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Neuromagnetic coherence of epileptic activity: An MEG study

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ABSTRACT

Purpose: This study was undertaken to test the hypothesis that patients with epilepsy have abnormal imaginary coherence compared with control subjects.
Methods: Thirty patients with seizures underwent magnetoencephalography (MEG) recording using a whole cortex MEG system. Conventional equivalent current dipoles (ECDs) and synthetic aperture magnetometry (SAM) were used to analyze MEG data. Neural synchronization was studied using imaginary coherence to analyze resting-state MEG data. The ECDs, SAM, and MEG results were then compared with intra/extra-operative EEG.
Results: Abnormal imaginary coherence was identified in all patients (30/30, 100%). The locations of abnormal imaginary coherence were in agreement with the ECDs locations of spikes in 23 patients (23/30, 76.7%). The ECD locations in 5 patients were scattered or located bilaterally. The locations of abnormal imaginary coherence were in agreement with SAM locations in 26 patients (26/30, 86.7%). One case of imaginary coherence was located in two lobes. The ECDs fit locations were in agreement with SAM locations in 21 patients (21/30, 70.0%). The locations of abnormal imaginary coherence, ECDs, and SAM were in agreement with intra/extra-operative EEG in 23 patients (23/30, 76.7%), 17 patients (17/30, 56.7%), and 20 patients (20/30, 66.7%), respectively. The results of ECDs location, SAM location, imaginary coherence, and intracranial EEG (iEEG) were consistent in 15 patients (15/30, 50%).
Conclusions: The results show that patients with epilepsy have abnormal imaginary coherence, and suggest that the location and coherence of epileptic activity could be quantitatively identified and analyzed using neuromagnetic signals.

1. Introduction

Non-invasive studies predicting regions of epileptogenic activity are important for successful epilepsy surgery. Among all recording modalities, magnetoencephalography (MEG) is advantageous because it can be used to noninvasively localize regions of neuronal activity within the brain.[1–3] The temporal resolution of MEG is less than 1 ms, significantly shorter than functional magnetic resonance imaging (fMRI),[4] and the spatial discrimination of MEG is 2–3 mm for sources in the cerebral cortex. It is considered a better clinical technique than electroencephalogram (EEG).[4] Prediction of intracerebral locations of sources for recorded extracranial MEG signals requires mathematical source localization algorithms. Multiple categories of algorithms have been developed.[3–7] At present, epileptiform discharges in MEG signals are visually identified. After labeling representative epileptic spikes, epileptic sources can be localized by fitting either equivalent current dipoles (ECDs)[3,5] or synthetic aperture magnetometry (SAM) models.[7,8] However, both methods are cumbersome and time consuming, and require considerable practical experience to minimize errors. A more efficient and temporally localizing method is needed.

Coherence has been defined as an intrinsic functional connectivity, and distinct networks have been identified.[9] Past studies have suggested that synchronization of neuronal discharges results from functional connectivity.[10–13] Thus, coherence is a good indicator of neural interactions. Coherence of epileptic activity has been studied using intracranial electroencephalogram (iEEG) recordings[14,15] However, the estimation of coherence was formed from a small number of independent sample spectra. The

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statistical significance of coherence estimates has also been studied using scalp EEG.[16,17] Compared with iEEG and EEG, MEG has a greater number of sensor channels and is more sensitive to deeper brain bioelectric discharges. Thus, MEG has significant advantages for the analysis of coherence of brain activity in distinct regions, and is especially useful for studying epilepsy.[18]

Previous EEG and MEG studies using coherence to assess functional connectivity in patients with brain lesions found a highly significant decrease in coherence in patients with lesions during the resting state.[19,20] However, because of volume conduction, single source activity may be measurable in channels, especially in adjacent channels.[21] Thus, the traditional approach of calculating coherence would induce redundancies in measurement and false brain interactions, rather than true brain interactions.[22] It has been argued that the traditional approach of calculating coherence is sensitive to volume conduction and may cause an overestimation of coherence.[23] In this study, we attempted to use coherence of MEG signals to reflect interactions between different brain areas. Mathematically, the physical part of coherence represents synchronization of two signals, which are zero-lagged to each other, while the imaginary part represents synchronizations with a time lag. Moreover, interactions between brain areas must occur with a certain time lag, but volume conduction causes zero time delay. Thus, the imaginary part of coherence can be used as an index of synchronization of brain areas, which is insensitive to volume conduction.[23,24]

The aim of the present study was to analyze the characteristics of the coherence of epileptic activity. Specifically, we wanted to explore whether and how the coherence of endogenous neuromagnetic signals associate with epileptic foci determined by clinical data. We hypothesized that neuromagnetic epileptic activity would be characterized by greater coherence of local cortical activity. Accordingly, coherence analysis should provide outstanding sensitivity in localizing epileptic areas compared with other existing methods.

2. Materials and methods

2.1. Patients and healthy control subjects

Thirty patients with epilepsy (age range: 6–45 years; mean age, 27 years; 14 females and 16 males) underwent MEG and MRI scans at the Nanjing Brain Hospital affiliated to Nanjing Medical University. To perform a comparison with the 30 patients with epilepsy, 30 age- and gender-matched healthy subjects were recruited. All patients and healthy control subjects had no visible lesions in structural MRI images. Additional patient inclusion criteria included: (1) less than 5 mm head movement during MEG recordings, (2) clinical diagnosis of epilepsy and MEG successfully obtained.

2.2. Ethics statement

An explanation of the study was provided to all patients and control subjects prior to enrollment. Patients and controls gave voluntary and written informed consent according to the standards set by the ethical committee of Nanjing Brain Hospital of Nanjing Medical University, who approved this study.

2.3. MEG recordings

MEG recordings were conducted in a magnetically shielded room. We used a whole-head CTF 275-Channel MEG system (VSM MedTech Systems Inc., Coquitlam, BC, Canada). Before data acquisition commenced, a small coil was attached to the nasion and left and right pre-auricular points on each subject. The three coils were subsequently activated at different frequencies for measuring each individual's head position relative to the MEG sensors. The system allowed for head localization to an accuracy of 1 mm. The sampling rate of MEG recordings was 1200 Hz. All MEG data were recorded with noise cancelation of third-order gradients. Each epoch took 120 s and 15 epochs were recorded for each subject. The head position was measured before and after each epoch. The limitation of head movement during MEG recording was 5 mm. Subjects were deprived of sleep the night before MEG and MRI. During the MEG recording, an audio–video system continuously monitored the subject. Subjects were kept in a resting state during the experiment, i.e., subjects were lying in a supine position awake and with their eyes closed. Specifically, the resting state in this study was defined as spontaneous activity not evoked by cognitive tasks and the absence of seizure activity.

2.4. MRI scan

MR images were acquired on a 3 T scanner (Siemens Medical Solutions, Erlangen, Germany). The protocol typically included the following sequences: (1) A T1-weighted, 3D spoiled gradient-recalled echo in a steady state sequence with TR 7.5 ms, TE min full, flip angle 15°, field of view 240 mm × 240 mm. (2) A 2D fluid attenuated inversion recovery (FLAIR) sequence with TR 8000 ms, TE 120 ms, TI 2000 ms, matrix 192 × 256, field of view 240 mm × 240 mm, slice thickness 5 mm in the coronal and axial planes. Three fiducial points were placed in identical locations to the positions of the three coils used in the MEG recordings to allow for an accurate co-registration of the two data sets. The MRI image was evaluated retrospectively by two neurologists blind to the study.

2.5. Data analysis

All MEG recordings were reviewed by two experienced epileptologists, and the peaks of all epileptic spikes were marked manually based on the MEG recordings. We chose MEG epochs with spikes to calculate ECDs locations, SAM locations, and imaginary coherence.

An ECDs model was fitted to the magnetic field recorded with the entire MEG sensor array. For each spike, the sampling point was used that yielded the model with the smallest residual variance. Only ECDs with a goodness-of-fit value $> 85\%$ and confidence volume $< 3\ \mathrm{mm}^3$ were accepted. Spike topography, moment strength, and orientation were also considered for the selection of ECDs. ECDs location estimation was not performed on MEG data of control subjects because no spikes were identified.

For analysis of SAM, the epoch which had the greatest amount of interictal epileptiform discharges was selected. The result was subjected to estimation of excess kurtosis and band power between 20 and 70 Hz at each 5 mm × 5 × 5 mm volume element in the brain.[25] We define SAM as a voxel that has a local kurtosis value higher than half of the maximum (highest) kurtosis value in each epoch.

The coherence between two MEG channel time series $x(t)$ and $y(t)$ is a measure of the linear relationship of the two signals at a specific frequency λ, which is defined as:

$$Coh_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \left| \frac{f_{xy}(\lambda)}{\sqrt{f_{xx}(\lambda)\, f_{yy}(\lambda)}} \right|^2 \quad (1)$$

where $R_{xy}(\lambda)$ is the complex valued coherence of $x(t)$ and $y(t)$, $f_{xy}(\lambda)$ is the cross spectral density (CSD) of $x(t)$ and $y(t)$, $f_{xx}(\lambda)$ and $f_{yy}(\lambda)$ are the power spectral densities (PSD) of $x(t)$ and $y(t)$, respectively. The CSD of $x(t)$ and $y(t)$ is calculated as $f_{xy}(\lambda) = X(\lambda)Y^*(\lambda)$, where $X(\lambda)$ and $Y(\lambda)$ are the Fourier-transformation of $x(t)$ and $y(t)$, and $Y^*(\lambda)$ indicates the complex conjugate of $Y(\lambda)$. During the CSD calculation, Welch's method was used, i.e., the signal is split up into

overlapping segments, each segment is 2 s long, Hanning-windowed, and overlapped with adjacent segments by 50% (1 s). Finally, $f_{xy}(\lambda)$ is averaged over all successive segments. The PSD of $x(t)$ or $y(t)$ can be computed using the same method as calculating the CSD.

Imaginary coherence can be calculated by taking the square value of the imaginary part of coherence[12,23] as follows:

$$IC_{xy}(\lambda) = |imag[R_{xy}(\lambda)]^2 \quad (2)$$

Clinical data were obtained by examining clinical symptoms, EEG, and MRI prior to surgery. Traditional epileptic sources were localized using the CTF program with the ECDs and SAM models. The results of ECDs location, SAM location, and imaginary coherence were compared with intra/extra-operative EEGs.

For patients with negative findings on MRI, the selection of a surgical approach for the resection of epileptogenic zones was very cautious. The pre-surgical workup for these patients included complete neurological examination, EEG, MEG and other tests. Surgical outcomes for these patients were routinely assayed 1 year later.

3. Results

After visual inspection of waveforms, we found that all patients (30/30, 100%) had clear epileptic spikes. A typical MEG spike is shown in the waveforms in Fig. 1. All 15 epochs with spikes were found in 18 patients, and 8–14 epochs with spikes were found in the remaining 12 patients. Thus, all patients in this study had MEG spikes in at least 8 epochs.

A summary of the clinical data, ECDs, SAM, imaginary coherence, scalp EEG, and intero/extra-operation EEG of all 30 patients is shown in Table 1. Abnormal imaginary coherence was identified in all patients (30/30, 100%). The locations of abnormal imaginary coherence were in agreement with the ECDs locations of spikes in 23 patients (23/30, 76.7%). The ECDs locations in five patients were scattered or located bilaterally. The locations of abnormal imaginary coherence were in agreement with SAM locations in 26 patients (26/30, 86.7%). The ECDs fit locations were in agreement with SAM locations in 21 patients (21/30, 70.0%).

The locations of abnormal imaginary coherence were in agreement with intra/extra-operative EEG in 23 patients (23/30, 76.7%). The locations of ECDs were in agreement with intra/extra-operative EEG in 17 patients (17/30, 56.7%). The locations of SAM were in agreement with intra/extra-operative EEG in 20 patients (20/30, 66.7%). The results of ECDs location, SAM location, imaginary coherence, and iEEG were consistent in 15 patients (15/30, 50%). A total of 9 out of these 15 patients underwent epilepsy surgery. Six out of the nine operated patients were followed-up for more than a year (follow-up

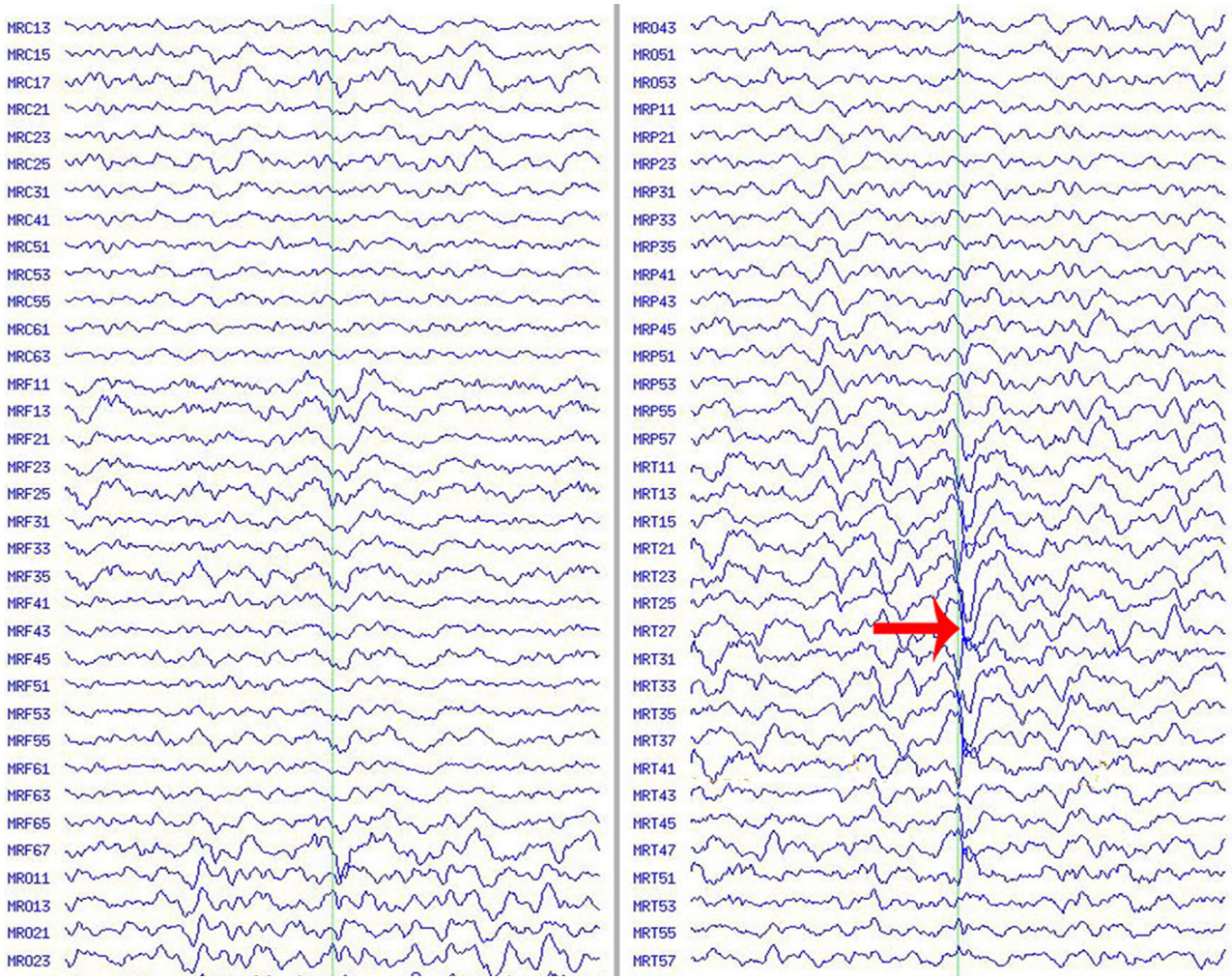

Fig. 1. MEG waveforms showing epileptic spikes. The red arrow denotes epileptic spikes. The amplitude of the spikes is significantly higher compared with the amplitude of background brainwave activity. The increased spikes are mainly distributed in the right temporal MEG sensors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1
Summarized the clinical data, ECD, SAM, coherence, scalp EEG and intero/extra-operation EEG of all 30 patients included in the study.

Patient No.	Sex	Age (year)	Seizure type	MEG			EEG	
				ECD	SAM	Coherence	Scalp	Intro/extraoperation
1	F	20	CP, 2G	RPO	RPO	RPO	Nonlaterlized	RP
2	M	41	CP	LT	LT	LT	LFT	LT
3	F	22	CP	LT	LT	LT	Nonlaterlized	LT
4	F	19	Aucr, CP, 2G	RT	RTO	RT	Billaterial F	RT
5	M	38	SP, 2G	RF	RF	RF	RFCT	RF
6	F	22	AA, CP	Bilateral T	LT	LT	NA	LT
7	M	37	AA, CP	Scatters	RT	RT	RT	RT
8	M	32	SP	RF	RF	RF	NA	RF
9	M	6	SP	RF	RF	RF	Nonlaterlized	RF
10	F	28	SP, 2G	RF	RF	RF	Nonlaterlized	NA
11	F	45	CP	LT	LT	LT	NA	LT
12	F	28	AA, CP	LTF	LTF	LTF	L-hemispheric	LTF
13	M	17	CP, 2G	Scatters	LTO	LTO	LPTO	LTO
14	M	26	SP, CP	LFT	LFT	LFT	Nonlaterlized	LFT
15	M	36	CP, 2G	LT	LT	Bilateral T	NA	Bilateral T
16	F	22	CP	RT	RT	RT	RTF	RT
17	M	20	CP, 2G	RPT	RPT	RPT	Nonlaterlized	RP
18	M	17	SP, 2G	RF	RF	RF	RF	RF
19	M	26	CP	LT	LT	LT	NA	LT
20	M	36	CP	LF	LF	LF	LTF	LF
21	F	25	CP	RF	RF	RF	Nonlaterlized	RF
22	F	15	SP, AA	LF	LTF, RF	LF	Nonlaterlized	LF, insular lobe
23	M	35	SP, 2G	LF	LF	LF	L-hemispheric	LF
24	M	27	CP	LT	LT	LT	Nonlaterlized	LF
25	M	37	CP, 2G	Bilateral F	RP	RP	Nonlaterlized	RP
26	F	22	AA, CP	Bilateral F, LT	LT	LT	L-hemispheric	LF
27	F	24	CP, 2G	LP	LT	LT	Bilateral F, T	LT
28	F	13	CP	RTP	RTP	RTP	R-hemispheric	RT
29	F	40	CP, 2G	LTF	LF	LTF	LF	LTF
30	M	34	CP	RT	RT	RT	R-hemispheric	RT

AA, atypical absence; CP, complex partial seizure; F, prefrontal; 2G, secondarily generalized seizure; L, left; NA, not available; O, occipital; P, parietal; R, right; SP, simple partial seizure; T, temporal.

was not done in two cases; one patient was followed-up, but for <1 year). Surgical outcome was classified using a modified Engel classification, 2 patients had Engle class I, and 3 patients had Engle class II, while 1 patient had Engle class III. The remaining six non-operated patients did not have surgery for economic and personal health reasons (4/15), and the epileptogenic zones were too close to the eloquent cortices (2/15).

Figs. 2 and 3 show typical results for imaginary coherence, ECDs location, SAM location, and iEEG location (for patient No. 30 and patient No. 3, Table 1). The imaginary coherence (Fig. 2a) for patient No. 30 in Table 1 was located in the right temporal lobe, which was in agreement with ECDs locations (Fig. 2b) and SAM locations (Fig. 2c). The onset of epileptiform discharges was located in the right temporal lobe (Fig. 2d). All location methods were consistent with each other. The imaginary coherence (Fig. 3a) for patient No. 3 was located in the left posterior temporal lobe. The location of higher imaginary coherence was in agreement with ECDs (Fig. 3b), SAM (Fig. 3c), and iEEG (Fig. 3d).

In this study, we also observed abnormal rhythm of imaginary coherence for patients compared with healthy control subjects. Fig. 4a shows typical results for patient No. 25 and patient No. 15 (Table 1) (values below threshold = 0.1 are not shown, while values above 0.3 are shown by red lines). The imaginary coherence results in the β band for patients (Fig. 4a) were higher compared with healthy control subjects (Fig. 4b). According to the patterns of imaginary coherence results shown in Fig. 4a, there was increased coherence in the β band for both patients. However, there was no obvious abnormal imaginary coherence for two healthy control subjects, No. 10 and No. 22 (Fig. 4b).

4. Discussion

Unlike previous studies[19,20] reporting decreased coherence over lesion locations, this study showed increased coherence over epileptic foci. A possible explanation is that decreased coherence reported in previous lesion studies may have resulted from abnormal integrity of gray matter and adjacent white matter, which in turn led to lower coherence between corresponding regions and remaining cortical areas. Although the definite cause for epilepsy is unclear, some patients present with normal tissue structure,[26] but characteristically abnormal rhythm, likely caused by excessive electrical activity in neurons. In the current study, we found abnormally increased coherence near epileptic zones. This result is in accordance with other epilepsy research, which has shown abnormally increased localized synchronized neuronal activity within epileptic zones.[27–29] Our results may reflect this phenomenon that patients with epilepsy tend to have abnormal imaginary coherence over their epileptic foci.

An ECDs model is used for visual analysis of spikes for ECDs source localization. When MEG epileptic spikes are visually identified, they are localized by fitting them to an ECDs model. The more points and high-amplitude wave spikes that are involved, the more concentrated dipole densities are and thus, the lower the error rate.[30] However, fitting an ECDs model is analogous to solving an inverse problem with limited measurement. Therefore, it often fails to estimate current sources with high accuracy.

SAM is another model using magnetic spatial filtering techniques to localize epileptic sources.[7] It is based on the nonlinear constrained minimum-variance beamformer method.[31] Beamforming is a method of source analysis for MEG sensor data in which a spatial filter is used to estimate the contribution of a given

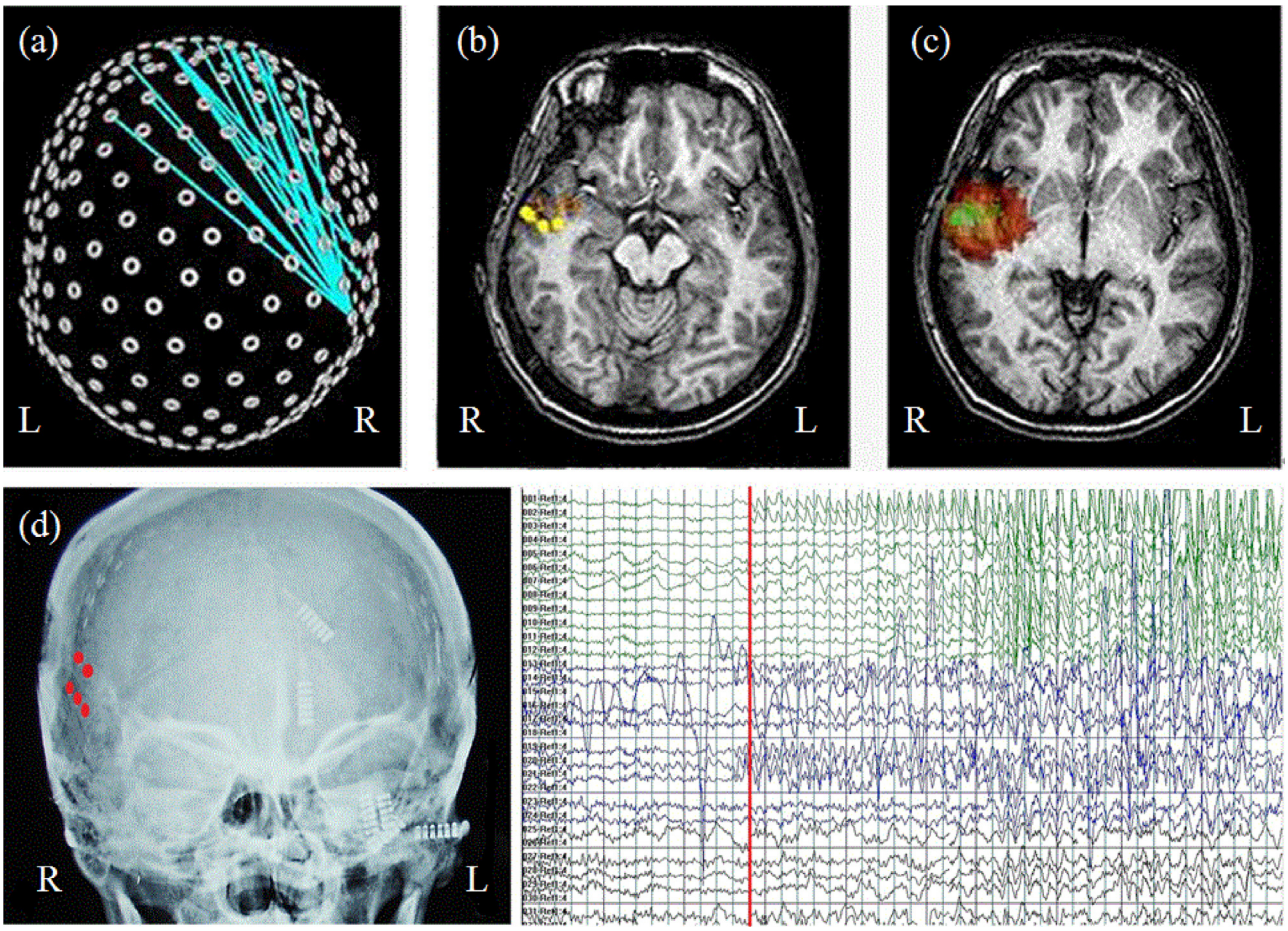

Fig. 2. Map of MR imaging with MEG spike sources in the right temporal lobe (Table 1: patient No. 30). The location of higher imaginary coherence is in agreement with the location of ECDs, SAM, and iEEG. (a) Increased imaginary coherence is located in the right temporal lobe. (b) Dipole spike sources are clustered in the right temporal lobe (yellow dots). (c) SAM image showing similar regions of power change (the orange region). The green dot indicates the peak of SAM results. (d) Skull X-ray film was obtained after placement of intracranial electrodes over the right temporal lobe and displays the location of the ictal onset zone (red dots) from the results of iEEG recordings (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

source location to the measured MEG sensor signal, while filtering out the contribution of other sources. The advantage of this method is that it is not necessary to impose constraints on the source solution by determining the number and positions of dipoles in advance. However, SAM analysis also requires considerable practical experience to minimize errors.

Conventional ECDs and SAM analysis can localize the areas of spike generation precisely. However, some research has pointed out that spikes may be generated in areas secondarily involved in the epileptogenic network, which may not be responsible for seizure generation.[32,33] At the origin of epileptic foci, magnetic signals are quite weak, but gradually enlarge during transmission. The spikes are the result of epileptic signal amplification. Therefore, not all peaks of spikes reflect the origin of epileptic activity.[32,33] The two methods described above may not objectively display the origin and transmission area of epileptic activity. For this reason, to avoid errors, in this study, we introduced imaginary coherence analysis, and attempted to combine imaginary coherence with ECDs and SAM analysis to identify the origin of epileptic activity.

Neuronal and cortical column oscillations give rise to large-scale oscillatory population dynamics reflecting the activity of millions of cells. When two neural populations oscillate synchronously, bursts of action potentials can be consistently exchanged during the depolarization phase of the target neuron's ongoing membrane potential fluctuations, thereby increasing fidelity of communication between these neurons.[34] Schevon et al.[29] found regions of high coherence primarily located in the cerebral cortex adjacent to seizure-onset zones. A seizure-free outcome was associated with removal of these highly coherent nodes.[29] A local increase of coherence during the interictal period has also been reported in some seizure studies.[35,36] Therefore, coherence analysis is considered an effective method to apply precise localization of epileptogenic zones. In this study, we combined imaginary coherence, ECDs, and SAM analysis results to obtain an integrated and comprehensive map of epileptogenic zones.

Clarification of the relationship between source location of neuromagnetic coherence and the epileptogenic zone is required. Theoretically, an epileptogenic zone is defined by a cortical area whose complete resection is necessary to free the patient from seizures.[37] However, it cannot be delineated preoperatively. Thus, we chose to use intra/operative EEGs as a reference standard to estimate diagnostic accuracy. The results of the comparison may help us to further optimize our methods for localizing epileptogenic zones. In the future, coherence analysis may improve neurosurgeons' placement of electrodes for intracranial recordings, or help to select an optimal surgical approach for epilepsy surgery.

Because of the limited number of cases in our post-surgical follow-up, the comparison of surgical outcomes with pre-surgical

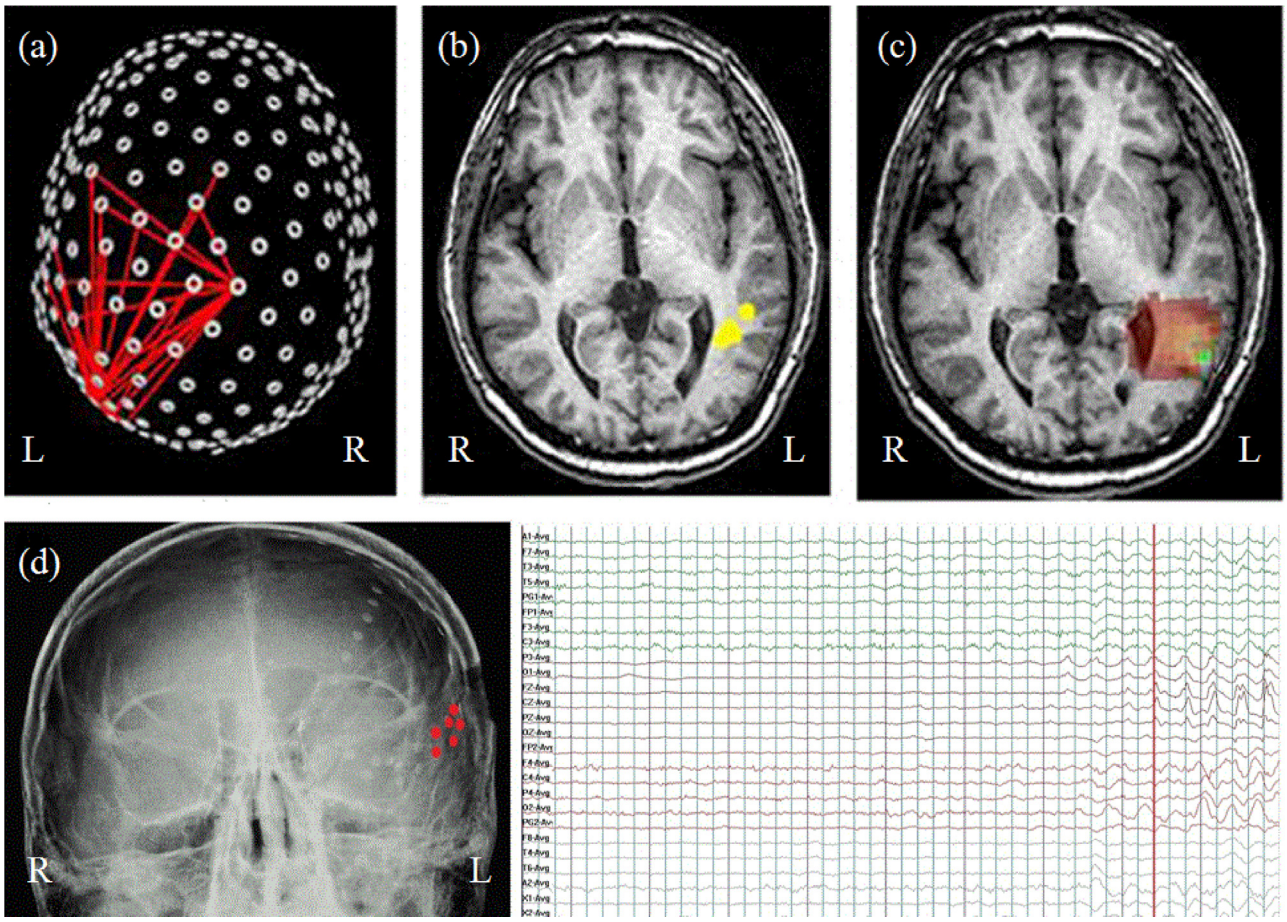

Fig. 3. Map of MR imaging with MEG spike sources in the left posterior temporal lobe (Table 1: patient No. 3). The location of higher imaginary coherence is in agreement with ECD, SAM, and iEEG. (a) Increased imaginary coherence is located in the left posterior temporal lobe. (b) Dipole spike sources are clustered in the left temporal lobe (yellow dots). (c) SAM image showing similar regions of power change (the orange region). The green dot indicates the peak of SAM results. (d) Skull X-ray shows that the intracranial electrodes were placed over the bilateral temporal lobe. The ictal onset zone (red dots) was located on the left temporal lobe, which was obtained from iEEG recordings (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

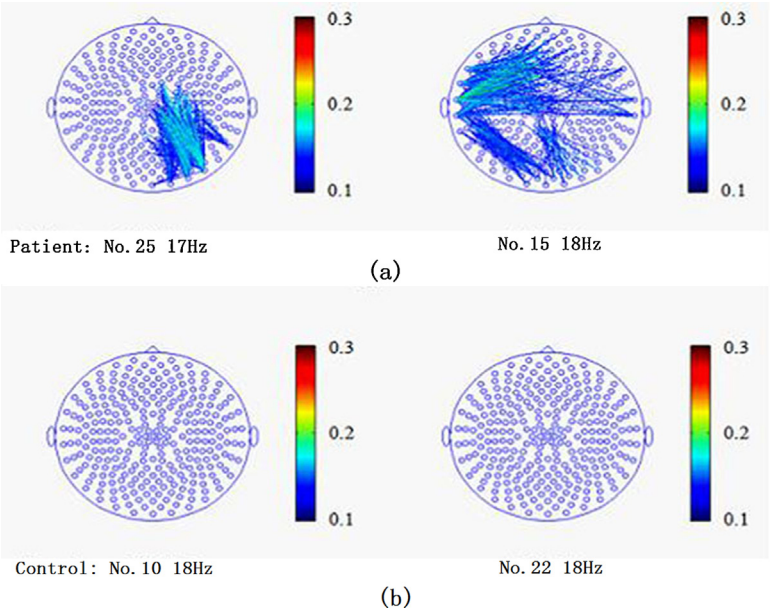

Fig. 4. Imaginary coherence connectivity maps for patients and control subjects. Patterns of imaginary coherence connectivity in the β band for patients are higher compared with healthy control subjects (values below the threshold = 0.1 are not shown, while values above 0.3 are shown by the red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

functional mapping was not possible in the present study. Consequently, this study focused on methodological exploration and we hope to address the other issues raised in future studies.

In summary, the results of the present study have demonstrated that the location of epileptic activity can be identified and analyzed using synchronization of neuronal discharges. Compared with conventional methods of visual identification of spikes, the approach presented here is objective and sensitive. Source analysis of neuromagnetic coherence may provide a novel approach to determine epileptogenic zones and the transmission area of epileptic activity non-invasively and preoperatively. The combination of imaginary coherence, ECDs, and SAM analysis may be a reliable and precise method to diagnose epileptogenic zones. The measurement of neuromagnetic signals in epilepsy may also enable researchers to noninvasively investigate the development of epilepsy.

Conflict of interest

None declared.

Acknowledgments

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