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Magnetoencephalographic mapping of epileptic spike population by using distributed source analysis: Comparison with intracranial electroencephalographic spikes

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Abstract

Introduction—This study evaluates magnetoencephalographic (MEG) spike population as compared with intracranial electroencephalographic (IEEG) spikes by using a quantitative method based on distributed source analysis.

Methods—We retrospectively studied eight patients with medically-intractable epilepsy who had a MEG and subsequent IEEG monitoring. Fifty MEG spikes were analyzed in each patient by using minimum norm estimate. For individual spikes, each vertex in the source space was considered activated when its source amplitude at the peak latency was higher than a threshold, which was set at 50% of the maximum amplitude over all vertices. We mapped the total count of activation at each vertex. We also analyzed 50 IEEG spikes in the same manner over the intracranial electrodes, and created the activation count map. The location of the electrodes was obtained in the MEG source space by co-registering post-implantation CT to MRI. We estimated the MEG- and IEEG-active regions associated with the spike populations by using the vertices/electrodes with a count over 25.

Results—The activation count maps of MEG spikes demonstrated the localization associated with the spike population by variable count values at each vertex. The MEG-active region overlapped with 65–85 % of the IEEG-active region in our patient group.

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Conflict of Interest

None declared

Conclusions—Mapping the MEG spike population is valid for demonstrating the trend of spikes clustering in patients with epilepsy. Additionally, comparison of MEG and IEEG spikes quantitatively may be informative for understanding their relationship.

Keywords

epilepsy; magnetoencephalography; distributed source analysis; intracranial electroencephalography; minimum norm estimate; spike population

Localization of epileptic discharges is critical for planning epilepsy surgery. The clinical gold standard for localization is invasive intracranial electroencephalography (IEEG) recording, but even this has limited coverage and a risk of complications (1). Magnetoencephalography (MEG) records neuromagnetic fields from the entire brain, and is completely non-invasive. The usefulness of MEG for investigating interictal epileptic spikes has been shown typically by using the conventional single dipole analysis that provides point sources representing the recorded signals (2, 3). Distributed source analyses, such as minimum norm estimate (MNE), are more reliable localization in some circumstances (4–6). This procedure demonstrates certain areas of cortical activation at each time point associated with epileptic spikes by calculating unit dipoles deployed on the cortical surface, i.e., different source maps are obtained from multiple individual spikes. Generating and reviewing of many source maps are necessary for understanding the trend of these spikes in each patient, which may not be convenient in clinical practice (6). There is no established mapping for representing the trend of entire spike populations with a distributed source solution.

The accuracy of distributed source analysis of MEG spikes has been investigated as compared with IEEG spikes by measuring the latency in spike propagation (7) and visual comparison of source distribution patterns (5). The spatial extent of source localization, however, has not been quantitatively evaluated between MEG and IEEG spike populations.

The purpose of this study is to investigate the MEG spike population by using a quantitative mapping method based on the distributed source analysis, and to validate this mapping with the localization of IEEG spikes in patients with epilepsy. This representation may be a more accurate and clinically useful method in the evaluation of surgical epilepsy patients.

Methods

Patients

We studied eight patients with medically-intractable epilepsy who underwent a MEG and subsequent IEEG monitoring as a part of presurgical evaluation. We analyzed the data retrospectively. All patients showed unilateral interictal MEG spikes, and intracranial electrodes were placed unilaterally. The study complies with the Declaration of Helsinki. Informed consent was obtained from all patients and their guardians. All aspects of the study were approved by the institutional review board. Table 1 gives an overview of the clinical profiles of the patients.

MEG recording

MEG was recorded with a 306-channel, whole-head MEG system (Elekta-Neuromag, Helsinki, Finland). The sampling frequency was 600Hz (patients 1–4) or 1000 Hz (patients 5–8) with a band-pass filter of 0.1–200 Hz. For the source analysis, the data were low-pass filtered at 40 Hz to reduce the contamination of high-frequency artifacts. The details of the MEG recording have previously been described (8).

In all patients, anatomical MRI data were acquired with magnetization-prepared rapid acquisition gradient-echo sequences (MPRAGE; TE=3.37 ms, TR=2000 ms, voxel size=1×1×1 mm) with a high-resolution 3T scanner (TIM TRIO, Siemens AG, Erlangen, Germany).

IEEG recording

IEEG was recorded with a digital EEG system (XLTEK EEG system; Excel-Tech Ltd, Oakville, Canada) with subdural grid electrodes (Ad-Tech, Racine, USA). Each electrode contact was 4 mm in diameter with 10 mm spacing. The sampling rate was 512 Hz (patient 4), 1000Hz (patient 1) and 2000Hz (patient 2, 3, 5–8). The data were low-pass filtered at 40 Hz for further analysis. All patients underwent computed tomography (CT) after implantation of intracranial electrodes. The details of the IEEG recording have been previously described (9).

MEG analysis

We visually examined the MEG data and selected 50 consecutive interictal spikes that were distinctive and distinguished from the background activity. Source distribution was calculated at the peak of these spikes by using MNE (Fig. 1A-left, B-left) (10). A realistic head model was created for calculating the source activation based on a boundary elemental method (11, 12) by using the cortical surface derived from each patient's MRI (13, 14). The sources are constrained to the source space on the cortex by deploying approximately 5000–6000 unit dipoles in each hemisphere (Fig. 1B-middle), representing cortical activation caused by epileptic spikes (4, 7, 15, 16).

Source waveforms of MEG were extracted at each vertex in the source space from the MNE source distribution of each individual spike, and the amplitude of these source waveforms was obtained at the peak latency. Each vertex was considered activated or non-activated when its source amplitude was higher or lower than a threshold, respectively (Fig. 1A-middle, right). The threshold was set at 50% of the maximum amplitude over all vertices at the peak latency. We assigned a value (called 'count') of 1 and 0 for the activated and non-activated vertices, respectively, and mapped these values in the source space (Fig 1B-right). This procedure was repeated for all 50 spikes; Thus, 50 maps with the count of 1 and 0 were created (Fig. 1C-left, middle, right). Finally, we mapped the total count obtained from the 50 spikes group for each vertex, creating an activation count map. Each vertex has the count from 0–50 (Fig. 1D-left).

For determining the MEG-active region, which is the active region associated with the overall MEG spike population, we selected vertices with a count over 25 (50% of the spike

population). The MEG-active region was determined by the sum of the vertices within 10 mm of these selected vertices (Fig. 1D-middle, right).

IEEG analysis

We analyzed IIEG data in a similar manner as the MEG analysis. First, locations of intracranial electrodes were determined by co-registering the patient's MRI and post-implantation CT (Fig. 2A-middle). The co-registration was performed based on a procedure described in previous literature (17). We visually reviewed the IIEG data and selected 50 consecutive interictal spikes that were distinctive and distinguished from the background activity in each patient. Maps with the activated (count=1)/non-activated (count=0) electrodes were created for each spike, by applying a threshold to the amplitude in each electrode at the peak latency (Fig. 2A-left, right). The threshold was set at 50% of the maximum amplitude over all electrodes at the peak latency. The total count was obtained at each electrode from the 50 spikes group, providing an activation count map (Fig. 2B-left, middle). We selected electrodes with a count over 25 as the active electrodes, and obtained the vertices nearest to the center of these electrodes. The IIEG-active region, which is the active region associated with the overall IIEG spike population, was determined as the sum of the vertices within 10 mm of these vertices (Fig. 2B-right).

Statistical analysis

We obtained the number of vertices within the hemispheric source space on the side of spikes, the MEG- and IIEG-active regions. The region, which was included in both of MEG- and IIEG-active regions, was considered overlapping, and the number of vertices in the overlapping region was also obtained. We calculated the following indices by using these numbers of vertices, indicating the concordance of MEG- and IIEG-active regions for each patient. Only one hemisphere was used for this calculation due to the unilateral MEG spikes and intracranial electrode placement.

Sensitivity of MEG relative to IIEG = Overlapping region/IIEG-active region

Specificity of MEG relative to IIEG = Area that was not included in either MEG-or IIEG-active region/ Area that was not included in IIEG-active region

Accuracy of MEG relative to IIEG = (Overlapping region + Area that was not included in either MEG – or IIEG-active region)/Hemispheric source space

Results

In each patient, MNE maps obtained from the MEG spikes showed various source distribution patterns. Representative MNE maps of a patient (patient 4) are shown in Fig. 3, where the maps demonstrate widespread (Fig. 3-left) or restricted (Fig. 3-right) source distribution for different spikes. Activation count maps of each patient, which were obtained from the spike population consisting of these individual spikes, had variable count values at each vertex. The MEG-active regions represented the estimated amount of cortical area based on the activation count maps. Representative maps of activation counts and MEG-active regions of a patient (patient 4) are shown in Fig. 4A-left and -right, respectively. Similarly, activation count maps of IIEG spike populations showed different count values between electrodes. The IIEG-active regions were obtained from 4–12 active electrodes

based on the activation count maps, estimating the cortical area associated with the spike population in each patient. Maps of a representative patient (patient 4) are shown in Fig. 4B-left and -right. The MEG-active regions were more widespread than the IIEG-active regions in three patients (patients 2, 6, 7), whereas other five patient (patient 1, 3–5, 8) showed similar active areas for MEG and IIEG spike populations.

The MEG-active regions partially overlapped the IIEG-active regions in all patients. The sensitivity of MEG relative to IIEG described above was 0.65–0.85. Especially, MEG showed a sensitivity over 0.80 in four patients. The specificity and accuracy were 0.94–0.99 and 0.93–0.98, respectively. Table 2 gives an overview of the results for all patients.

Discussion

In this study, we mapped and evaluated MEG spike populations with a distributed source analysis by using a new, quantitative method. The method provides a single map showing the estimated active cortex associated with spike population, instead of multiple series of maps obtained from individual spikes. Previous studies presented maps of representative spikes (4, 15), that require numerous source maps for evaluation (6). Averaging spikes, which increases the signal-to-noise ratio, may be useful for analyzing and representing the entire spike population (16, 18, 19); however, this method may distort important information of individual spikes due to cancellation of signals (20). Our method preserves and represents the spatial involvement of individual spikes effectively: The locations activated by the majority of spikes have a high count, and the involvement of infrequent, a small number of spikes is shown by a low count. On the other hand, the activation count maps do not contain the information of dipole orientations as demonstrated by the single dipole analysis.

In our method, the spatial involvement of spikes with low amplitude can be estimated, because the threshold, which is used for obtaining the activation count maps, is determined based on the peak amplitude of each individual spike. However, these small spikes may show a localization error caused by their low signal-to-noise ratio. Such spike selection may affect the activation count maps, especially when the spike population is small. Our method can calculate the activation count maps for small spike populations containing less than 50 spikes, although such maps may be less reliable due to their small activation counts. Mapping larger spike populations will provide precise information for the entire trend of spike localization, by overcoming the bias caused by erroneous localization of each single spike, selection of spikes, and small sample size. All steps of our analysis are fully- or semi-automated, except for detecting spikes, and a combined approach of our method and an automated spike detector will be useful for analyzing large numbers of spikes.

Our MEG analysis showed a good concordance with IIEG spike localization in the patients. Previous studies have demonstrated a high sensitivity of MEG for detecting epileptic spikes simultaneously recorded on IIEG (21, 22). The overlap of the MEG- and IIEG-active regions would depend on the IIEG electrode placement in relation to the epileptogenic zone. Moreover, spread of spikes from a distant origin may affect the source distribution patterns in some patients (7). Analyzing the early phase of spikes will be useful for comparing spike onsets on MEG and IIEG (6).

The accuracy of MEG spike localization has been traditionally investigated by using a single dipole analysis as compared with IEEG spikes (23–33). Some of these studies qualitatively determined the active, frequent spiking electrodes after reviewing spikes on IEEG data (23, 25, 26). The location of the electrodes was sometimes not examined in the same space system due to the lack of fusion of the MEG source space and the IEEG electrode space, which were typically based on MRI and CT/x-ray/intraoperative observation, respectively (24, 26, 27). The overall localization of MEG spikes was also evaluated qualitatively by reviewing the dipole maps (24, 25, 28). The concordance of MEG and IEEG spikes was obtained at a lobar or sublobar level despite a high spatial resolution of MEG (29, 30, 31). Moreover, the dipole evaluation includes selection of dipoles by certain parameters such as correlation coefficient, goodness of fit and dipole moment (25, 29, 32), although the evaluation of IEEG spikes does not contain such processes. Recent studies have compared MEG and IEEG more objectively by co-registering post-implantation CT images onto the patient's MRI (32, 33), and evaluating the dipole localization in a quantitative procedure (31, 33).

In addition to the single dipole analysis, advanced mapping of MEG spikes, such as multiple signal classification (MUSIC), synthetic aperture magnetometry (SAM) and MNE, has demonstrated a good concordance of MEG and IEEG spike localization at a sublobar level (34–36). Shirozu et al. (37) reported that the gradient magnetic-field topography of MEG spikes was highly concordant with voltage topography of IEEG spikes by using simultaneous recording MEG and IEEG data. Several studies showed the usefulness of the maximum entropy on the mean for estimating IEEG potentials from the MEG sources (38, 39). Our method could be modified to use any other distributed source method to evaluate the characteristics of populations of discharges.

The comparison presented in our study uses the same space system of the brain for analyzing both MEG and IEEG spikes obtained by co-registering post-implantation CT images onto MRI of the patients. The amplitudes of MEG source waveforms and IEEG spikes are processed by the same procedure using a threshold, and the count value is calculated for both MEG and IEEG spike populations at each location of the space. We estimate the amount of active cortex by measuring numbers of locations in the space and obtain the overlap of activation associated with MEG and IEEG spike populations quantitatively, instead of providing the concordance at a lobar or sublobar level.

This study has several limitations. First, MEG and IEEG were separately recorded. The duration of recording was significantly different between MEG and IEEG in our procedures (8, 9). While previous studies of simultaneous MEG-IEEG recordings have shown that MEG spike amplitude is correlated with the amplitude of IEEG spikes, the size of cortical areas involved by the IEEG spiking is critically important (21, 22). The amplitude of an IEEG spike may not have the same implications as in MEG. Simultaneous recording is necessary to investigate the exact correspondence of each spike between MEG and IEEG. Second, we applied a predefined threshold to the source amplitude for selecting the activated vertices. Similar thresholds have been applied for determining the amount of activated cortex (16, 40, 41); however, determination of such thresholds has not been well established. More objective approaches may be useful to determine the appropriate threshold (42). Similarly,

we predefined a threshold of 25 counts or above for selecting the MEG- or IEEG-active locations, i.e., these locations are activated by 50% or above of the spike population. The MEG- and IEEG-active regions included the vertices within 10 mm from the active locations. Considering that the spacing of IEEG electrodes was 10 mm, this distance might represent a possible area to be included regarding an activity at a single location, but it is still empirically determined. Analyzing spike populations with various thresholds will reveal their effect on the MEG- and IEEG-active regions. Finally, the number of patients studied here is small. Investigating larger patient groups will be necessary for understanding the pathophysiology of various types of epilepsy.

In conclusion, mapping MEG spike population by using distributed source analysis provides useful information for demonstrating the entire trend of spikes in patients with epilepsy. The estimated active regions associated with MEG and IEEG spike populations were concordant in our patient group. Comparison of MEG and IEEG spikes quantitatively in the same system may be informative for understanding their relationship in patients with epilepsy.

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Figure 1.

Schematic representation of the MEG analysis. (A) Analysis of each individual spike. A source distribution map is obtained at the spike peak by using MNE (A-Left, B-Left). Source waveforms are extracted at all vertices (B-Middle) and each vertex is considered activated (count=1) or non-activated (count=0) by a threshold (A-Middle, Right). Thus, a map with count 1/0 is created for each spike (B-Right). (B) Analysis of spike population. A series of maps with count 1/0 are created from each spike of the population (C-Left, Middle, Right). The total count at each vertex is mapped in the source space, creating an activation count map (D-Left). The vertices with count over 25 of 50 spikes are selected, and the vertices within 10mm of these vertices are estimated as the MEG-active region, which is the active region associated with the spike population (D-Middle, Right).

Figure 2.

Schematic representation of the IEEG analysis. (A) Analysis of each individual spike. A map with the activated (count=1) and non-activated (count=0) electrodes is created for each spike (A-Left, Middle, Right) by using the same manner as shown on Fig. 1A, B. (B) Analysis of spike population. An activation count map is created (B-Left, Middle) from the spikes by using the same manner as shown in Fig. 1C, D-Left. The electrodes with count over 25 of 50 spikes are selected, and the vertices within 10mm of the vertices nearest to the center of these electrodes are estimated as the IEEG-active region, which is the active region associated with the spike population (B-Right).

Figure 3.
MNE maps of a representative patient (patient 4). (Left) The maps demonstrate widespread (Left) and restricted (Right) source distribution for different individual spikes.

Figure 4.

Maps of activation counts, MEG- and IEEG-active regions in a representative patient (patient 4). (A) An activation count map obtained from 50 MEG spikes (Left) and the estimated MEG-active region (Right). (B) An activation count map obtained from 50 IEEG spikes (Left) and the estimated IEEG-active region (Right).

Table 1

Patient profile

Patient	Age/Sex	Diagnosis	IID (MEG)	IID (IEEG)	MRI	Surgery	Follow up (month)	Outcome
1	14/F	R OLE	RO	RO	Normal	No resection	NA	NA
2	8/M	R FLE	RF, RP	RF, RP	Normal	R frontal lobe resection	41	Engel Ia
3	14/M	L FLE	LF	LF	Normal	L frontal lobe resection	35	Engel III
4	8/F	L FLE	LF, LP	LF, LP	L precentral cortical dysplasia	L frontal/parietal lobes resection	25	Engel III
5	9/M	R OLE	RT, RO	RT, RO	R occipital encephalomalacia	R occipital/temporal lobes resection and disconnection	28	Engel Ia
6	11/M	Multifocal	LF, LT, LP	LF, LT, LP	L parietal/STG encephalomalacia	L parietal/superior temporal lobes resection	8	Rare seizures
7	5/M	R FLE	RF, RP	RF, RP	Normal	R frontal lobe resection	15	Engel Ia
8	17/F	L FLE	LF	LF	Normal	L frontal lobe resection	2	No seizures

M: male, F: female, L: left, R: right, OLE: occipital lobe epilepsy, FLE: frontal lobe epilepsy, IID: interictal discharges, RO: right occipital, LF(RF): left(right) frontal, LP(RP): left(right) parietal, LT(RT): left(right) temporal, STG: superior temporal gyrus, NA: not applicable

Table 2

Results

Patient	MEG-active region	IEEG-active region	No of active electrodes (IEEG)	sensitivity	specificity	accuracy
1	R medial occipital	R medial occipital	6	0.65	0.96	0.95
2	R precentral, R postcentral, R middle frontal	R precentral, R postcentral	7	0.73	0.96	0.94
3	L superior/middle frontal	L superior/middle frontal	7	0.78	0.96	0.95
4	L precentral, L postcentral, L inferior frontal	L precentral, L postcentral, L inferior frontal	4	0.81	0.99	0.98
5	R basal occipital, R basal temporal	R basal occipital, R basal temporal	4	0.85	0.99	0.99
6	L inferior frontal, L supramarginal, L inferior parietal, L superior/middle temporal	L middle/inferior frontal, L supramarginal, L superior temporal	12	0.71	0.95	0.93
7	R precentral, R postcentral, R superior temporal	R precentral, R postcentral	6	0.80	0.99	0.98
8	L middle/inferior frontal	L middle/inferior frontal	6	0.82	0.94	0.94

L: left, R: right