes the individual head size and thickness of individual skull into the consideration.

Results—The results from computer simulations indicate that the improvement of source spatial resolvability and localization accuracy of FINE as compared with MUSIC is significant when simulated sources are closely spaced, deep, or signal-to-noise-ratio is low in a clinical electrode set-up. The interictal electrical generators estimated by FINE and MUSIC are in concordance with the patients' structural abnormality, i.e. MRI lesions, in all three patients. The higher R^2 values achieved by FINE than MUSIC indicate that FINE provides a more satisfactory fitting of the scalp potential measurements than MUSIC in all patients.

Conclusions—The present results suggest that FINE provides a useful brain source imaging technique, from clinical EEG recordings, for identifying and localizing epileptogenic regions in epilepsy patients with focal partial seizures.

Significance—The present study may lead to establishment of a high resolution source localization technique from the scalp recorded EEGs for aiding presurgical planning in epilepsy patients.

Keywords

source localization; high-resolution EEG; FINE; MUSIC; epilepsy; interictal; presurgical planning

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1. Introduction

For patients with recurrent unprovoked seizures originating from a focal region of the brain that are not controlled with medication, medically refractory partial epilepsy, surgical resection of the brain region generating the seizures can be curative (Engel, 1993). Successful epilepsy surgery depends on the accurate localization of epileptogenic brain, the focal region of brain generating the partial onset seizures, and is the goal of the presurgical evaluation. The rapid advance in imaging technologies, has significantly enhanced the identification of potential regions of epileptogenic brain; Magnetic resonance imaging (MRI) has made routine the detection of structural lesions (tumors, vascular malformations, encephalomalacia, neuronal migration abnormalities, etc.) and functional imaging with PET and SPECT can identify regions of functional abnormality that may not have a corresponding structural lesion (non-lesional MRI). Despite the rapid advance of imaging modalities the electroencephalogram (EEG) continues to play a critical role in the selection of patients for epilepsy surgery.

Potential candidates for epilepsy surgery have their habitual seizures recorded with video scalp EEG in an effort to localize the focal region of seizure onset. Recording the patients' habitual seizures using intracranial subdural electrodes and/or intraparenchyma depth electrodes remains the gold standard for identifying epileptogenic brain. However, the extent of implantation with intracranial electrodes is limited by the increased risk of serious complication with increasing number of intracranial electrodes. Thus, the non-invasive evaluation (most commonly including: MRI, SPECT, PET, video scalp EEG, and seizure semiology) is used to develop a clinical hypothesis for the location(s) of epileptogenic brain and to guide the location of implantation of intracranial electrodes.

High-resolution EEG imaging, achieved using scalp recorded EEGs and solving the inverse problem, have been extensively explored and developed in the past several decades. These achievements make scalp EEG-based imaging approaches more interesting and potentially clinically useful for localization of sources of seizures and interictal epileptiform activity, which may ultimately help guide implantation of intracranial electrodes and guide epilepsy surgery. These efforts include dipole source localization (Kavanagh et al., 1978; Scherg and Von Cramon, 1985; He et al., 1987; Ebersole, 1994; Roth et al., 1997; Mosher et al., 1992; Sekihara et al., 1997; Mosher and Leahy, 1999) and distributed current source estimation (Hamalainen and Ilmoniemi, 1984; Dale and Sereno, 1993; Pascual-Marqui et al., 1994; Michel et al., 1999; Worrell et al., 2000; He et al., 2002a, 2002b; He & Lian, 2005). Among them, several techniques have been directly applied to the source localization of seizures and interictal spikes in epilepsy patients (Ebersole, 1994; Roth et al., 1997; Michel et al., 1999; Worrell et al., 2000). Another useful source characterization approach is known as cortical potential imaging (CPI) technique (Sidman et al., 1990; Gevins et al., 1994; He et al., 1996; Babiloni et al., 1997; He et al., 2002c; Zhang et al., 2003), which reconstructs the epicortical potential distribution from a recorded scalp potential distribution. This method shows promise for reconstructing the intracranial potential obtained from electrocorticogram (ECoG) recordings from subdural grid electrodes (He et al., 2002c; Zhang et al., 2003), which are widely used for defining epileptogenic brain regions clinically (Engel et al., 1981).

The objective of the present study is to test the applicability of a new high-resolution three dimensional (3D) subspace source localization approach (first principle vectors, FINE) (Xu et al., 2004) in imaging the cerebral sources of focal interictal epileptogenic activity. The subspace source localization approach was first introduced by Mosher et al. (1992) in magnetoencephalogram (MEG) source localization problem using dipole source model, known as multiple signal classification (MUSIC). The subspace source localizations use a scanning technique instead of solving difficult multi-dimensional nonlinear optimization problems (Kavanagh et al., 1978; He et al., 1987; Ebersole, 1994; Roth et al., 1997). The imaging results

from the subspace source localization approaches will directly provide estimate of the source distribution in the 3D brain volume and gain the depth information of sources which cannot be obtained by surface recordings, e.g. ECoG, or cortical surface source imaging techniques. As compared with the distributed current source model used in the distributed source estimation approaches, multiple equivalent current dipoles are often sufficient to accurately represent sources of the measured scalp potential data in epilepsy patients with focal origin. Of particular importance is that the inverse problem with the 3D distributed current source model is highly underdetermined and thus necessitates the introduction of priors in order to solve the inverse problem, which typically smoothes the estimation (Hamalainen and Ilmoniemi, 1984; Jeffs et al., 1987; Pascual-Marqui et al., 1994; He et al., 2002a). Subspace source localization approaches have promised to reveal more detailed neural activities within the 3D brain volume from noninvasive EEG/MEG measurements. In an effort to enhance the spatial resolution of the subspace source localization approaches, the recursively applied and projected MUSIC (RAP-MUSIC) algorithm (Mosher and Leahy, 1999) was developed and its improved performance in two highly correlated sources was demonstrated. Sekihara et al. (1997) incorporated the noise characteristics of the background brain activity into the MUSIC algorithm, which improved its performance in the presence of the background activity. In our previous study (Xu et al., 2004), a new subspace source localization algorithm – FINE was proposed and evaluated via computer simulations using 128 electrodes in a 3-concentric-spheres head model, which suggested that FINE provided enhanced ability of estimating multiple closely-spaced sources, as compared with MUSIC and RAP-MUSIC.

In the present study, we assess the feasibility and ability of FINE to localize brain sources within the 3D space in a clinical electrode set-up. Computer simulations were conducted to evaluate its source localization performance in comparison with MUSIC using 32 electrodes in both simulated Gaussian white noise (GWN) and real noise recorded in a subject during rest condition. The results from FINE and MUSIC were statistically assessed by the paired t-test and ANOVA. After the characterization of the performance of the different methods in simulation studies, both of them were applied to localizing epileptogenic region from the interictal scalp EEG in patients with medically intractable partial epilepsy who have clear symptomatic lesions on MRI. The performance of FINE and MUSIC was compared in terms of goodness-of-fit (GOF) indicated by R^2 statistic. The imaged results from subspace source localization methods were then validated in reference to MRI lesions.

2. Methods

2.1. FINE

The FINE algorithm (Xu et al., 2004) is developed under the framework of the subspace source localization approach (Mosher et al., 1992) and solves the spatio-temporal source localization problem using a scanning strategy instead of optimizing a multidimensional cost function, which is prevailing in the traditional dipole source localization. In principle, the subspace source localization approach scans the entire possible source space and calculates the subspace correlation (Mosher and Leahy, 1998) of two subspaces. One subspace is spanned by each scanned point and another one is estimated from the scalp EEG, which is known as the noise-only subspace. If the subspace correlation is approximate to zero against the noise-only subspace for one possible source point, this point is regarded as a source. Multiple sources could thus be obtained at multiple extreme values. The FINE algorithm calculates the correlation to a particular subset of the noise-only subspace instead of the entire noise-only subspace, which helps to achieve high spatial resolution.

The spatial correlation matrix R_Φ of scalp EEG measurement can be expressed as

$$R_{\Phi} = AR_S A^T + R_N \quad (1)$$

where Φ is a spatio-temporal data matrix representing the scalp EEG on the measurement electrodes over a period of time. A is the gain matrix and $R_S = \frac{1}{M}SS^T$, where M is number of time samples, is the signal correlation matrix. Considering spatio-temporal Gaussian white noise and homogeneous noise level among different electrodes, the noise correlation matrix $R_N = \sigma^2 I$. Otherwise, R_N is a non-diagonal matrix in which the non-diagonal elements indicate the noise correlation among different electrodes. The measurement space spanned by $R_{\Phi} = \frac{1}{N}\Phi\Phi^T$ can be partitioned into the signal subspace E_s and the noise-only subspace E_n (Schmidt, 1979) using eigen-decomposition. The MUSIC algorithm can thus be defined on the noise-only subspace as

$$J_{MUSIC}(r) = \lambda_{\min} \left[U_{A(r)}^T E_n E_n^T U_{A(r)} \right] \quad (2)$$

where $J_{MUSIC}(r)$ is the MUSIC estimator at possible source location r , $U_{A(r)}$ contains left singular vectors of the gain vector $A(r)$, which is the subspace span of the scanned source point. And $\lambda_{\min}$ is the smallest eigenvalue of the given bracketed items (see Mosher et al., 1992 for details). In the algorithm implementation, a 3D scanning is performed on a 3D grid to obtain MUSIC estimator value at each possible source location r . Each local extreme value close to zero on the 3D grid will be regarded as a source.

The MUSIC estimator projects the gain vector $A(r)$ at each possible source location onto the entire noise-only subspace and thus sums up the projections over all the vectors in the span of the noise-only subspace. Due to summation, the MUSIC results are smoothed out and its spatial resolution is limited, which decreases its ability to detect closely-spaced sources. In the FINE algorithm, for each scanned point, a region θ , which surrounds the scanned point, could be found and a small set of vectors in the noise-only subspace, denoted by FINE vector set F_{θ} , could be identified as an intersection set between the noise-only subspace and the array manifold spanned by the specific region θ based on the concept of principal angles (Golub and Van Loan, 1983; Buckley and Xu, 1990). We have found that the projection over FINE vector set F_{θ} could lower down the spatial resolution threshold for closely-spaced sources as compared with the projection over the entire noise-only subspace, especially under the condition with low signal-noise-ratio (SNR) which was discussed as SNR resolution threshold in spectrum analysis by Buckley and Xu (1990). Thus, the FINE vector set consists of the influential vectors from the noise-only subspace in terms of spatial resolution. By abandoning the remaining less important vectors, FINE, thus, reduces the smoothing effect. The FINE estimator can then be expressed finally as (see Xu et al., 2004 for details)

$$J_{FINE}(r) = \lambda_{\min} \left[U_{A(r)}^T F_{\Phi} F_{\Phi}^T U_{A(r)} \right] \quad (3)$$

The FINE algorithm, like all other subspace source localization approaches, uses the separated steps to estimate source locations and orientations. The first step to estimate the source locations is achieved by (3). Because the assumed current dipole source in the EEG inverse problem is a vector field, the bracketed item in (3) is a 3×3 matrix and its eigenvalues after eigen-decomposition form a 3D vector which defines the subspace correlations of the vector field. If only the smallest eigenvalue, which is denoted by $\lambda_{\min}$, is approximately zero, it indicates that the dipole at the estimated location is fixed. Otherwise, the dipole is rotating with some freedoms, 2 or 3, depending on how many eigenvalues are approximately zero. The orientations of the dipole are the eigenvectors associated with those eigenvalues close to zero.

With the known location and orientation of the estimated dipoles, the gain matrix A is given for these dipoles. The amplitudes of the estimated dipoles in the time series can be estimated as

$$S = A^+ \Phi \quad (4)$$

where A^+ is the well-known pseudoinverse solution (Mosher et al., 1992).

$$A^+ = (A^T A)^{-1} A^T \quad (5)$$

We will focus on discussing the source localization ability of the FINE algorithm in this article. On the other hand, in order to evaluate the source localization accuracy in clinical data analysis, the R^2 statistic, as described below, will be calculated to estimate the goodness-of-fit (GOF) for source localization results from FINE and MUSIC. Such GOF analysis needs the complete estimation of dipole parameters including location, orientation, and amplitude.

2.2. Goodness-of-Fit

In the interictal data analysis from epilepsy patients, after fitting the scalp EEG data with the estimated dipoles, the goodness-of-fit (GOF) is calculated and evaluated using R^2 statistic. The R^2 statistic measures how successful the fit is in explaining the variation of the data. R^2 is the square of the correlation between the scalp EEG data and the predicted values from the estimated dipoles by solving the forward problem, which is defined as the ratio of the sum of squares of the regression (SSR) and the total sum of squares (SST). It is defined as

$$SSR = \sum_{i=1}^n (\hat{\varphi}_i - \bar{\varphi})^2; \quad SST = \sum_{i=1}^n (\varphi_i - \bar{\varphi})^2; \quad R^2 = \frac{SSR}{SST} \quad (6)$$

where $\hat{\varphi}_i$, $i = 1, \dots, n$ is the predicted scalp potential from the estimated dipoles at each electrode and n is the number of electrodes. φ_i , $i = 1, \dots, n$ is the measured scalp potential at each electrode site and $\bar{\varphi}$ is its average. The SSR and SST are calculated at each time point and two types of R^2 values are used in this study. The R^2 statistic is firstly calculated at the interictal spike peak, which is the time point with maximal SNR. Then, the R^2 statistic over the entire spike period (see section 2.5 on how to define the spike period) are calculated and averaged to evaluate the average fit over the observation period.

2.3. Simulation protocol

Computer simulations using the clinical electrode number, i.e. 32, were conducted to evaluate the FINE algorithm and compared with the MUSIC algorithm in a three-sphere concentric head model, which simulates the scalp, skull, and brain. The radii of three spheres are 100 mm, 92 mm, and 87 mm from the outmost to the innermost. The conductivities for the scalp and brain tissue were same with value of $0.33/\Omega \cdot m$. And the conductivity ratio between the brain and skull was 1:1/20, as suggested in a recent *in vivo* human brain-to-skull conductivity ratio study (Lai et al., 2004), instead of 1:1/80 (Rush and Driscoll, 1968; Cuffin, 1990). The values of estimators were scanned on a discrete cubic grid with more than 170,000 grid points. The inter-grid distance was 2 millimeter (mm). Furthermore, a small local refined cubic grid with an inter-grid distance of 0.5 mm was formed at each identified peak on the sparse 2 mm-grid and a local scan on the high-density grid was performed.

The effects of SNR, distance between two closely-spaced sources (DISTANCE), and source depth (ECCENTRICITY) on source imaging accuracy were investigated by the computer simulations. In each source configuration, two closely-spaced radial current sources which were uncorrelated in time domain were simulated. Both sources had damped sinusoid

waveforms with frequency of 5 Hz and 7.5 Hz, respectively. The time interval was 100 ms and the sampling frequency was assumed to be 1 kHz. The distance between the two simulated sources ranged from 10 mm to 30 mm. The three different SNR values, i.e. 8 decibels (db), 12 db, and 16db, were considered. The eccentricity of the sources varied from 35 mm to 80 mm. All computer simulations for each set of parameters were repeated 200 times using randomly generated GWN to reduce the uncertainty and bias during the realization of a random process. The same simulations were also performed 200 times using real noise collected in a subject who was in rest condition with eyes open. The noises obtained from the subject were scaled to different levels as to simulated signals in order to achieve different SNR values. We first defined the detection rate (DR) as a criterion to evaluate the spatial resolvability of methods to distinguish two simulated sources. A trial was defined as a successful trial only if two sources were both identified. The DR was thus defined as the ratio between the number of successful trials and the total number of trials, i.e. 200, in each simulation condition. The source localization error defined as the distance between simulated source and estimated source was further used in those successful trials to access the accuracy of methods. The results were then statistically evaluated by the paired t-test since both methods were applied in same simulated conditions. It is noted that a trial is excluded from paired data pool if it is an unsuccessful trial in either method otherwise it leads to imperfect paired data. We further examined the results from different conditions, e.g. type of noise (TYPE), SNR, DISTANCE, and ECCENTRICITY, statistically by analysis of variance (ANOVA) for multiple comparison problems.

2.4. Patients and data acquisition

Three patients with medically intractable partial epilepsy and symptomatic lesions on MRI were studied using a protocol approved by the Institutional Review Boards of the University of Minnesota and Mayo Clinic. Each patient was admitted to the Mayo Clinic epilepsy monitoring unit for presurgical evaluation that included structural MRI, interictal, and ictal long-term video scalp EEG monitoring.

The patients' EEGs were recorded using 31 electrodes in the modified 10/20 system and were collected continuously using a C_z reference montage at a sampling rate of 200 Hz with a bandpass filter of 1.0 to 35 Hz and a highpass filter of 4 Hz was applied to the interictal EEG. The positions of electrodes as well as the positions of 3 fiducial points on the head (nasion and left and right preauricular points) were digitized by using a handheld magnetic digitizer (Polhemus, Inc., Colchester, VT). For each patient, 3 independent measurements were digitized and the average of these 3 measurements was obtained while discarding outliers. The average electrode position was then used for all subsequent analysis.

Each patient had a standardized seizure protocol MRI (Jack 1995), which demonstrated a potentially epileptogenic structural abnormality. The MRI was acquired on a 1.5-Tesla GE Signa using a SPGR sequence (TR = 24 ms, TE = 5.4 ms) with a 220 mm field of view. The 120-coronal-slice protocol produces a voxel dimension of $0.9375 \times 0.9375 \times 1.6$ mm.

2.5. Analysis protocol

The interictal EEG records were reviewed for the occurrence of interictal spikes via the visual inspection of the EEG by experienced epileptologists (GW and TL). Fig. 2(a), Fig. 3(a), and Fig. 4(a) show the half-second-long 31-channel scalp waveforms from Patient 1, Patient 2, and Patient 3, respectively. The EEG was reformatted to an average reference montage for illustration and analysis. The peaks of the interictals were marked with the vertical black bars on the channels with maximal signal strength. Fig. 2(b), Fig. 3(b), and Fig. 4(b) show the successive scalp potential maps around the interictal peaks at every 20 ms, which are plotted using EEGLAB (Delorme and Makeig, 2004). The temporal evolution of the interictal spikes

was examined using time-frequency representation (TFR), which convolute the signal by complex Morlet's wavelets (Tallon-Baudry et al., 1997; Qin et al., 2004) and provides a time-varying energy of the signal in each frequency band, to identify the segment in the time domain for the spatio-temporal analysis of FINE and MUSIC. The frequency bin with the maximal signal energy was identified from each TFR, which represents the average intensity over all electrodes, for each patient. The temporal window was defined by the full width at half maximum (FWHM) principle at the identified frequency bin. This procedure gave time points within the FWHM one and half to two and half times more than the electrode number, i.e. 31, which satisfies the required condition for the spatio-temporal data analysis in the FINE algorithm that the number of time samples is greater than the number of sensors in order to make the satisfactory estimates of the noise-only subspace. Fig. 2(c), Fig. 3(c), and Fig. 4(c) show the TFRs for interictal spikes from Patient 1, Patient 2, and Patient 3, respectively. The interictal data was analyzed by using both the FINE and MUSIC algorithm. The p largest eigenvalues were chosen based on the singular value decomposition (SVD) according to the following procedure. In each patient, data just before spike with the same length as the spike period defined above was chosen as pre-spike data. The singular value curves for both pre-spike and spike data were plotted together and the merging point between two curves was selected to decide p value. The procedure is similar to the method adopted in other researchers' work (Mosher et al., 1992). The peaks were selected when the subspace correlation values were less than 0.05 against the noise-only subspace (Mosher and Leahy, 1998). The p values for these three patients are 5, 4, and 5, respectively.

The spatio-temporal FINE source imaging was performed using the three-sphere concentric inhomogeneous head model, which best fits onto the geometry of the patients obtained based on MRI. The co-registration procedure minimized the fitting distance defined on the surface of electrode positions and the upper hemisphere of the spherical surface. The imaged sources of neural activity from FINE were compared with the locations of the patients' lesions on MRI by coregistration (Fig. 2–4 (d–e)). Coregistration was achieved by matching the location of 3 fiducial points (nasion and left and right preauricular points) on the MRI to the digitized coordinates of these points. The segmentations of the scalp and skull for three patients were performed on the MRI images using Curry software (NeuroScan Labs, TX) individually. The thicknesses of the scalp and skull for each head model are decided by the segmentation results in an average fashion and, thus, vary among the three patients. The conductivities for the scalp and brain tissue are 0.33/ Ω .m and the conductivity ratio between the brain and skull is 1:1/20 (Lai et al., 2004).

3. Results

3.1. Simulation results

Fig. 1 summarizes the computer simulation results in the six plots for both GWN (Fig. 1(a–c)) and real noise (Fig. 1(d–e)). Comparing the results for FINE and MUSIC in each plot, FINE shows better spatial resolvability than MUSIC as indicated by the criterion DR. For real noise, FINE has higher DR values than MUSIC in most simulated conditions except when sources are well separated (DISTANCE = 25 or 30 mm (Fig. 1(d))). In conditions of GWN, the DR values between FINE and MUSIC only show large difference when sources are closely spaced (Fig. 1(a)) and in low SNR (Fig. 1(b)). The paired t-tests further show significant difference in source localization errors between FINE and MUSIC for conditions using GWN which are marked by stars. When the two sources are closely spaced, FINE has smaller localization errors than MUSIC ($P < 0.0005$, $n = 173$ for DISTANCE = 15 mm and $P < 0.05$, $n = 11$ for DISTANCE = 10 mm) (Fig. 1(a)). FINE has better source localization accuracy in different SNR ($P < 0.005$, $n = 200$ for SNR = 16 db and $P < 0.0005$, $n = 173$ for SNR = 12 db). The FINE algorithm also shows better performance for the deep sources than the MUSIC algorithm ($P < 10^{-8}$ when

ECCENTRICITY = 57 mm, 45 mm, and 35 mm) while their performance is similar for the superficial sources (ECCENTRICITY = 81 mm and 70 mm). While the paired t-test was also applied to real noise conditions, no statistical significance ($P < 0.05$) was observed in all simulated conditions, which must be due to the greater difference in DR. In most conditions, the DRs for MUSIC are less than 0.3 and some of them are close to zero detection (such as DR = 0 for DISTANCE = 10 mm, DR = 0.06 for DISTANCE = 15 mm (Fig. 1(d)), and DR = 0.01 for SNR = 12 db (Fig. 1 (e))), which led to the limited trial number for statistical evaluation.

In the ANOVA analysis, the dependent variable was the source localization errors, representing the average errors over the two simulated sources. The results revealed a strong statistical influence of the main factors DISTANCE ($F = 174$, $P < 10^{-8}$), SNR ($F = 299$, $P < 10^{-8}$), ECCENTRICITY ($F = 144$, $P < 10^{-8}$), and TYPE ($F = 2279$, $P < 10^{-8}$ for data shown in Fig. 1(a) and (d)). Figs. 1(a) and (d) show the DISTANCE effect on the source localization accuracies when considering GWN and real noise, respectively. In both conditions, while the eccentricities of the two simulated sources are the same of 75 mm, SNR is 12 db for GWN and 16 db for real noise. When DISTANCE decreases, the DR values decrease and the localization errors increase. Post-hoc tests (Duncan at 0.5%) revealed that there are significant differences among all levels of factor DISTANCE except between DISTANCE = 30 mm and 25 mm. Figs. 1(b) and (e) show the SNR effect on the source localization accuracy at three levels, i.e. 16 db, 12 db, and 8 db, when considering GWN and real noise. The distance of the two simulated sources is 15 mm and their eccentricities are around 75 mm. Post-hoc tests (Duncan at 0.5%) revealed that there are significant differences among all levels of factor SNR. Fig. 1(c) (for GWNs) and (f) (for real noises) shows the depth effect on the source localization accuracy of the subspace source localization approach. The distance of the two simulated sources is 20 mm and the SNR is 12 db for conditions with GWNs or 16 db for conditions with real noises. The source localization accuracies of both MUSIC and FINE algorithms are depth dependent. Generally, when the depth increases, the localization error increases. Post-hoc tests (Duncan at 0.5%) revealed that there are significant differences between superficial sources (ECCENTRICITY = 81 mm or 70 mm) and deep sources (ECCENTRICITY = 57 mm, 45 mm, or 35 mm). The most superficial simulated sources (ECCENTRICITY = 81 mm) exhibit worse performance as compared with their neighbored sources in term of depth, which may be due to their closeness to the boundary between the brain and skull. The reduction of source localization errors at ECCENTRICITY = 35 mm as at ECCENTRICITY = 45 mm may be caused by the different selections of region θ at different locations. Furthermore, by comparing the data in the right of Fig. 1 to the data from its left, the DR values decrease and localization errors increase dramatically in conditions with real noises. This is also indicated by ANOVA analysis ($F = 2279$, $P < 10^{-8}$ for data shown in Fig. 1 (a) and (d), $F = 536$, $P < 10^{-8}$ for data shown in Fig. 1(b) and (e), $F = 2049$, $P < 10^{-8}$ for data shown in Fig. 1(c) and (f)).

3.2. Patient 1

Fig. 2(a) shows the 31-channel waveforms for Patient 1 in one interictal recording with length of 0.5 s. Fig. 2(b) shows the successive scalp potential maps around the interictal peak at every 20 ms and Fig. 2(c) shows the TFR energy distribution for the patient averaged over all channels and normalized with its maximal value. The time window defined by the FWFEM principle is about 0.3 s which consists of 63 time samples. For the head model of this patient, the ratio between the radius of the innermost sphere and of the outmost sphere is 0.8935, and the ratio between the radius of the middle sphere and of the outmost sphere is 0.9468. Fig. 2(d) show the FINE-imaged interictal sources with MR images as background and Fig. 2(e) show the MUSIC-imaged interictal source. All sub-plots are normalized by their own maximal value of $1/J(r)$ and certain extents with consistent display percentage, e.g. 0.95 for this patient, are shown with pseudo-color in order to indicate the sharpness of peaks obtained from algorithms.

The waveforms for reconstructed current sources, which indicate the strengths of sources, are plotted in the small inset figures related to each source shown in Fig. 2(d–e).

This patient has a right frontal cavernous hemangioma which is clearly demonstrated by the MR images (Fig. 2(d–e)). The scalp EEG shows the strong activity at the front area of the right hemisphere and both individual EEG maps at single times of 240 ms and 260 ms indicate their positivity moving to the right temporal area, but with associated negativity on the left front area. Two peaks are identified in the FINE result, both of which are within the right posterior inferior frontal lobe. One (Fig. 2(d), left) appears at the border of the MRI lesion and the second peak (Fig. 2(d), right) is 19.0 mm away from the first one, which is more lateral than the MRI lesion. Only one peak is identified in the MUSIC result (Fig. 2(e)). It is corresponded to one of the FINE peaks (Fig. 2(d)) with distance of 7.3 mm. The subspace correlations are 0.0097 and 0.0120 against the noise-only subspace for the two FINE peaks, respectively, while the subspace correlation is 0.0098 for the MUSIC peak.

3.3. Patient 2

Fig. 3(a) shows the 31-channel waveforms for Patient 2 from one interictal recording with length of 0.5 s and Fig 3(b) shows the successive scalp potential maps around the interictal peak at every 20 ms and Fig. 3(c) shows the averaged TFR energy distribution for the patient. The time window defined by the FWFM principle is about 0.37 s which consists of 74 time samples. For the head model of this patient, the radius ratios, between the innermost sphere or middle sphere and the outmost sphere, are 0.8391 and 0.9296, respectively. Fig. 3(d) show the FINE-imaged interictal sources with MR images and their waveforms and Fig. 3(e) shows the MUSIC-imaged interictal source with its waveform.

This patient has a right frontal tumor, seen in the MR images (Fig. 3(d–e)). The major EEG also shows a strong electrical activity at the front area of the right hemisphere and an individual EEG map at single time of 245 ms seems more temporal in its positivity as compared with maps from other time points, with its associated negativity on the central front area. Two peaks are identified in the FINE result and only one peak is identified in the MUSIC result. The MUSIC peak (Fig. 3 (e)) is close to one of the FINE peaks (Fig. 3 (d)) with distance of 2 mm and both appear at the edge of the MRI lesion. The second peak (Fig. 3 (d)) identified in the FINE result is 23.6 mm away from the first FINE peak, which is more lateral, frontal, and superior. It is also at the border of the MRI lesion. The subspace correlations are 0.0092 and 0.0093 against the noise-only subspace for the two FINE peaks and the subspace correlation is 0.0096 for the MUSIC peak.

3.4. Patient 3

As above, Fig. 4 (a), (b), and (c) show the 31-channel waveforms of a 0.5 s-long interictal data, the scalp potential maps around the interictal peak, and the averaged TFR energy distribution for Patient 3, respectively. The time window defined by the FWFM principle is about 0.26 s which consists of 52 time samples. For the head model of this patient, the radius ratios, between the innermost sphere or middle sphere and the outmost sphere, are 0.8379 and 0.9109, respectively. Fig. 4(d) and (e) show the FINE-imaged and MUSIC-imaged, respectively, interictal sources with MR images and their waveforms.

This patient has a right frontal abscess with residual encephalomalacia. MR images indicate a large region damaged brain tissue in the right frontal area as showed in Fig. 4 (d–e). The scalp EEG shows a lasting electrical activity in the right frontal lobe. One peak (Fig. 4(d)) is identified by both the FINE (Fig. 4(d)) and MUSIC (Fig. 4 (e)) within the right anterior frontal lobe and at the edge of the MRI lesion. The distance between the MUSIC peak and the FINE peak is 3.5 mm. The subspace correlation is 0.0084. Another peak is also identified in the sensory-

motor cortex with the subspace correlation of 0.0113 by both algorithms, which may be caused by the movement of the patient during the recording.

3.5. Goodness-of-Fit

The GOF of multiple-dipole fitting is evaluated by the R^2 statistic in this study and the results from both MUSIC and FINE algorithm are summarized in Table 1. The R^2 statistic is both calculated at the spike peak, which is marked on the channel waveform with the maximal signal strength by a vertical black bar in Fig. 2–4 (a), and in the entire spike period, which is identified by the FWHM principle. The R^2 statistic over the entire spike period is the average of the R^2 statistic values on each time point within the period. For Patient 1 and Patient 2, the explained variations by multiple-dipole fitting from the FINE algorithm are about 10 percents higher, for both spike peak and spike period, than the result from the MUSIC algorithm. For patient 3, the explained variation by the FINE result and MUSIC result are close and there is about 3 percents increase when using the FINE algorithm, still for both spike peak and spike period. The fitting at the maximal SNR time point is obviously better than the average fitting within the entire time window for all patients and all algorithms. The average R^2 statistic value over three patients at the spike peak is 0.9507 for FINE while it is 0.8637 for MUSIC. And the average R^2 statistic value over three patients within the spike period is 0.8726 for FINE while it is 0.7780 for MUSIC.

4. Discussion

The present study provides the first clinical results with regard to the feasibility of localizing epileptiform activity by means of FINE from interictal spikes recorded using a clinical electrode configuration. Three patients with MRI lesions were subjected to the FINE analysis using a three-sphere concentric head model. The computer simulation study was also performed using a standard clinical electrode setting to evaluate the performance of FINE for source localization. The computer simulation results show FINE has higher spatial resolvability than MUSIC in terms of detection rate for two closely spaced sources and is also more accurate when simulated sources are close, at low SNR levels, and when simulated sources are deep, which is evaluated by the source localization error criterion. On the side of clinical data analysis, both the FINE-imaged and MUSIC-imaged sources are well correlated with the MRI lesions in the patients studied. The electrical sources from FINE and MUSIC for each patient are either at the border of the corresponding MRI lesions or their vicinities (Fig. 2–4 (d–e)). Furthermore, the results from FINE show multiple sources while MUSIC only reveal single source in each patient, which indicates the higher spatial resolvability of FINE. The higher accuracy of multiple source fitting from FINE is also supported by the higher R^2 statistic values as compared with single source fitting from MUSIC defined on both spike peaks and spike periods.

In the computer simulations, the effects of type of noises, SNR, distance, and depth have been further investigated by using subspace source localization methods and statistically evaluated by ANOVA. Of most importance, subspace source localization methods show significant performance reductions in conditions with real noises (comparing Fig. 1(a–c) with Fig. 1(d–e)), which indicates the simulation results from real noises, instead of simulated noises (i.e. GWNs), should be used to guide the interpretations of results from clinical and experiment data analysis. The performance of subspace source localizations can be improved if the characteristics of real noises can be evaluated (Sekihara et al., 1997), which is also applicable to FINE. Furthermore, FINE has higher spatial source resolvability and lower source localization error when SNR is high and it has better source localization accuracy when sources are not close. FINE also shows depth dependency by comparing the results for superficial

sources and deep sources, which indicates higher accuracy for superficial sources. Such effects are turned out to be statistically significant indicated by ANOVA.

In the present study, the MRI lesion is used as reference to validate the electrical sources imaged by FINE and MUSIC since it is well known that epileptic activity often arises from the neuronal tissue within the confines, or at least in the vicinity, of a brain lesion (Munari et al., 1986; Engel, 1987; Gloor, 1987) in lesional epilepsy patients. The activity in the vicinity area may be explained by fast propagation with the latencies in the order of 10 to 50 ms within close areas as observed in ECoG study (Alarcon et al., 1997). Therefore, if we regard MRI lesion as the best available indicator to the focus of epileptogenesis, the FINE-imaged and MUSIC-imaged epileptic sources from the interictal EEG are consistent with their anatomical abnormalities. It is worth to mention that, although the source localization ability of FINE is assessed here by using independent measurements, i.e. MRI, in lesional epilepsy patients, the clinic value of its application should not be limited to this specific population. It is argued that FINE will be able to localize epileptogenic foci in patients without explicit brain tumors or lesions where MRI modality may fail to identify the possible epileptogenic regions.

The advantage of FINE is its ability in imaging the electrical sources in the 3D brain volume. This method can gain the depth information of electrical activities which cannot be obtained in the surface recordings including EEG (and sometimes even with ECoG in some adult epilepsy patients). However, the subspace source localization approach is based on the current dipole source model which represents the focal electrical activities by multiple dipoles. Although this method does not provide the information regarding the extent of sources, it may identify the gravities of the epileptic activities. The modeling of extended dipole sources has been explored by other researchers in MEG (Jerbi et al., 2002) and such model can be incorporated in our current EEG study for epilepsy patients to gain source extent, possible by a mapping procedure (Mosher et al., 1999). FINE is also a spatio-temporal multiple-dipole fitting technique as compared with the multiple-dipole fitting techniques performed on a single time point. The efficient usage of spatial and temporal data simultaneously is achieved by singular value decomposition (SVD) to estimate the span of the so-called noise-only subspace. It detects the main activity patterns among the defined time windows, which are also observable in all three patients with a successive sequence of scalp EEG maps, and makes a fit over the whole temporal samples instead of individual one at each time point. The average 86% variation explained by FINE-imaged sources over the entire spike peak in all three patients suggests the ability of FINE to reveal the main activity patterns during the interictal spikes considering the measurement noise and background activities. More specially, the average 95% variation explanation by FINE at the spike peak in all patients also indicates the sufficiency of multiple-dipole fitting results. Such high fit is reasonable at the spike peak because it is the time point with the maximal SNR value. Although we only analyzed the interictal data in the present study, the spatio-temporal model is also suitable for ictal event which is naturally a time evolving process.

Note that the present study is limited in that we only used the 3-concentric-spheres head model instead of RG head model. A previous study (Silva et al., 1999) has reported that use of RG head model increased the dipole localization accuracy for epileptiform spikes as compared to the use of spherical head model. A plausible explanation to why the second peak identified by FINE in Patient 1 was lateral may be due to the same reason. The coregistration of spherical model with measurement electrodes will have relatively larger mismatch in the temporal area than the other areas. While beyond the scope of the present work, future investigation should include RG head model, either using boundary element method (BEM) or finite element method (FEM). It is also noted that the p value for the largest eigenvalues must be estimated in clinical data analysis since the number of sources is generally unknown. We used a method which is similar to the method used in other researchers' work (Mosher et al., 1992), which

works well and consistently in current clinical data analysis. However, the method may not be the only choice or the optimal choice. Other reported methods to determine the number of sources are also available (Knosche et al., 1998), which is shown to be promising especially in the presence of spatially correlated noise.

In summary, we have tested the feasibility of localizing epileptiform activity from interictal spikes by means of a new subspace source localization approach, i.e. FINE. The FINE localization results from three epilepsy patients with explicit MRI lesions are promising. The present study suggests that FINE provides high-resolution source localization capability and may potentially become useful for presurgical planning in identifying epileptic foci in epilepsy patients.

Acknowledgements

This work was supported in part by NIH EB00178, NSF BES-0411898, and a grant from the Biomedical Engineering Institute of the University of Minnesota. L.D. was supported in part by the Doctoral Dissertation Fellowship from the Graduate School of the University of Minnesota.

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Figure 1.

Detection rate (DR) and source localization accuracy comparison between the FINE and MUSIC algorithm. DISTANCE effect: (a) GWNs, ECCENTRICITY = 75 mm, SNR = 12 db; (e) real noises, ECCENTRICITY = 75 mm, SNR = 16 db. SNR effect: (b) GWNs, ECCENTRICITY = 75 mm, DISTANCE = 15 mm; (f) real noises, ECCENTRICITY = 75 mm, DISTANCE = 15 mm. ECCENTRICITY effect: (c) GWNs, SNR = 12 db, DISTANCE = 20 mm; (g) real noises, SNR = 16 db, DISTANCE = 20 mm. * indicates the significant improvement from FINE as compared with MUSIC in the plotted simulation condition.

Figure 2.

Interictal data for Patient 1. (a) 31-channel waveforms with length of 0.5 s. (b) the scalp EEG around the interictal peak at every 20 ms. (c) Average time-frequency representation over 31 channels; time window: 0.5 s; frequency window: 0 – 30 Hz. (d) The two peaks identified by FINE and (e) the peak identified by MUSIC for the interictal data and displayed with MR images and their waveforms.

Figure 3. Interictal data for Patient 2. (a) 31-channel waveforms with length of 0.5 s. (b) the scalp EEG around the interictal peak at every 20 ms. (c) Average time-frequency representation over 31 channels; time window: 0.5 s; frequency window: 0 – 30 Hz. (d) The two peaks identified by FINE and (e) the peak identified by MUSIC for the interictal data and displayed with MR images and their waveforms.

Figure 4.

Interictal data for Patient 3. (a) 31-channel waveforms with length of 0.5 s. (b) the scalp EEG around the interictal peak at every 20 ms. (c) Average time-frequency representation over 31 channels; time window: 0.5 s; frequency window: 0 – 30 Hz. (d) The peak identified by FINE and (e) the peak identified by MUSIC for the interictal data and displayed with MR images and their waveforms.

Table 1

R^2 statistic values at the spike peak and within the spike period (average value) for three patients from both FINE and MUSIC

R^2		Patient 1	Patient 2	Patient 3
Spike Peak	FINE	0.9910	0.9363	0.9247
	MUSIC	0.8977	0.8089	0.8845
Spike Period	FINE	0.9087	0.8650	0.8442
	MUSIC	0.7398	0.7800	0.8142