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Comparison of Three Methods for Localizing Interictal Epileptiform Discharges with Magnetoencephalography

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Abstract

Purpose—To compare three methods of localizing the source of epileptiform activity recorded with magnetoencephalography (MEG): equivalent current dipole (ECD), minimum current estimate (MCE), and dynamic statistical parametric mapping (dSPM), and to evaluate the solutions by comparison with clinical symptoms and other electrophysiological and neuroradiological findings.

Methods—Fourteen children of 3 to 15 years old were studied. MEG was collected with a whole-head 204-channel helmet-shaped sensor array. We calculated ECDs and made MCE and dSPM movies to estimate the cortical distribution of interictal epileptic discharges (IED) in these patients.

Results—The results for 4 patients with localization related epilepsy (LRE) and 1 patient with Landau-Kleffner Syndrome were consistent among all 3 analysis methods. In the rest of the patients MCE and dSPM suggested multifocal or widespread activity; in these patients the ECD results were so scattered that interpretation of the results was not possible. For 9 patients with LRE and generalized epilepsy, the epileptiform discharges were wide-spread or only slow waves, but dSPM suggested a possible propagation path of the IED.

Conclusion—MCE and dSPM could identify the propagation of epileptiform activity with high temporal resolution. The results of dSPM were more stable because the solutions were less sensitive to background brain activity.

Keywords

MEG; epilepsy; dynamic statistical parametric mapping; minimum current estimate; minimum norm estimate; equivalent current dipole

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Introduction

In addition to seizures, the spontaneous activity of epileptogenic tissue is characterized by interictal epileptiform discharges (IED), consisting of spikes, sharp waves, and slow waves (Pedley, 1984; Penfield and Jasper, 1954). There are usually thousands of IEDs to each seizure; thus, IEDs are easier to record than ictal discharges (IDs). Patients with focal, medically refractory epilepsies may have the chance to undergo epilepsy surgery. In those patients, a comprehensive and careful presurgical evaluation including an estimate of the seizure onset zone and the irritative zone generating the IED is crucial (Rosenow and Lüders, 2001; Doherty and Cole, 2001; Ebersole and Pacia, 1996). The utility of IEDs in predicting the epileptogenic focus and in defining the surgical target is becoming better appreciated, and may become increasingly useful as the physiological relation of ictal and interictal discharges becomes better understood (Baumgartner et al., 1995; Blume, 2001; Cascino et al., 1996; Cendes et al., 2000). A correct identification of the irritative zone by EEG recordings contributes to the definition of the epilepsy syndrome and to planning of a resective procedure or of invasive studies using subdural or depth electrodes when non-invasive studies remain inconclusive or discordant (Knake et al., 2006).

To localize the surgical target, seizure semiology and information from multiple techniques, including MEG, EEG, MRI, SPECT, and PET (Adelson et al., 1995; Danielpour and Peacock, 2000; Duchowny et al., 2000; Madsen et al., 1995; Nordli, 2000), are commonly compared for concordance (Spencer, 1994; Spencer and Bautista, 2000). MEG and EEG can provide valuable measures of normal and abnormal electrical activity in the brain (Humphrey, 1968; Nunez, 1981). Determining the extra-cranial magnetic fields and scalp potentials generated by a given source, known as the forward problem, is relatively well understood, and efficient and accurate algorithms are available (Hämäläinen & Sarvas, 1989; Liu et al., 2002; Oostendorp and Van Oosterom, 1989). However, in general there is no unique solution to the inverse problem of estimating the source currents based on the MEG and EEG recordings, i.e., it is not possible to fully determine the pattern of sources from external measurements (Dale and Sereno, 1993; Hämäläinen et al., 1993; Baillet et al., 2001).

Early attempts to localize the source currents were based on topographic maps of the scalp potential or its spatial derivatives. The spatial spread of the scalp potential is wide, even when the underlying source is focal. Hjorth's source derivative (also known as scalp current density or Laplacian) (Hjorth 1970) improves this situation by tightening the topographic pattern near the source. A similar effect is obtained by estimating the potential at the brain surface (Gevins et al. 1994).

The most popular source model is the equivalent current dipole (ECD) (Scherg, 1992; Hämäläinen et al., 1993). If the true pattern of activity consists of only one or a few focal sources, they can be modeled with ECDs; the locations and dipole moments are determined using parameter optimization techniques. The ECD model may fail to give meaningful results, however, if the underlying assumption about focality is not valid (Ossenblock et al., 1999). The problem of determining the locations of multiple simultaneous dipoles becomes prohibitively difficult when the number of dipoles increases. Good results have been obtained with spatiotemporal dipole modeling (Scherg 1992; Scherg et al., 1999), in which the locations of a relatively small number of dipoles are assumed not to change over the analysis period. Typically, however, multidipole modeling is a tedious and time-consuming process and to some extent gives results that depend on the experience of the person analyzing the data.

In the present study, we explored the use of two source estimation methods based on distributed source models, minimum current estimate (MCE) (Uutela et al., 1999) and dynamic statistical parametric mapping (dSPM) (Dale et al., 2000), in patients with different epilepsy syndromes. In distributed models, the sources are not restricted to a small number of focal sources. Instead, the brain is partitioned into a large number of small patches, each represented by a current dipole, approximating any arbitrary spatial distribution of cortical activity. Because the number of sensors is typically less than the number of unknown dipole amplitudes, additional prior assumptions are made about the properties of the sources. The dSPM is based on the minimum-L2 norm estimate, minimizing the square sum of the dipole element amplitudes (Hämäläinen and Ilmoniemi, 1994), whereas the MCE is a minimum-L1 norm estimate, which minimizes the sum of absolute values of source amplitudes (Matsuura and Okabe 1997). These approaches result in spatiotemporal maps (or movies) of brain activity with millisecond time resolution (Liu et al., 1998). In dSPM, a further step of normalizing the spatiotemporal estimates for noise sensitivity yields dynamic statistical parametric maps of brain activity (Dale et al., 2000). Besides decisions about prior assumptions, the methods based on distributed source models require little interference from the person analyzing the data.

We compared dSPM, MCE and a single-ECD analysis of IEDs in magnetoencephalography (MEG) from a clinical viewpoint. In particular, we evaluated whether the methods give concordant localization results in the case of patients whose clinical symptoms suggest a focal abnormality. Hence we examined the concordance between seizure semiology and/or MRI findings, and MEG findings obtained by ECD, MCE, and dSPM analyses. Furthermore, we studied the suitability and usefulness of the distributed models for identifying widespread activity or multiple simultaneous foci. We also examined whether these models can be used to determine the sequence of propagation of epileptic activity.

Patients and Methods

Patients

We studied 14 patients with different epilepsy syndromes who were treated at the Department of Pediatrics in Hokkaido University Hospital (Table 1.). The patients (eight male and six female) were three to 15 years old (mean 8.9 year) at the time of recording. We classified the epilepsies and epileptic syndromes of these patients according to the criteria of the ILAE (Commission of ILAE 1989). Eight patients with symptomatic localization related epilepsy (SLRE), two patients with idiopathic localization related epilepsy (ILRE), two patients with symptomatic generalized epilepsy (SGE), a patient with idiopathic generalized epilepsy (IGE), and a patient with undetermined epilepsy (UDE) were included in the present study. Among the patients with SLRE, there were four patients with frontal lobe epilepsy (FLE), a patient with temporal lobe epilepsy (TLE), and a patient with parietal lobe epilepsy (PLE). The localization of epileptogenic zone in two patients with SLRE could not be further specified. Among the patients with ILRE, a patient was with Benign Partial Epilepsy with Centro-temporal spikes (BECT) and a patient was with Atypical Benign Partial Epilepsy in Infancy (ABPE) with hemi-convulsive seizures and complex partial seizures (CPS) accompanied by atonic seizures (Aicardi and Chevrie 1982). One of the SGE patients had Lennox-Gastaut Syndrome (LGS) (Gastaut et al. 1966). The patient with UDE had Landau-Kleffner Syndrome (LKS) (Landau and Kleffner 1957).

The ECD and dSPM results of three of the present patients were discussed also in two previous reports: Patients 6 and 9 were presented in Shiraishi et al., 2005a (their Cases 1 and 2) as an example of the applicability of MEG to epilepsy patients with widespread spike and slow-wave activity, and Patients 2 and 6 were included in Shiraishi et al. 2005b (their Cases 1 and 2). Here we present the additional new results of MCE analysis on these patients.

MEG, EEG, and MRI acquisition

The subjects' parents or guardians gave their written informed consent for the MEG studies. The study was approved by the local IRB. The MEG and EEG recordings were made in a magnetically shielded room at Hokkaido University Hospital. MEG was recorded using a system with 204 superconducting quantum interference devices (SQUIDs) (Vectorview; Elekta-Neuromag Ltd., Helsinki, Finland.). This instrument has 204 planar gradiometers arranged in orthogonal pairs in a helmet-shaped array covering the entire scalp. These types of sensors detect the maximum signal right above the source current. The MEG data were band pass filtered between 0.03 and 133 Hz and sampled at 400 Hz. EEG was recorded simultaneously for visual screening using 20 scalp electrodes, placed according to the international 10-20 system, with two additional electrodes for electrocardiogram (ECG) monitoring. The EEG high-pass filtering time constant was 0.3 s. We usually recorded for a duration of >1 hour for each patient, collecting data in four-minute blocks. The patients were in a prone position. Sedative agent was used for child patients. The relative position of the head and the MEG sensors were determined by attaching three small head-position indicator (HPI) coils to the head. The position of the coils was digitized and subsequently recorded by the MEG sensors for co-registration with MRI (Hämäläinen et al. 1993).

High-resolution magnetic resonance images (MRI) were acquired with a 1.5 T scanner (Magnetom VISION; Siemens AG, Erlangen, Germany) for diagnostic purposes and for supporting the analysis and interpretation of the MEG data. (TE = 60, TR = 100 ms, voxel size $1.5 \times 1.5 \times 1.5 \text{ mm}^3$).

MEG source analysis

The distribution of the brain activity generating the spikes was determined using three source estimation approaches: Equivalent Current Dipole (ECD), Minimum Current Estimate (MCE), and dynamic Statistical Parametric Mapping (dSPM). The ECD is a good model when the underlying activity is focal, i.e., restricted to a relatively small region in the brain. For non-focal activity, distributed source models such as the MCE and the dSPM are expected to be better suited than the ECD model. ECD and MCE solutions were computed using “xfit” and “MCE” software, respectively, from Elekta-Neuromag Ltd. (Finland). The dSPM analysis was performed with in-house software (Dale et al., 2000).

The conductivity geometry of the head was assumed spherically symmetric in the ECD analysis, whereas a boundary element model (BEM) for the head (Oostendorp and Van Oosterom 1989, Hämäläinen and Sarvas 1989) was used for MCE and dSPM. The conductivity boundaries for the BEM were determined from MRI; only the inner surface of the skull is needed for MEG (Meijs et al. 1987a, 1987b, Hämäläinen and Sarvas 1989). The effect of the volume conductor model is expected to be minor in the present study. In general, the spherical model is quite accurate for MEG data: the error in the dipole location due to the spherical approximation as compared with more realistic head models is expected to be small, typically less than 1 cm (Hämäläinen and Sarvas 1989, Leahy et al. 1998).

ECDs were calculated using the single-dipole model. All sensors were included in the analysis. The ECD that had the best goodness of fit (GOF) was selected as the representative ECD of that particular MEG spike. GOF is a measure of how well the ECD model explains the measured signals. A dipole fit was accepted when the GOF was more than 70%. The relatively low GOF threshold was chosen, because only a small number of planar gradiometer MEG sensors show a prominent signal for a single source (Hämäläinen et al., 1993), and the inclusion of the sensors with little or no signal makes the GOF values lower than is typically seen when source localization is based on fewer channels, or with, axial

gradiometers. The ECDs were superimposed on each patient's MRI to visualize their anatomical location.

For MCE, source distributions within the brain volume were estimated by assuming that they minimized the L1 norm, i.e., the sum of the absolute values of the source amplitudes (Uutela et al. 1999). A characteristic feature of the maps obtained with the MCE method is that the patterns of estimated activity are relatively focal, compared with the minimum L2-norm estimates. The MCE results were projected to the surface of the brain boundary for visualization.

The dSPM method is based on the generalized least-squares or weighted minimum-norm estimate (Dale and Sereno, 1993; Hämäläinen and Ilmoniemi, 1994), which is normalized for noise sensitivity (Dale et al., 2000). The noise-normalization provides a statistical parametric map, similar to the statistical maps typically generated using fMRI or PET data, but with a millisecond temporal resolution. For the dSPM analysis, we used an anatomically constrained distributed source model, which assumed that the sources are located in the cerebral cortex. The cortical surface was segmented from the high-resolution MRI using FreeSurfer software (Dale et al., 1999; Fischl et al. 1999). The source model consisted of current dipole vectors at about 2500 locations on the cortical surface in each hemisphere. The noise normalization reduces the variation in the point-spread function between locations (Liu et al., 2002). Simulations have suggested that the spatial resolution is 15 mm or better (Dale et al., 2000; Liu et al., 2002). The significance of modulation at each site was calculated using an F-test (Dale et al., 2000; Dhond et al., 2001). These statistical maps differ from maps of estimated source strengths, since the estimated noise variance is not constant across different cortical locations. However, since the same noise covariance estimates are used at all time points for a given cortical location, the source strength at a given location over time are directly proportional to the statistical maps.

All source estimation was based on MEG data only; EEG data was inspected visually. The MEG data were digitally filtered with a pass band of 3 to 30 Hz for offline analysis. Segments containing abnormal paroxysms were selected manually. In addition to individual spikes, for some patients with localized spikes we also analyzed averages of 10–20 spikes selected for their consistent sensor topography, and aligned on the basis of their peak time. ECDs and dSPM maps were calculated at 2.5-ms intervals within a period of 100 ms at the vicinity of each MEG spike. The MCE solutions were calculated for 20-ms time windows at and around the peak of each spike. Initially, we tried single time instants at 2.5-ms intervals for the MCE analysis as well; however, to improve the stability of the MCE solutions, averaging over a 20-ms time window was necessary. A potential caveat in smoothing the data by low-pass filtering and time-window averaging is that one may diminish the early part of the IED that has been found to be important in determining the initial part of the activity (Ossenblok et al., 2007). In the present study we mainly examined the activity during the peak of a spike.

Concordance of the MEG results provided by the three source localization methods (ECD, MCE, and dSPM) with a clinical hypothesis, based on semiology, EEG, and MRI, was determined at the hemispheric and lobar levels.

Results

Patients with localized spikes

Concordant localization results were found between the ECD, MCE, and dSPM methods in Patients 1, 2 and 3 of patients with SLRE, in Patient 4 with ILRE, and Patient 5 with UDE (Table 1).

Patient 5 was an eight-year-old girl who had LKS with acquired aphasia accompanied by hemi-convulsive seizures (Figure 1). This patient had frequent or continuous spikes dominantly at the left middle temporal and central regions in EEG and MEG. ECDs were located mainly in the left superior temporal gyrus, although some were located in the left inferior frontal gyrus (Fig. 1A). The direction of the ECDs suggests a temporal rather than frontal origin. MCE and dSPM suggested that most active area during the peak of the spike was in the superior temporal gyrus, with some simultaneous additional activity in the dSPM in the inferior frontal gyrus, adjacent to the superior temporal gyrus activity (Fig. 1B-C).

Patients with diffuse spikes

In Patients 6, 7, 8, 9 and 10 with SLRE and Patient 11 with ILRE, qualitative differences were found between the ECD model and the distributed source estimates (MCE and dSPM). The distributed estimates suggested multifocal or widespread activations, sometimes with notable propagation over time, whereas the ECDs were either localized to one region only, widely scattered, or could not be calculated at all (Table 1).

Distributed source estimates for diffuse spikes are illustrated in Fig. 2. Patient 10 was an 8-year-old boy with tuberous sclerosis. MRI indicated multiple tubers in the frontal and parietal lobes. His seizures manifested as bilateral numbness of the foot, face and eyeballs, evolving to complex gestural manual automatisms with impairment of consciousness. Diffuse spikes with slow waves over bilateral, but predominantly posterior cerebral cortices could be seen in EEG. The ECDs were widespread over the right occipital and parietal lobe and an exact epileptogenic focus could not be determined. dSPM suggested widespread activation of the right inferior and superior frontal gyri (Fig. 2A, C). Activity in these multiple areas appeared almost simultaneously and sometimes expanded within milliseconds over wide areas of the right frontal lobe in the dSPM movies. In MCE, the most active area at the peak of the spike was in the supra-marginal gyrus in the right parietal lobe, although an additional active area was seen in the left inferior frontal gyrus (Fig. 2B, D). These areas remained active after the peak, but the most active area moved to the left frontal lobe. However, the propagation in the right frontal areas seen in dSPM was not evident in MCE. The patient's seizure manifestation was thought to arise most likely from involvement of the frontal lobe, especially in the cingulate gyrus in the medial frontal lobe. Thus, the dSPM results were the most concordant with his seizure manifestation.

Patients with generalized epilepsy

In Patients 12, 13, and 14 with generalized epilepsy (GE), interictal EEG showed diffuse discharges and widespread activation was expected. In these three patients, reliable ECD results could not be obtained because the spikes were too widespread. The locations of the ECDs were scattered and the goodness-of-fit was low. MCE and dSPM analyses suggested widespread activity, both simultaneous and propagating (Table 1).

Figure 3 shows examples of distributed source estimates in a patient with GE. Patient 13 was 14 years old with LGS who had tonic seizures and atypical absence seizures. His EEG showed two types of IED patterns: bilateral diffuse spike rhythm, and diffuse slow spike and wave complex. Gliosis was found in bilateral peri-Sylvian and occipital regions supplied by the middle and posterior cerebral arteries in diagnostic MRI. This lesion was probably related to asphyxia during the peri-natal period. The dSPM for both types of epileptiform discharges suggested that the largest activation during the spiking period was in both inferior frontal and superior temporal gyri bilaterally, which then suddenly propagated widely to the frontal and temporal lobes. The distribution of activity for the diffuse spike rhythm was wider than that for the diffuse spike and wave complex (Fig. 3A, C). MCE of the above two

epileptiform discharges showed separate regions of activity in the frontal and temporal lobes (Fig. 3B, D).

Discussion

The three different source estimation methods, ECD, MCE, and dSPM, provided consistent results for very focal IEDs. In many cases with a less focal irritative zone, the distributed source estimates (MCE and dSPM) suggested multifocal or widespread activation that was in concordant with the patient's clinical symptoms. Typically, the single-ECD model was inadequate in these cases. Propagation of activity among multiple areas was often easier to detect and interpret using dSPM than using MCE, making dSPM a superior choice in these cases. Below we will discuss the applicability and relative advantages of the different source estimation methods as a diagnostic tool assisting in syndrome classification in epilepsy.

Localization of focal activity

ECDs have been the main method of analysis in MEG investigations of patients with epilepsy so far (Nakasato et al 1994, Sutherling et al. 1987, Shiraishi et al. 2001, Stefan et al. 2000). Previously the ECD localization of IEDs has been found to be closely correlated to the location of epileptogenic area in intracranial recordings (Oishi et al. 2006). The ECD method is a useful tool for localizing very focal activity that is restricted to a small region of the cortex. This is often the case, e.g., with early sensory evoked responses, such as somatosensory evoked fields (SEFs) (Hari et al. 1993, Kakigi 1994, Kawamura et al. 1996) or auditory evoked fields (AEFs) (Hari et al. 1980, Elberling et al. 1980, Yamamoto et al. 1988, Pantev et al. 1990). For example, an ECD model of SEFs can provide precise information about the position of the central sulcus, thereby helping to preserve the primary motor and sensory areas in surgery (Gallen et al. 1995, Ishitobi et al. 2005, Inoue et al. 1999, Nakasato and Yoshimoto 2000). The ECDs of the epileptic discharge can also give useful information about the relationship between the epileptogenic area and organic lesions, e.g., dysembryoplastic neuroepithelial tumor (DNT) or focal cortical dysplasia (FCD), critical for defining the operative approach (Otsubo et al. 2001).

For those patients in our study whose ECDs for IEDs were well clustered at one part in their brain (Patients 1, 2, 3, 4, 5, 7, and 11), also the distributed source estimates showed a localized maximum, indicating that the dSPM and the MCE can localize an abnormal epileptic focus. Typically, the peak location of a focus can be determined with higher precision than what is the spatial resolution of dissociating two separate foci, which has been found in simulations to be about 15 mm or better (Dale et al., 2000). An example of how MEG can provide valuable information can be seen by comparing Patients 1 and 11. The distributed source estimates distinguished the difference in the abnormal areas between Patient 1 with symptomatic frontal lobe epilepsy and Patient 11 with ABPE, even although their EEG findings seemed identical. The MEG-derived locations were concordant with the seizure type and epileptic syndrome of each patient.

Characterization of multifocal and widespread activity

The single-ECD method may fail to give meaningful results in the case of widespread or propagating epileptic activity (see, e.g., Ossenblok et al., 1999; Hisada et al., 2001; Hattori et al., 2001, Shiraishi et al., 2005a, Oishi et al., 2006). Clusters of ECDs may reflect both the initial and propagated activity (Bast et al., 2006; Ossenblok et al. 2007). An advantage of the dSPM and MCE methods is that, in addition to the identification of multiple simultaneously active areas, the spatiotemporal maps can indicate dynamic changes in brain activity, thereby revealing patterns of propagation of the IEDs with high temporal resolution (Shiraishi et al., 2005b).

Previously, the dSPM technique has been used to analyze highly integrated brain activities related to cognitive tasks (Dale et al 2000, Dhond et al 2001); in these studies, dSPM identified activity occurring in various lobes simultaneously and multifocally. Similarly, the MCE method has been successfully used for the analysis of a variety of event-related activity (Raij et al. 2000, Levanen et al. 2001, Rinne et al. 2000). The distributed source models allow detection of multiple simultaneously active areas, even when the single-ECD model may reveal only one active region or does not provide interpretable results at all (Shiraishi et al., 2005b). For example, in Patient10, dSPM suggested maximum activation at two separate locations: the lower part of the right motor strip and the premotor area. Such information could not be obtained with the single-ECD technique only. Furthermore, EEG findings also indicated widespread spikes, and the ECDs for the MEG data did not cluster well; however, the dSPM showed a consistent, rather widespread epileptogenic region.

Propagation of activity was more difficult to identify in the MCE than in the dSPM solutions, because the MCE solutions appeared to be sensitive to background noise and the most active location in the MCE often suddenly changed between subsequent time points. Therefore, even if the most active areas were the same in the MCE and the dSPM at the peak of the epileptic spikes, the instability of the solution made it difficult to identify the propagation of the spikes in the MCE. The MCE results were similar to the dSPM ones mainly for the averaged spikes only. For example, the dSPM and the MCE differed in Patient 10 and 13. In Patient 10, the MCE showed the left frontal activity and did not show the spatiotemporal evolution of the interictal discharge, presumably because the MCE solution was influenced by background noise. In Patient 13, the dSPM did not show activation at the parietal region, hence the scattered MCE results in this case were interpreted as not reflective of significant activation.

Minor differences between the dSPM and MCE results were due to the different definition of the source space, i.e., the cortical surface in dSPM vs. the brain volume in MCE. For example, MCE did not indicate activity in the medial frontal lobe in Patient 2 and in the medial structure or peri-Sylvian area in Patient 3 since the version of the MCE software used in the present study did not include the medial surfaces in the visualization of the results. These were specific properties of the software that was available to us; however, there is no reason in principle why the same source space could not be used for dSPM and MCE. It would be interesting to compare the present results with those obtained with modified minimum-current estimate methods with temporally and spatially smooth solutions (Huang et al, 2006).

The dSPM maps were often found to show more widespread source estimates for averaged spikes than for individual spikes. A likely explanation for this was the overall increase in SNR for averaged spikes, which is what is depicted by the dSPM maps: a lower level of noise provided a more reliable detection of the spike itself, but does not significantly affect the spatial pattern of the background noise in the data, only the noise amplitude is reduced. Therefore, in the noise-normalized maps a wider portion around the peak activation, caused by the point-spread function of the inverse solution (Dale et al., 2000), is above the visualization threshold.

The interpretation of our results was limited by the lack of independent validation of the true pattern of activation. Our MEG studies were performed for diagnostic purposes only, not for presurgical evaluation. Therefore, the results have not been validated by invasive monitoring or postsurgical outcome. However comparison of the ECD, MCE, and dSPM results with the seizure semiology and MRI findings suggested the feasibility of the advanced distributed source estimation approaches in characterizing widespread and propagating activity for the purpose of syndrome classification in epilepsy.

Because the ECD technique has been the main method for the analysis of MEG data, typically only patients with SLRE whose epileptiform activity was anticipated to be focal in onset have been studied with MEG. The dSPM technique could also be useful for the analysis of diffuse spikes or slow waves, even when both hemispheres are involved (Shiraishi et al., 2005a). The dSPM technique also suggested bilateral diffuse discharges in both hemispheres in the patients with GE, such as Patients 13 and 14. Our results from Patient 13 with Lennox-Gastaut syndrome, however, are not concordant with the results of MEG and EEG-fMRI studies in patients with idiopathic generalized epilepsy (absence epilepsy), which show involvement of bilateral frontal and posterior temporal or parietal regions and middle frontal regions (Moeller et al., 2010, Westmijse et al., 2009). It is possible that the localization results for this patient correspond not to absence seizure but to more diffuse epileptic paroxysms. Although we have no validation of the difference, dSPM might indicate a clinical difference among patients with GE. The diagnosis of the epileptic syndrome is usually based on EEG findings and clinical manifestations. Our present study suggests that the dSPM technique could make the MEG examination more widely applicable, not only for SLRE, but also for GE. The temporal and spatial resolution of dSPM may suggest the mechanism of epileptogenesis, e.g. dSPM helped differentiate the epileptic syndromes of Patient 11 as focal and 13 as generalized, although the EEGs of both patients were diffuse spikes.

The ability of the dSPM method to characterize widespread and propagating activity suggests that the dSPM may be suitable also for the analysis of IDs as well as IEDs. For the diagnosis of the epileptic syndrome, IDs can provide valuable information. Earlier, the application of MEG for IDs in patients with epilepsy was limited by small sensor arrays that covered only a part of the brain (Shiraishi et al. 2001, Watanabe et al. 1996, Shigeto et al. 1997, Uesaka et al. 1996, Oishi et al. 2002). The availability of helmet-shaped multi-SQUID systems makes it possible to detect the IDs over most of the brain. For these types of data, distributed source estimates, such as the dSPM, are clearly expected to be superior.

Our current results provide evidence of the usefulness of analyzing MEG data with methods that go beyond the ECD, warranting further evaluation of these methods in future studies. We hypothesize that for clinical applications, an initial spatial filtering analysis such as dSPM could indicate whether the epileptic discharge is focal or diffuse. If the activity focal, ECD analysis is expected to provide valuable localization information. If the activity is diffuse, examination of the dSPM movie will suggest how the discharge propagates over space and time.

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Figure 1. Case 5: ECD, dSPM, and MCE results for localized spikes in a patient with Landau-Kleffner Syndrome

A) ECDs for individual spikes (red dots) were located in the left superior temporal gyrus and inferior frontal gyrus; ECD for the averaged spike was located in the left superior temporal gyrus (green dot). Only the peak point (0 ms) was used for the analysis of the averaged spike.

B) dSPM (top) and MCE (bottom) results for an individual spike. dSPM suggested activity in the left superior temporal gyrus at -40 ms (left), in the same area more strongly at 0 ms (middle) and near the left supramarginal gyrus at +60 ms (right). MCE showed activity in the left inferior frontal and superior temporal gyri at -50 to -30 ms (left), in the same area at -10 to +10 ms (middle), and near the left supramarginal gyrus at +50 to +70 ms (right).

C) dSPM (top) for the averaged spike suggested largest activation area at 0 ms mainly in the left superior temporal gyrus and, additionally, in the lower operculum in the left frontal and parietal lobes, similar to the results for the individual spikes. MCE (bottom) for the averaged spike also suggested largest activation in the left inferior frontal and superior temporal gyri at -10 to +10 ms.

Figure 2. Case 10: dSPM and MCE results for diffuse spikes

A) dSPM results for one spike (lateral and medial views of the left and right hemisphere). At the peak of the spike (0 ms), dSPM suggested widespread simultaneous activation in the right inferior and superior frontal gyri. Weaker activity was also seen at the right anterior cingulate gyrus. The activation patterns remained similar after 10 ms and did not propagate to another lobe.

B) MCE results for the same spike (lateral views of the left and right hemisphere). The MCE suggested largest activation in the right temporo-parieto-occipital (TPO) junction (near the supramarginal and angular gyri), and minor activation in the right inferior Rolandic and left inferior frontal gyrus from -10 to +10 ms. Activity in the right TPO junction was reduced, and left Rolandic activity was slightly increased, during the later period (0 to +20 ms).

C) For another spike, dSPM showed activation in the right Rolandic and inferior frontal gyri simultaneously at 0 ms. The activity propagated over most of the right frontal lobe by +68 ms.

D) For the second spike, MCE showed largest activation around the right TPO junction and inferior frontal gyrus from -10 to $+10$ ms. The active area in MCE moved to the right superior frontal and left inferior frontal gyri with multiple foci from $+58$ to $+78$ ms.

Figure 3. Case 13: dSPM and MCE results for a diffuse spike and slow wave complex and diffuse spike rhythm

A) dSPM results for a diffuse spike and slow wave complex (lateral views of the left and right hemispheres). At the peak of the spike (0 ms), the most active area was seen in the left inferior frontal and superior temporal gyri simultaneously. Later (24 ms after the peak), dSPM spread to include also right anterior temporal and prefrontal cortices.

B) MCE results for the same complex (lateral views of the left and right hemisphere). MCE suggested several foci of activity over both the frontal and the parietal lobes, bilaterally, during the spike period (−10 to 10 ms). For the later period (+14 to 34 ms), multiple MCE foci are noted over the right frontal, central and temporal areas, and left frontal pole.

C) dSPM results for a diffuse spike rhythm. Bilateral inferior frontal and anterior temporal activation of varying extent is seen at three successive spike peaks (0 +60 ms, and +188 ms).

D) MCE results for the diffuse spike rhythm showed less consistent activation, predominantly over the right frontal lobe for the first spike (−10 to +10 ms), over both frontal lobes, right temporal and left central for the second spike (+50 to +70 ms), and over bilateral frontal, left central, and right parietal for the third (+178 to +198 ms).

Table 1

Clinical profiles, ECD, MCE and dSPM findings of the 14 patients.

Case	Age	Sex	Classification	Syndrome	Seizure types	EEG	MRI	Assumed foci	ECD (Category*)	MCE (Category*)	dSPM (Category*)
Patients with localized spikes											
1	5	M	SLRE	FLE	FMS, HC	L F-C, CSWS	NF	L F	L F	##	L F
2	7	M	SLRE	FLE	FMS	Cz	NF	R F	R F	##	R F
3	15	M	SLRE	TLE	SPS, SCPS	L T	B MTS	L T	L T, HP	##	L T, INS
4	8	F	ILRE	BECT	pGTC	R T-O	NF	R F	R F	##	R F
5	8	F	UDE	LKS	HC	L C-F, CSWS	NF	L T, L F	L T, L F	##	L T, L F
Patients with diffuse spikes											
6	3	M	SLRE	PLE	SPS, HC, pGTC	L FSL	NF	left hemispheric	scattered	##	L P, L F, L P
7	10	M	SLRE	FLE	CPS	B DSP	NF	left hemispheric	L F	##	L F
8	13	F	SLRE	FU	SPS, pGTC	L DSP	NF	left hemispheric	scattered	##	L F, L P, R F
9	13	F	SLRE	FLE	CPS	L Fp-F	L F OS (PNET)	L F, LT	L F	##	L F, L T
10	8	M	SLRE	FU	SPS, SCPS	B DSL	L OP tuber (TS)	multiple focus	R OP broad	##	R F
11	4	F	ILRE	ABPE	HC, CPS	L C-P, CSWS	NF	left hemispheric	L F, L T	##	L F, L P
Patients with generalized epilepsy											
12	14	F	SGE	Others	ToS	B DSP	NF	bilateral diffuse	scattered	##	L F
13	14	M	SGE	LGS	ToS, AABS	B DSP, DSW	B OP gliosis	bilateral diffuse	scattered	##	B F, B T broad
14	3	M	IGE	Others	ABS, MS, GTCS	B DSL	NF	bilateral diffuse	scattered	##	B F broad

Abbreviations: AABS, atypical absence seizure; ABPE, Atypical Benign Partial Epilepsy in Infancy; ABS, absence seizure; BECT, Benign Partial Epilepsy with Centro-temporal spikes; C, central; CPS, complex partial seizure; CSWS, continuous spikes and waves during sleep; DSL, diffuse slow wave; DSP, diffuse spike; DSW, diffuse spikes and slow waves; F, frontal; FLE, frontal lobe epilepsy; FMS, focal motor seizure; FSL, focal slow wave; FU, focus unknown; GTCS, generalized tonic-clonic seizure; HC, hemi-conjunctive seizure; HP, hippocampus; IGE, idiopathic generalized epilepsy; ILRE, idiopathic localization related epilepsy; INS, insular cortex; L, left; LGS, Lennox-Gastaut Syndrome; LKS, Landau-Kleffner Syndrome; MS, myoclonic seizure; MTS, medial temporal sclerosis; NF, no finding; O, occipital; OS, operation scar; P, parietal region; pGTC, partial seizure evolved to generalized tonic-clonic seizure; PLE, parietal lobe epilepsy; PNET, primitive neuro-ectodermal tumor; R, right; SCPS, simple partial seizure evolved to complex partial seizure; SGE, symptomatic generalized epilepsy; SLRE, symptomatic localization related epilepsy; SPS, simple partial seizure; T, temporal; TLE, temporal lobe epilepsy; ToS, tonic seizure; TS, tuberous sclerosis; UDE, undetermined epilepsy;

Category*

(1) MEG results concordant with clinical hypothesis;

(2) MEG results ipsilateral to clinical hypothesis, but different area;