Case Report

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Localization of Extratemporal Seizure with Noninvasive Dense-Array EEG

Comparison with Intracranial Recordings

Mark D. Holmes[a] Micah Brown[e] Don M. Tucker[e, f] Russell P. Saneto[a, d]
Kai J. Miller[b] Gagan S. Wig[g] Jeffrey G. Ojemann[c]

Departments of [a]Neurology, [b]Physics and [c]Neurological Surgery, and [d]Division of Pediatric Neurology, University of Washington, Seattle, Wash.; [e]Electrical Geodesics, Inc. and [f]Department of Psychology, University of Oregon, Eugene, Oreg.; [g]Department of Psychological and Brain Sciences, Center of Cognitive Neuroscience, Dartmouth College, Hanover, N.H., USA

Key Words
Refractory epilepsy · Extratemporal seizures · Source analysis · Dense-array EEG · Epilepsy surgery

Abstract
A 13-year-old girl presented with refractory seizures since the age of 5 years. Clinical exam and MRI studies were normal. Ictal EEG discharges suggested possible left posterior quadrant distribution but were not well localized with standard methods. A seizure was recorded during 128-channel EEG video long-term monitoring prior to invasive recordings. Applying a source analysis method, seizure onset and propagation patterns were calculated and displayed on an MRI model. The onset was localized to the left inferior posterior occipital cortex, followed by propagation to the right, then left, posterior cerebral hemispheres, and finally to the left superior-medial parietal lobe. These patterns were replicated closely on subsequent invasive recordings. Surgery was based on intracranial findings and she is seizure-free 30 months after resection. Noninvasive dense-array EEG, used in conjunction with realistic source analysis methods, may have the potential to assist in localizing seizure onsets when standard methods fail.

Introduction

Surgery is an effective treatment for many patients with medically intractable seizures [1]. The evaluation for surgical candidacy requires at a minimum a detailed assessment of clinical, neuroimaging, neuropsychological and EEG findings. For most surgical candidates, long-term EEG video monitoring (LTM) is necessary in order to record the patient's habitual seizures. However, conventional scalp EEG recordings utilize a decades-long standard approach (the international 10-20 system), whereby only 19–21 electrodes are typically applied to the scalp. This method results in interelectrode distances of several centimeters and has the effect of producing relatively poor spatial resolution. As a consequence, the initial noninvasive EEG evaluation is often inadequate, necessitating the need for intracranial EEG studies (with subdural, epidural or depth electrodes) to localize ictal onsets [2]. This is especially true for subjects with extratemporal seizures. At the University of Washington, for example, between 1991 and 2006, about one third of surgical candidates with temporal lobe epilepsy underwent invasive LTM, while the majority of individuals with extratemporal seizures required preoperative intracranial

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Mark D. Holmes, MD
Regional Epilepsy Center, Department of Neurology
Harborview Medical Center, 325 Ninth Ave., Box 359722
Seattle, WA 98105 (USA)
Tel. +1 206 731 3539, Fax +1 206 731 4409, E-Mail mdholmes@u.washington.edu

EEG evaluation. Better methods are needed to improve the noninvasive phase of the evaluation of refractory epilepsy and reduce the costs, consumption of resources and occasional morbidity associated with invasive LTM.

Application of major technological advances will likely change the current state of affairs and lead to improvement in the noninvasive assessment. One of these advances is the capability to record subjects with a dense array of EEG electrodes. Using many more electrodes than conventional systems, dense-array EEG includes coverage of portions of the face and neck (allowing for sampling of basal brain regions) and, by decreasing the distance between electrodes, greatly improves the scalp EEG spatial resolution [3]. In the ideal situation, to maximize the spatial information that can be extracted from scalp recordings, the sampling with dense-array EEG should be sufficient to encompass as much of the spatial frequency spectrum as possible ('spatial Nyquist') [4, 5]. Another major technological advance is in the development of physical models of the neural sources of the EEG [6]. A combination of superior spatial resolution, sophisticated methods of source analysis and coregistration of results with realistic magnetic resonance imaging (MRI) models should result in the enhanced ability to localize epileptiform discharges from the scalp recordings [7–9]. A new perception of the spatiotemporal dynamics and localized nature of the epileptiform discharges in absence seizures was achieved by application of these methods [10].

With this background in mind, the present study was designed to directly compare the localization of a clinical seizure that was obtained by using dense-array EEG and source analysis with intracranial EEG recordings in a patient with refractory epilepsy. The subject was a candidate for epilepsy surgery and invasive EEG studies were carried out as part of a standard preoperative evaluation. A comparison of this nature is likely to yield insight into the potential usefulness of the new methods of noninvasive EEG assessment.

Methods

Standard Noninvasive Evaluation

A 13-year-old girl, a potential candidate for epilepsy surgery, presented with daily complex partial seizures. Her first seizure occurred at the age of 5 years. She has no obvious risk factors for epilepsy. Her review of systems and family history were unremarkable, and the clinical general and neurological examinations were normal. Though she functioned in a regular classroom setting, formal neuropsychological assessment demonstrated low average intelligence with relative impairment of receptive and expressive language function. MRI of the brain was normal, except for an incidental right choroidal fissure cyst. Conventional EEGs demonstrated abundant interictal discharges maximally distributed over the left posterior quadrant; independent discharges were also observed over left superior parietal regions. Standard LTM recorded seizures of probable left posterior quadrant origin, but ictal onsets could not be well localized electrographically.

Dense-Array LTM

Following conventional LTM and after receiving approval from the University of Washington Human Subjects Review Committee, informed consent was obtained for LTM with dense-array EEG. A 128-channel electrode net was applied, requiring about 30 min for application and adjustment. The device covers portions of the face and neck, permitting electrographic 'sampling' of basal regions. The EEG amplifier characteristics included a bandpass of 0.1–400 Hz and a sampling rate of 1,000 Hz. The patient underwent 48 h of continuous dense-array EEG recording. One of her habitual clinical seizures was captured during this study. Ictal EEG waveforms were examined, the onset was determined, and source analysis was applied to the data at the onset of the seizure and at discrete time intervals after onset. There were no complications during this evaluation.

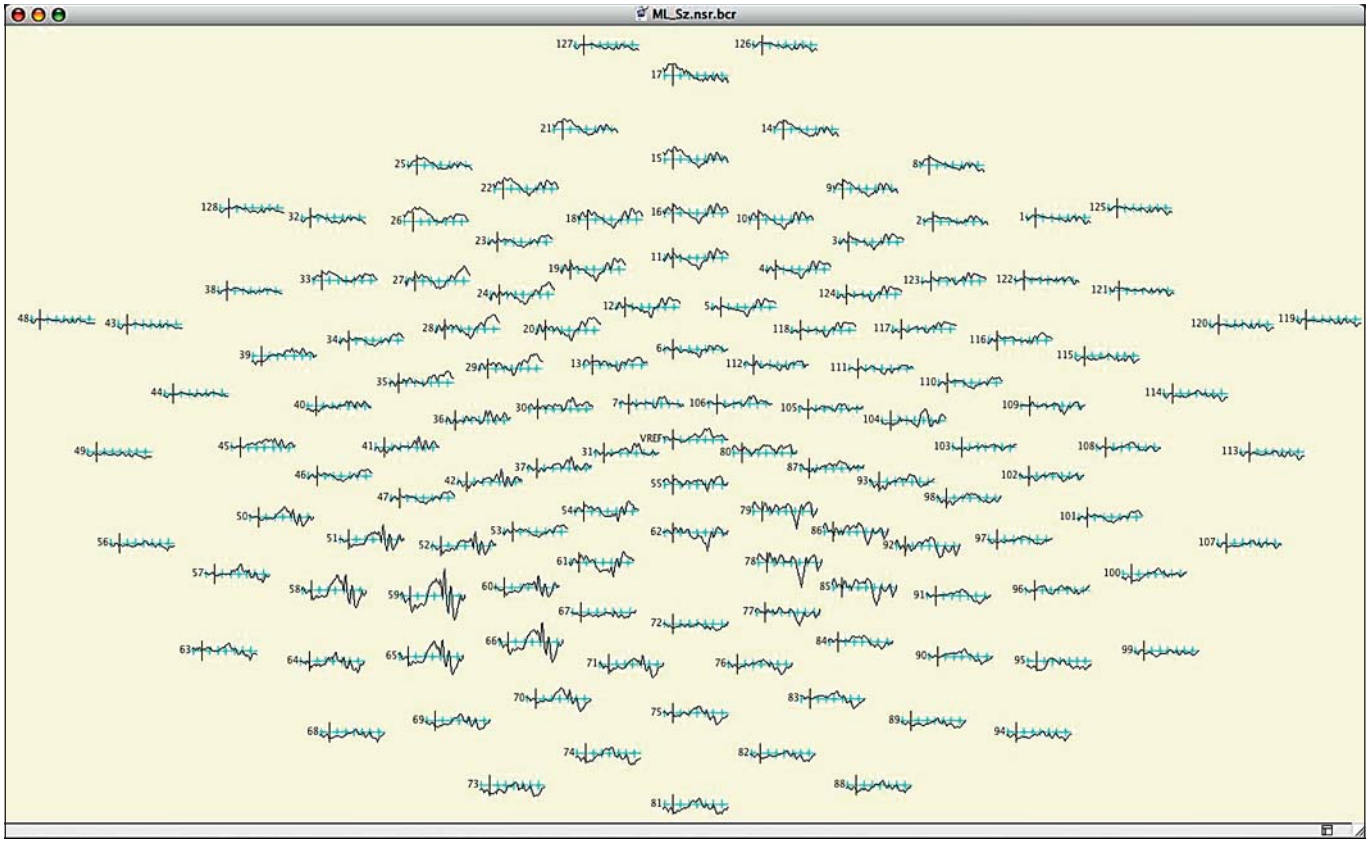
EEG Referencing and Mapping

The dense-array EEG was recorded with a common vertex reference and rereferenced digitally to various montages for inspection, including the average reference. Since the geodesic electrode net results in improved coverage of the inferior head surface, the average reference permits the potential at each index electrode to be examined with reference to an estimate of the zero potential of the head [11, 12]. The average-referenced EEG waveforms were examined with topographic waveform plots, a method that allows for inspection of geometric distribution of the potential fields. In addition, topographic maps were created with spherical spline interpolation [13].

Source Analysis

As the first step in source analysis, we specified a spherical head model with 4 shells (brain, CSF, skull, and scalp). The conductivity ratios were 1 (CSF), 0.3300 (brain), 0.0042 (skull) and 0.3300 (scalp). The thicknesses were 1 mm (CSF), 7 mm (skull) and 6 mm (scalp) [14]. Dipole locations were visualized in relation to a standard brain MRI model obtained from the Montreal Neurological Institute atlas (www.bic.mni.mcgill.ca). Positions of electrodes with respect to the model were determined by fitting locations to that used in the source localization software, being average cartesian coordinates of digitized locations from 5 normal adults. We identified the apparent electrographic ictal onset though visual inspection of the topographic display of all 128 channels to perform source analysis estimates at the seizure onset and at serial time points during seizure evolution (fig. 1).

We applied the cortically constrained linear inverse method of local autoregressive average in order to weight the source solutions [15]. Vector fields of electrical sources fall off with the cube of distance (potential fields with square of distance), and



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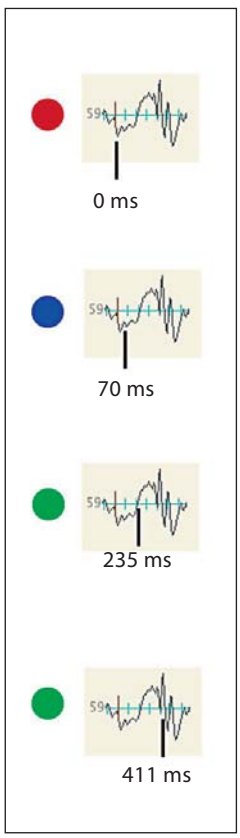

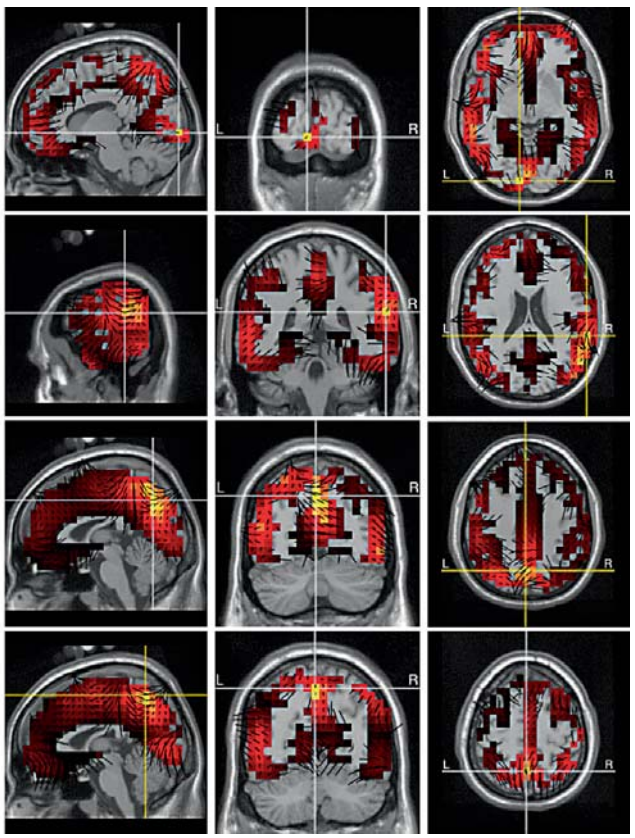

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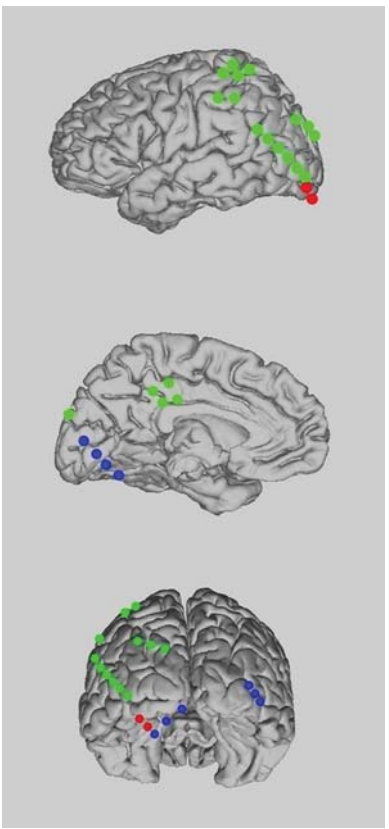

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local autoregressive average constrains the solution with a function that assumes the results will have this property. Local autoregressive average solutions were implemented within GESI software package utilized in our analysis (http://www.egi.com), using gray matter locations from the Montreal Neurological Institute atlas and a conductivity model. Source analysis calculations were conducted prior to the placement of intracranial electrodes.

For purposes of visualizing the results of analysis, figures were constructed that include an 850-ms segment of topographic EEG at the beginning of the seizure, the specific time point on that EEG (demarcated by the vertical brown lines in fig. 2) where source calculations were made, and simultaneous placement of source locations on the MRI model. The MRI components show standard coronal, sagittal and axial images, with 'source orientation vectors' indicating the direction of the net orientation of the sources represented by each colored voxel. The voxel palette represents the source strength, ranging from yellow (maximum) to red (medium) to black (minimum), with crosshairs denoting sites of maximal intensity in each slice.

Fig. 1. Topographic waveform plot shows the 128-channel scalp array, with 850-ms segment at time of seizure onset (marked by vertical line). The segments are arranged in a schematic of their positions on the head, to allow visualization of the distribution of the waveforms by looking on top of the head. The nose is at the top and inferior electrodes (face and neck) are spread out to the sides on the display; upward deflection denotes voltage negativity. The onset of the seizure was marked in the scalp EEG by a slow transient developing into a slow wave and multiple spike complex in the left posterior quadrant.

Fig. 2. Source analysis estimates of the maximal intensity of the initial onset of the seizure, marked as 0 ms, shows localization to the left posterior inferior occipital lobe (crosshairs). At 70 ms after onset, the EEG source model estimates that maximal activation shifts to the right posterior cerebral hemisphere. At the onset of the surface-negative slow wave, 235 ms after the onset, the largest source estimate value is in the left superior parietal region. The multiple spike complex, modeled at 411 ms after onset, begins with a large positive (downward) deflection over both left and right posterior sites in the topographic waveform plot, followed by multiple phases over the left hemisphere only. The source model over this interval suggests that the scalp field is produced by activation across the superior and medial walls of the left parietal lobe. The lines on the figures denote source vectors; the colored dots on the left refer to intracranial electrodes involved at similar time points during the seizure (fig. 3).

Fig. 3. Location of intracranial electrodes involved within the first second following seizure onset. Electrodes showing ictal onset are marked in red. Electrodes showing spread within about 100 ms are marked in blue and those with spread after about 250 ms in green. These results compare closely with the noninvasive estimates (fig. 2).

Intracranial EEG Studies

Following noninvasive conventional studies and dense-array LTM, intracranial LTM assessment was undertaken. A subdural grid of electrodes was inserted over the left posterior hemisphere and subdural strips were placed along the left interhemispheric space and over the bilateral lateral temporal, subtemporal and occipital regions. Clinical seizures were recorded. Invasive EEG studies were interpreted by a physician (R.P.S.) who had no prior knowledge of the results of the source analysis of dense-array EEG ictal recordings. The localization of seizure onsets and patterns of ictal propagation based on invasive LTM were then compared to the localizations obtained with noninvasive source analysis by coregistering the postoperative head CT scan with a template MRI scan [16]. The location of the electrodes showing ictal onset and subsequent spread were documented.

Results

Source Analysis of Dense-Array EEG

Analysis of dense-array data predicted that seizure onset occurred at the left inferior posterior occipital cortex, based on maximal source localization at ictal onset. The first electrographic ictal change, based on visual inspection of the full topographic waveform plot (fig. 1), consisted of a surface-positive deflection maximally distributed over the left posterior quadrant. This method of presenting the dense array arranges short segments of the EEG (850 ms) in a schematic approximation to the location of the scalp electrodes.

The first source analysis determination, indicative of ictal onset, was made at the onset of a slow positive transient immediately preceding the slow wave of the left-posterior-wave/multiple-spike complex (fig. 2). In the MRI slice view, the moment of the cortical source estimate is shown by the color palette (brighter is stronger), and the positive orientation of the dipoles is indicated by source orientation vectors.

From the initial onset in the left inferior occipital region, the source estimates suggested rapid ictal propagation to the right posterior hemispheric regions (fig. 2). With the onset of the negative slow wave, the maximal source activation shifted to the superior left parietal region. Coincident with the occurrence of the multiple spike discharges, source analysis indicated involvement of additional regions of the left superior parietal lobe.

Intracranial Localization of Seizure Onset and Propagation

Five clinical seizures were recorded during invasive LTM. Clinical seizure electrographic patterns were stereotyped; the semiology was that of the subject's habitual

seizures. Source analysis predictions of seizure onset and propagation patterns were replicated very closely on review of each one of her invasive ictal EEG recordings. Figure 3 displays the ictal EEG patterns for the onset of one of the intracranially recorded seizures. The first electrographic ictal EEG changes consisted of ictal patterns first observed at subdural electrodes positioned over the left posterior inferior occipital cortex. Within 100 ms, there was rapid spread to right hemisphere sites as well as more medial regions of the left occipital lobe (blue). Ictal propagation to more superior and lateral left posterior sites was then observed.

Clinical Outcome

Surgery was carried out based on the invasive EEG findings, and a left posterior parietal, occipital and posterior basal temporal resection was performed. Other than the expected contralateral hemianopsia, there were no perioperative complications. Pathology of resected tissue showed only nonspecific gliosis. She remains without clinical seizures 30 months after resection.

Discussion

The EEG and magnetoencephalogram (MEG) give investigators time resolution of brain activity on the order of milliseconds. However, until recently, spatial resolution, particularly in the case of conventional EEG, has been very poor. The spatial resolution of functional neuroimaging (e.g. functional MRI), on the other hand, is good, although the temporal resolution is poorer than in EEG [17, 18]. Technological advances that include the capability to increase spatial sampling with whole-head coverage promise to combine the temporal resolution of EEG or MEG with the spatial resolution of MRI. Progress with electrical and magnetic source imaging now allows increasing confidence in attributing both EEG and MEG measures to activity in specific regions of neural tissue. This confidence is linked directly to empirical constraints on the source analysis, provided by probabilistic knowledge, such as of the location of gray matter or (for EEG) the conductivity of head tissues, and by improved measurement, such as low-noise recordings with dense arrays of scalp EEG sensors or MEG superconducting quantum interference devices. The advances in research technology may ultimately be translated to clinical practice. In particular, the advent of LTM with dense-array EEG may result in an opportunity to capture and better noninvasively localize epileptic seizures.

Advances in sensor net design now permit LTM with 256 EEG channels, using low-profile sensor pedestals, low-noise leads and hydrogel electrolytes that provide stable recordings for multiple-day applications. We are now applying the methods described in this paper to localize the onset of clinical seizures with preoperative 256-channel recordings in a series of patients with intractable epilepsy who will require invasive recordings as part of a standard presurgical evaluation.

Investigators find that high-frequency electrical oscillations often mark seizure onset in intracranial recordings [19], while other researchers report that changes in EEG spatial patterns using high-density subdural recordings may herald the onset of epileptic seizures [20]. Applying filtering to the present patient's EEG, we observed fast gamma (90 Hz) activity in the scalp EEG in the same electrodes showing the slow wave and polyspike, at the apparent time of seizure onset (fig. 1). However, preliminary analysis in the ongoing 256-channel studies has shown that the fast gamma responses in the scalp EEG are not consistently identified at seizure onset, and are often masked by electromyographic artifact. If the source analysis of the scalp data focuses on slow ictal discharges, whereas observation from intracranial recordings concentrates on high-frequency oscillations, the alignment of scalp with intracranial data will be difficult.

Another caveat in our study is that the electrographic data are coregistered to a standard MRI, rather than to the individual patient's own MRI. Routine clinical MRIs often do not yield sufficient information to allow the construction of a 'whole-head' model. Future routine clinical application of the new technology will require coregistration of EEG data to an individual patient's own whole-head high-resolution structural MRI to better constrain both unique conductivity estimation and electrographic source solutions. Improvements in modeling technology and software development must eventually account for individual variations in brain and skull anatomy, differences in thicknesses and electrical conductivity values of multiple tissues, and for the presence or absence of abnormal skull openings, such as surgically induced bur holes [21].

Noninvasive dense-array EEG, used in conjunction with realistic methods of source analysis and MRI models, may have the potential to assist in localizing seizure onsets and propagation patterns when standard noninvasive methods fail. Future research with improved methods that examine series of patients will establish if application of these tools will ultimately reduce the need for invasive LTM in the presurgical evaluation of patients with refractory epilepsy.

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