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Sparse MEG Source Imaging in Landau-Kleffner Syndrome

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Abstract—**Epilepsy patients with Landau-Kleffner syndrome (LKS) usually have a normal brain structure, which makes it a challenge to identify the epileptogenic zone only based on magnetic resonance imaging (MRI) data. A sparse source imaging technique called variation based sparse cortical current density (VB-SCCD) imaging was adopted here to reconstruct cortical sources of magnetoencephalography (MEG) interictal spikes from an LKS patient. Realistic boundary element (BE) head and cortex models were built by segmenting structural MRI. 148-channel MEG was recorded for 10 minutes between seizures. Total 29 epileptiform spikes were selected for analysis. The primary cortical sources were observed locating at the left intra- and perisylvian cortex. Multiple extrasylvian sources were identified as the secondary sources. The spatio-temporal patterns of cortical sources provide more insights about the neuronal synchrony and propagation of epileptic discharges. Our observations were consistent with presurgical diagnosis for this patient and observation of aphasia in LKS. The present results suggest that the promising of VB-SCCD technique in assisting with presurgical planning and studying the neural network for LKS in determining the lateralization of epileptic origins. It can further be applied to non-invasively localize and/or lateralize eloquent cortex for language for epilepsy patients in general in the future.**

I. Introduction

Landau-Kleffner syndrome (LKS) is a childhood disorder, which is characterized by the sudden or gradual development of aphasia (the inability to understand and express language) [1]. Most of children with LKS suffer with very frequent large-amplitude epileptiform discharges which can be recorded by electroencephalography (EEG) and/or magnetoencephalography (MEG). Surgical treatment has been proposed for LKS patients once the epileptiform activity can be localized to a single hemisphere [2]. However, many EEG/MEG epileptiform activities have been observed bilaterally from both hemispheres while it is likely that such phenomenon is caused by neuronal propagation of focal spikes between them. Furthermore, patients with LKS generally do not have demonstrable structural lesions to help localization and lateralization of epileptic origins.

Pharmacological tests have been used to lateralize epileptic origins while the procedure is invasive and hard to interpret [2]. Signal processing techniques exploring EEG/MEG features, such as latency analysis, are also being developed and tested [3]. The limitation of such techniques is that all surface recordings of electrical and magnetic signals are complicated by the so-called volume conductor effect [4]. The localization and lateralization of epileptic origins can be achieved via deconvoluting the volume conductor effect and reconstructing electrical current sources in the brain from surface electrodes/sensors, which is known as the EEG/MEG inverse problem.

It is relevant that the eloquent cortex for language in epilepsy patients also needs to be localized during the presurgical evaluations. Currently, the Wada test, which involves injection of barbiturates, is the standard clinical procedure [5]. The procedure results in temporary arrest of the function of each hemisphere in order to test the function of non-anesthetized hemisphere. It is suggested that the hemispheric dominance for language function can be tested using noninvasive EEG/MEG methods, which is also implemented to solve inverse problems for localization [5]. Since the LKS disorder disturbs the language function, in both cases, the task is expected to handle EEG/MEG inverse problems in identifying the cortical structure for language related functions.

Currently, routine clinical application of MEG mostly uses the equivalent current dipole (ECD) inverse solutions, which assumes the electrical currents of epileptic origins as ideal point sources [5]-[7]. This has been demonstrated to be generally successful in localization for focal sources. The ECD model without information of source extent turns out to be limited and inappropriate for extensive or bilateral diffuse sources. To estimate the extent of epileptic sources, multiple ECDs during a special duration, e.g., ascending phase of interictal spikes (IISs), are estimated one by one for each time point. The cluster formed by these ECDs indicates possible extent of epileptic sources. The same method has been used to localize eloquent cortex, e.g., language cortex, in attempt to provide a noninvasive alternative for Wada test [5], [7]. In the cluster analysis, the extent is obtained by sacrificing temporal resolution. Furthermore, the estimated extent by a cluster of dipoles might not be accurate for the same reason discussed above for the ECD model, which probably leads to inaccuracy in estimating the entire cluster.

Distributed source models are believed to be more suitable in reconstructing extended cortical sources at each moment, without losing any temporal information [8]. In the cortical current density (CCD) model, the interface between gray and white matter is numerically represented by continuous dipole elements and reconstruction algorithms are designed to find the most probable distribution of current dipoles that explains the measured MEG data. In such a mathematical problem, the number of elements to be reconstructed is usually larger than

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the number of EEG/MEG measurements, which makes it highly ill-posed (i.e., no unique solution). Various L2/L1-norm regularization techniques have been implemented to search for unique solutions [9], [10]. However, both L2-norm and L1-norm regularization techniques introduce systematical biases in estimating extent of sources. Recently, a novel L1-norm regularization scheme named variation based sparse cortical current density (VB-SCCD) is developed to compensate the biases by directly searching the boundaries of active and inactive areas. And the simulation study demonstrated the promising of this source imaging technique in reconstructing cortical sources on EEG [11], which is also applicable to MEG. If this novel source imaging technique can accurately localize cortical sources of epileptiform discharge, it may play a role of delineating the epileptogenic origins of functional abnormalities depicted in imaging.

In the present study, this new source imaging technique was applied to reconstruct cortical sources of 29 interictal spikes from an epilepsy patient with LKS. The estimated location and extent of epileptic origins were then compared with presurgical evaluation results. We investigated the dynamic changes of cortical current sources, at the millisecond resolution, which provided a valuable mean to study the neuronal synchrony between both hemispheres and propagation of epileptiform activity. Such dynamic patterns revealed that the bilateral MEG observations of epileptiform activity were caused by the inter-hemishperic propagation in the LKS patient, which suggested the patient had unilateral epileptic origin and was suitable for the surgical treatment.

II. METHOD

A. Variation based sparse cortical current density (VB-SCCD) imaging

The CCD source model is constructed by continuous distributed triangles, and each triangle is treated as a source with a dipole located in the center and paralleled to the local norm. The relationship between the magnetic fields Φ derived from M scalp sensors and the dipole moment s from N cortical triangular elements can be expressed as a simple linear equation:

$$\phi = \mathbf{A}s + n \qquad (1)$$

where A is the matrix for the lead field and n is the vector of noises. The general idea of VB-SCCD is to search for the suitable current density with the sparseness occurring on the boundaries between active and inactive areas. And the operator V is designed to calculate the variation between two neighboring elements:

$$\mathbf{V} = \begin{bmatrix} v_{11} & v_{12} & \cdots & v_{1N} \\ v_{21} & v_{22} & \cdots & v_{2N} \\ \vdots & \vdots & \ddots & \vdots \\ v_{P1} & v_{P2} & \cdots & v_{PN} \end{bmatrix}$$

$$\begin{cases} v_{ij} = 1; v_{ik} = -1; & \text{if elements } j,k \text{ share the same edge } i \\ v_{ij} = 0; & \text{otherwise} \end{cases}$$

where V is a $P \times N$ matrix and P is the total number of edges of triangle elements. The objective function of the VB-SCCD can be written as:

$$\min \left\| \mathbf{V}s \right\|_1 \quad \text{subject to} \quad \left\| \phi - \mathbf{A}s \right\|_2 < \beta \qquad (2)$$

Equation (3) is a convex optimization problem, which can be solved by global optimal solutions [12]. The second-order cone programming (SOCP) is adopted here to solve this optimization problem [13]. The regularization parameter β is estimated by applying the discrepancy principle [14], which has to be high enough to include more possible solutions. Here, β is chosen as the up bound of [0 β] which integrates to 0.99 probabilities.

B. Data acquisition

The patient had medically refractory partial epilepsy and was undergoing presurgical evaluation at Minnesota Epilepsy Group. All procedures were conducted according to a protocol approved by Institutional Review Board of University of Oklahoma, Norman, OK. The patient received a whole head MRI scan and 10 minutes MEG recording between seizures. The 3D axial T1-weighted MR images were obtained from GE 3 Tesla scanner using a SPGR sequence (TR=7ms, TE=3ms, FOV=24×24cm, slice thickness=1.4mm). High density MEG was recorded using a whole head, 148-channel Magnes WH2500 neuromagnetometer array (4-D Neuroimaging, San Diego, CA, USA) in a magnetically shield room. The sampling rate for MEG recording is 508.63Hz. And an online band-pass filter from 1 to 70 Hz was applied.

C. Analysis protocol

The head model with three layers (scalp, skull and brain) and the CCD cortex model were obtained by segmenting the structural MRI using BrainSuite [15]. The conductivities for those tissues between three lays are set to 0.33/Ω.m, 0.0165/ Ω.m, and 0.33/ Ω.m respectively [16]. The high resolution CCD models contain more than 50000 triangle elements.

The co-registration between MEG sensors and BEM head model and CCD cortex model was conducted by aligning fiducial points (nasion, left and right preauriculars) and further refined by the fitting between digitized head surface points and the first lay of BEM model. Fig. 1(a) shows the results of co-registration.

The epileptic interictal spikes (IISs) were identified by experienced epileptologists. 29 IISs with less associated artifacts (e.g. heartbeat, muscle movement, or eye blinks) were chosen to reconstruct the cortical sources by VB-SCCD imaging technique. The active areas on the reconstructed current densities were then compared with presurgical diagnosis and observation of aphasia.

III. RESULTS

The patient studied in this paper was a boy with 6 years old, who had LKS and suffered daily multiple medically refractory complex partial seizures. This patient had a normal MRI without any lesions. During the presurgical evaluation,

the seizure focus was diagnosed on the left sylvian fissure. This patient has been treated by multiple subpial transections (MST) surgery on his left supratemopral cortex.

Twenty-nine IISs were selected based on the criterion described above for source analysis. Fig. 1(b) gives two examples of reconstructed cortical sources by VB-SCCD at the peaks of IISs. The first example implies a left perisylvian cortical source, which covers part of Broca's area (associated with language reproduction and comprehension). The second cortical source located at the posterior part of the left sylvian fissure, which is at the Wernick's area (associated with auditory processing). The intra- and perisylvian cortical sources were found in all 29 IISs. The results are consistent with the seizure focus on the left sylvian fissure.

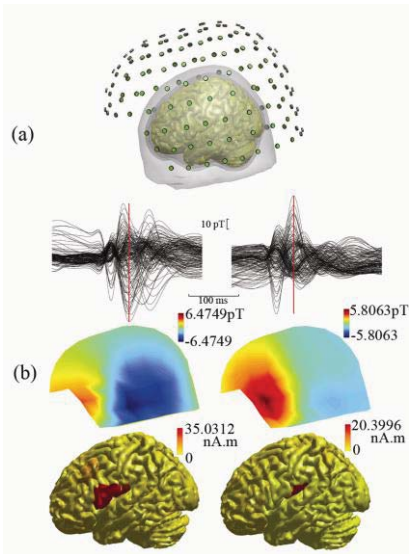

Fig. 1 (a) Co-registration between MEG sensors, BEM head, and cortical source models. (b) Two examples of cortical sources reconstructed by VB-SCCD

Taking advantage of the high temporal resolution of MEG, snaps of cortical current density for each 2 ms allow us to explore the dynamic changes for epileptiform activities. Figs. 2-4 present three different types of propagation patterns for this LKS patient. Fig. 2 shows one example of propagation to adjacent areas within the same cerebral hemisphere of the localized epileptic source. The earliest MEG activity (at -32 ms) originated exclusively in the left hemisphere with the primary MEG source in the intrasylvian cortex. After 32 ms (at 0 ms), the MEG IIS reached its peak and the cortical source started to propagate to the left inferior frontal gyrus, which overlaps with Broca's area. At 32 ms, the central motor cortex was also slightly activated, possibly caused by the propagation too.

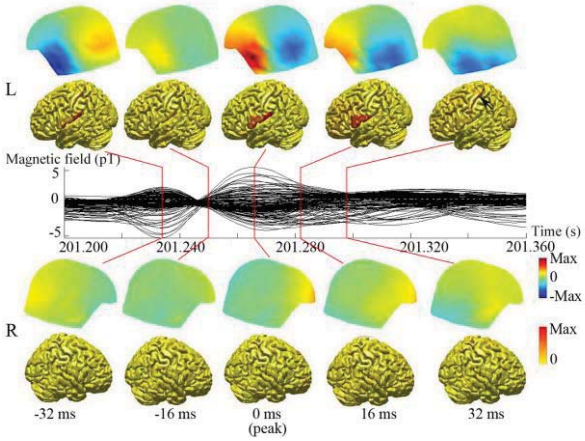

Fig. 2 An example of in-hemisphere propagation of cortical activity. Up: left views of scalp magnetic fields and reconstructed cortical sources. Middle: Butterfly plot of MEG interictal spike. Red vertical bars indicate the corresponding times. Down: right views of the same data.

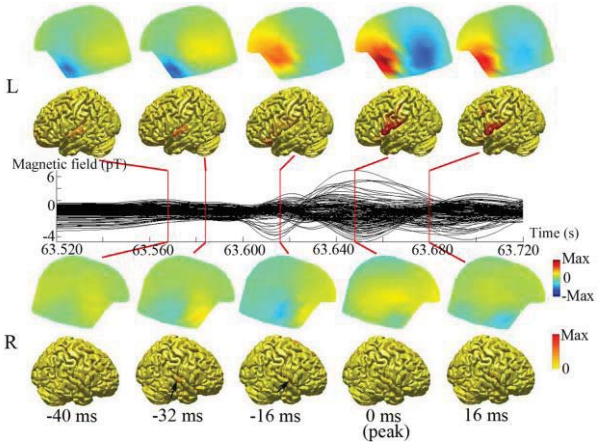

Fig. 3 An example of fast cross-hemisphere propagation of cortical activity. Up: left views of scalp magnetic fields and reconstructed cortical sources. Middle: Butterfly plot of MEG interictal spike. Red vertical bars indicate the corresponding times. Down: right views of the same data.

Fig. 3 illustrates an example of cross-hemispheric propagation at the symmetric cortical structure. The earliest MEG activity was found focused at the left superior temporal gyrus at -40 ms. After 8 ms (at -32 ms), the right hemisphere also showed epileptic MEG activity at the symmetric area (right superior temporal gyrus). The strength of the symmetric MEG activity at both hemispheres started to decrease since -16 ms. When the IIS reached its peak (0 ms), the cortical source was reactivated exclusively on the right sylvian cortex. At 16 ms, the cortical source stayed on the left hemisphere and extended to the left posterior inferior frontal cortex (as in the previous example from Fig. 2) and at the

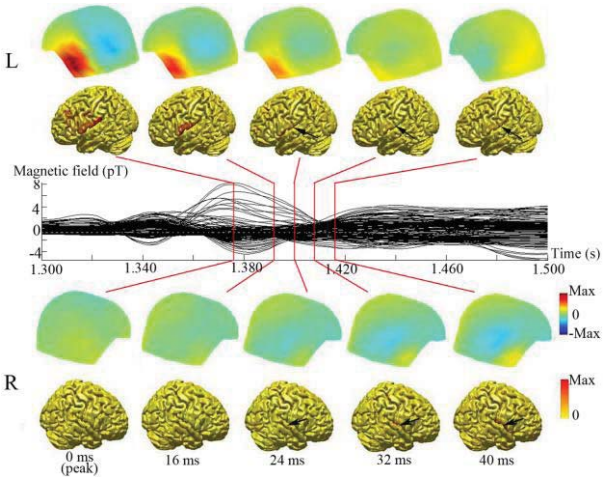

Fig. 4 An example of slow cross-hemisphere propagation of cortical activity. Up: left views of scalp magnetic fields and reconstructed cortical sources. Middle: Butterfly plot of MEG interictal spike. Red vertical bars indicate the corresponding times. Down: right views of the same data.

same time multiple extrasylvian sources within the superior frontal cortex were also observed.

A similar left to right hemisphere activation sequence was also indicated in Fig. 4. At the peak of IIS (0 ms), the MEG epileptic activity focused on the left sylvian fissure with multiple small extrasylvian activations. From 16 ms, the strength of MEG activity on the left hemisphere started to decrease, and at the same time, the symmetric structure on the right hemisphere started to be slightly activated. The strength of the MEG activity was increasing on the right intrasylvian cortex with the strength decreasing on the left hemisphere simultaneously from -16 ms to 16 ms. The cross-hemisphere propagation phenomenon was observed both before or after the IISs reached their peaks. As indicated in Figs. 1-4, the cortical sources at IIS peaks were always focal and located at the left intra- or perisylvian cortex, which is true in all 29 IISs.

IV. DISCUSSION

In the present study, a novel MEG source imaging technique (VB-SCCD) was adopted to estimate the epileptic origins in an epilepsy patient with LKS. Our data suggest the left intra- and perisylvian cortex is the main generator of epileptic interictal spike activity for this LKS patient as consistently indicated by total 20 IISs studied. The activity within the extrasylvian cortex is usually secondary to the primary generator as indicated by the dynamics of sources. The location estimation of epileptic origins is consistent with the presurgical evaluation based on seizure data. Furthermore, similar intra- and perisylvian generators for LKS patients have been identified in previously reported studies [17] using ECD models. Compared with inverse solutions from ECD models, the gain of using distributed cortical source model (i.e., CCD) is that VS-SCCD is able to suggest the extent of cortical sources of interictal spikes (Figs. 1-4). The spatial distributions of those cortical sources include areas related to language (e.g., Broca's area and Wernick's area), which is collaborative to the symbolic observation of aphasia in LKS. In more details, the intra- and perisylvian temporal lobe covers primary and associate auditory area [17]. The posterior perisylvian area is close to the Wernicke's area, which is engaged in integration of auditory, visual and tactile information. The inferior perisylvian are covers part of Broca's area, supporting somatomotor oral function and verbal output.

The dynamic patterns of interictal spike sources reveal important information regarding the propagation of interictal epileptiform activity and the neural synchrony between symmetric structures in both hemispheres which are functionally related. The propagation from the posterior perisylvian area to the inferior perisylvian indicates the epileptic discharge for the LKS patient may originate from the cortex supporting auditory processing to language comprehension, speech production, and possibly other cognitive functions. The cross-hemisphere propagation to symmetric anatomic structures observed in this patient also supported by other studies [17]. The inspection into the dynamic connection between left and right perisylvian cortex help to identify the dominant MEG spike generator for the LKS patient is unilateral, which is suitable to receive surgeries.

In summary, the sparse MEG source imaging applied to a Landau-Kleffner sydrome patient reveals the promising performance in estimating the location and extent of epileptic origin for presurgical planning. The dynamics of cortical sources provide a valuable mean to inspect the functional connectivity within the cortical network for epileptiform activity, which can help in determination whether it is unilateral dominant epileptic origins in LKS patients. Such localization and lateralization capabilities via integrating location, extent, and dynamics of sources are also valuable for other types of epilepsy patients in noninvasively locating eloquent cortex for language, which will be investigated in our future studies.

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