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Interictal magnetoencephalographic findings related with surgical outcomes in lesional and nonlesional neocortical epilepsy

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ABSTRACT

Purpose: To investigate whether interictal magnetoencephalography (MEG) concordant with other techniques can predict surgical outcome in patients with lesional and nonlesional refractory neocortical epilepsy (NE).

Methods: 23 Patients with lesional NE and 20 patients with nonlesional NE were studied. MEG was recorded for all patients with a 275 channel whole-head system. Synthetic aperture magnetometry (SAM) with excess kurtosis (g2) and conventional Equivalent Current Dipole (ECD) were used for MEG data analysis. 27 Patients underwent long-term extraoperative intracranial video electroencephalography (iVEEG) monitoring. Surgical outcomes were assessed based on more than 1-year of post-surgical follow-up using Engel classification system.

Results: As we expected, both favorable outcomes (Engel class I or II) and seizure freedom outcomes (Engel class IA) were higher for the concordance condition (MEG findings are concordant with MRI or iVEEG findings) versus the discordance condition. Also the seizure free rate was significantly higher ($\chi^2 = 5.24$, $P < 0.05$) for the patients with lesional NE than for the patients with nonlesional NE. In 30% of the patients with nonlesional NE, the MEG findings proved to be valuable for intracranial electrode implantation.

Conclusions: This study demonstrates that a favorable post-surgical outcome can be obtained in most patients with concordant MEG and MRI results even without extraoperative iVEEG monitoring, which indicates that the concordance among different modalities could indicate a likelihood of better postsurgical outcomes. However, extraoperative iVEEG monitoring remains prerequisite to the patients with discordant MEG and MRI findings. For nonlesional cases, our results showed that MEG could provide critical information in the placement of intracranial electrodes.

1. Introduction

Epilepsy surgery is an option for patients with medically refractory epilepsy. To achieve a better outcome post surgery, it is very important to take various presurgical evaluations into account for determining an appropriate surgical plan. Over the past two decades, more comprehensive presurgical assessments and advanced techniques have become available. High-resolution magnetic resonance imaging (MRI) has been known as the best preoperative diagnosis for patients with lesional refractory neocortical epilepsy (NE).[1–3] Digital video electroencephalography (VEEG) provides us with a definitive diagnosis of seizure-like events, while intracranial VEEG (iVEEG) is commonly used to define the ictal onset zone (IOZ). However, surgical resection of the IOZ alone does not always yield a favorable operative outcome because iVEEG electrodes only record signals in their direct vicinity and are blind for other areas, making it difficult to judge whether the IOZ really represents the ictal generator or is the result of propagation from elsewhere.[4] However, in a number of reports,[5] it was pointed out that it is also difficult to judge whether spike foci represent the epileptogenic zone. Furthermore, Holmes et al.[6] reported that only unifocal interictal epileptiform discharges (IEDs) restricted to the seizure onset zone could be used as a marker for epileptogenicity, while others showed that (rapid) spike

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onset discharges may be useful for defining the epileptogenic zone but not the subsequent propagation of the discharges, for both EEG[7] and MEG.[8] Thus, precise identification of epileptogenic zone remains one of the greatest challenges for successful epilepsy surgery.

Magnetoencephalography (MEG) was first introduced in 1968,[9] and it detects magnetic fields generated by cortical neuronal activity. As a new and noninvasive technique, it has shined a light on localizing epileptogenic zones. In comparison to the conventional electroencephalography (EEG), MEG has potential advantages in precisely localizing epileptogenic zones because magnetic signals can pass through the human skull and other tissues without significant distortion while electrical signals can be significantly distorted by brain tissues. In addition, MEG spikes usually have a shorter duration and a steeper ascending slope than EEG spikes. So the signal-to-noise ratio (SNR) of more superficial sources is larger in MEG than in EEG, which indicates MEG is more suitable for accurate localization of neocortical epileptiform sources.[10,11] Consequently, interictal MEG is increasingly used in epilepsy presurgical evaluation, and MEG localization of interictal spike zone has shown excellent agreement with invasive iVEEG.[12–14] MEG is not suitable for chronic recording. Therefore, MEG signals typically provide interictal but rarely ictal data, which is usually distorted by head movement.[15] The advancements of MEG techniques have allowed it to become a clinically valuable diagnostic tool[14–25] in presurgical evaluation for both the localization of the epileptogenic zone and the prognosis of surgical outcome. Although MEG cannot totally substitute for ECoG yet, the noninvasively detected interictal MEG regions, which are highly associated with interictal intracranial subdural electrocorticography (ECoG), have been used to assist in the placements of intracranial electrodes and provide complementary information for presurgical evaluation.[26] However, interictal MEG spikes which define the so-called irritative zone for prognosis of surgical outcome is still under discussion. It has been found that successful surgical outcome usually is associated with the high agreements among MRI, interictal EEG and together with iVEEG which converge to a singular zone of ictal onset.[26,27] Thus, the message that concordance of (either EEG or MEG) spike foci and MRI or iVEEG better predicts outcome is not new. The question remains, however, as to whether MEG has any additional value compared to EEG for prediction. Or in other words, is there a better concordance for MEG than for EEG in relation to MRI or iVEEG for the patients studied? Our hypothesis is that the high concordance between interictal MEG and MRI findings for patients with lesional NE and the high concordance between interictal MEG and iVEEG for patients with nonlesional NE can be a better predictor of post surgical outcomes than EEG in some cases.

Although MRI plays an important role in presurgical evaluation for lesional NE patients, it does not aid in the presurgical evaluation for patients who had a normal MRI or showed nonspecific findings in their MRI.[28] The nonlesional NE patients are the true challenges in the presurgical evaluation for epilepsy surgery. As a gold standard, long-term extraoperative iVEEG monitoring was needed for almost all patients with nonlesional NE. However, the surgical outcomes in nonlesional NE patients were not as ideal as in patients with lesional NE. Moreover, the contribution of MEG during presurgical evaluation in comparison with other techniques was assessed by several studies.[29,30,31,46] Stefan et al. presented the largest series consisting of 455 epilepsy patients undergoing MEG investigations. In 131 of the 455 patients (28.8%) who underwent surgical treatment, MEG succeeded in identifying the epileptogenic zone in 89% of patients. The authors quantified the contribution of MEG to the general result of presurgical evaluation in 104 patients. MEG supplied additional information in 5% of patients and crucial information for the final decision in 10% of patients.

Synthetic aperture magnetometry (SAM) is an adaptive beamformer technique using a spatial filtering algorithm on MEG signals to estimate the magnetic activities at specified region of interest (ROI). Excess kurtosis (g2) is a statistical measurement of the steepness of spikes at each voxel. A method called SAM (g2), which is a combination of SAM and g2 and an automated interictal spike localization approach, provides source locations of intracranial epileptic discharges. Previous studies have shown that SAM (g2) can localize MEG interictal spikes[31–35] and has several advantages compared with conventional Equivalent Current Dipole (ECD) method.[36] First, SAM (g2) analysis identifies and localizes spikes in one step. Second, it can automatically analyze MEG signals, including spikes. And finally, it is considerably computationally faster than the conventional ECD analysis which requires manual spike marking and dipole fit. However, there is one important disadvantage of SAM (g2) compared to ECD that is highly relevant when trying to localize the interictal onset zone. SAM (g2) yields a stationary distribution of the source strength and makes it difficult to distinguish the interictal onset (irritative) zone and the subsequent propagation areas. Thus, in the present study, we reported not only on the interictal MEG with regard to the spatially related SAM (g2), but we also list the distinct clusters of spikes.

In this study, we implemented SAM (g2) and conventional Equivalent Current Dipole (ECD) methods on interictal MEG data. We also retrospectively analyzed clinical profiles, iVEEG findings from extraoperative intracranial invasive monitoring, surgical procedures, and pathology as to their relation to post-surgical seizure outcomes in a cohort of patients with either lesional or nonlesional NE, who underwent epilepsy surgery for refractory NE. We investigated the spatial correlation between MEG and MRI findings for patients with lesional NE, and the spatial correlation between MEG and resection volume for patients with nonlesional NE. By studying these spatial correlations between interictal MEG and other modalities, we hope to associate concordant MEG findings with better postsurgical outcomes.

2. Methods

2.1. Patients

During the period of January, 2006 and June, 2009, 147 patients with refractory epilepsy were admitted to the epilepsy center of the Brain Hospital of Nanjing Medical University (Nanjing, China) and underwent presurgical evaluation. 79 Patients (53.7%) ultimately had cortical resection to treat their epilepsy. Exclusion criteria included (1) patients with generalized seizure; (2) patients who did not have surgery; (3) patients with mesial temporal lobe epilepsy (MTLE); (4) patients who could not be classified as having either MTLE or temporal neocortical epilepsy (TNE); (5) patients with no MEG examination; (6) patients with follow-up time less than 12 months. According to the above exclusion criteria, 36 patients were excluded, including 21 patients with MTLE, 6 patients who could not be classified as having either MTLE or TNE, and 9 patients without interictal MEG examination. The remaining 43 patients fulfilled inclusion criteria and refractory NE diagnostic criteria. Inclusion criteria included (1) partial seizure or second generalized seizure; (2) epileptogenic zone which was located in the neocortical region; (3) non MTLE or non TLE with dual pathology; (4) patients who underwent surgery for resection of epileptogenic zone; (5) follow-up time >12 months. The mean age of the patient group was 19.9 ± 9.4 years old. There were 26 males and 17 females in the group. The mean duration of epilepsy prior to surgery was 8.9 ± 5.8 years. 24 Patients had more than one type of seizure. All patients were treated in the epilepsy center of the Brain Hospital of Nanjing Medical University. The study was approved by

the Medical Ethics Committee of the hospital. Informed consent for the study was obtained from all participants.

2.2. MRI scan

All patients had MRI scans with a GE Sigma scanner (GE Healthcare, Milwaukee, WI, USA). The protocol included the following sequences: axial and sagittal T1 weighted, axial and coronal T2 weighted, axial and coronal fluid-attenuated inversion recovery (FLAIR) images, and three-dimensional (3D) Spoiled Gradient Recalled (SPGR). Three fiducial points were placed in identical locations as the ones used in the MEG recordings so that 3D MRI and MEG data could be co-registered precisely to yield a MSI using these three landmarks. Two neuroradiologists, who were blinded to the clinical information analyzed all the MRI images preoperatively. We defined nonlesional findings in MRI as normal findings or nonfocal abnormalities, such as diffuse brain atrophy, nonspecific white matter signal changes and periventricular leukomalacia et al. MRI criteria used in this study were adapted from previous studies.[37,38] Based on MRI findings, the patients were divided into group A consisting of 23 patients with lesional epilepsy and group B consisting of 20 patients with nonlesional epilepsy.

2.3. MEG recording

MEG data acquisitions were performed using a 275 channel whole-head system (CTF VSM MedTech Systems Inc., Coquitlam, BC, Canada) in a magnetically shield room (MSR) (Vacuum-Schmelze, Hanau, Germany) that was designed to reduce environmental magnetic noise. Before the MEG scan, there was no reduction in the antiepileptic medication due to the potential risk factor. To increase the likelihood of capturing spike events, we used sleep deprivation. The head position relative to the sensor arrays for each patient was measured using three coils affixed to the nasion and preauricular points before MEG data recording. We recorded 15 epochs (120 s long per epoch) of spontaneous MEG recording for each patient. If the head movement during the recording was greater than 5 millimeters (mm), the epoch was recorded again. Seizures were not recorded during MEG recording.

Synthetic aperture magnetometry (SAM) with excess kurtosis (g2) and conventional Equivalent Current Dipole (ECD) methods were used to analyze our MEG data. We defined the MEG spike distributions by the number and density according to dipole. Clusters consisted of six or more spikes with 1 cm between adjacent sources; scatters consisted of fewer than six spikes regardless of the distance between spikes or with >1 cm between sources regardless of the number of sources in a group.[39,40] SAM (g2) is a novel epilepsy analysis based on spatial filtering technique, which automatically estimates spike locations from raw MEG signals and provides source waveforms for these spike locations. The SAM (g2) images were computed for the whole head in 5 mm steps using 20–70 Hz frequency range which provided optimal image contrast for interictal spike activity. The SAM (g2) results generated a list of the local maxima, and SAM virtual sensors were computed for each location in the list to obtain the source time series. The SAM (g2) image was then co-registered with the corresponding MRI of each patient using Magnetic Source Locator (MSL) software.[41,42] We define evSAM (g2) as a voxel that has a local kurtosis value higher than half of the maximum (highest) kurtosis value in each data set.[35] The distance between the lesion margin and the evSAM (g2) was quantitatively measured for each patient with lesional NE, and it was used as an indicator for the spatial relationship between the focal lesion on the MRI and the evSAM (g2). If the location of evSAM (g2) was on the lesion margin or within 2 cm, we classified these patients with lesional NE to one sub-group A1 (MEG findings were concordant with MRI findings). Otherwise, we classified them to the other sub-group A2 (MEG findings were discordant with MRI findings). The determination criteria for dividing group A to two sub-groups was based on the results from Awad et al.[21] and Stefan et al.[43]

2.4. Video EEG monitoring

All patients had long-term scalp digital video-EEG (VEEG) monitoring using a 32-channel Bio-Logic digital VEEG system (Natus medical Inc., San Carlos, CA, USA) with 19 scalp electrodes according to international 10–20 scalp electrode placement system. Three or more seizures were captured during VEEG monitoring. Both interictal and ictal epileptic discharges were analyzed by a neurologist. 27 Patients (7 patients with lesional MRI findings in group A; all 20 patients with nonlesional MRI findings in group B) had extraoperative intracranial VEEG (iVEEG) monitoring from subdural grid or strip electrodes with a 128 channel Bio-Logic digital VEEG system (Natus medical Inc., San Carlos, CA, USA). We placed intracranial electrodes based on evidence from MRI, VEEG, MEG, seizure semiology, and neurologic examination. On average, 2–12 seizures were captured during iVEEG recording.

2.5. Surgery and outcome

A 2 * 6 surface electrode array for intraoperative electrocorticography (ECoG) was placed on the group A1 patients. For this group of patients, the area of resection was primarily determined by the cross results from MRI-visible lesions, interictal irritative zone based on evSAM (g2) and intraoperative ECoG. For the groups A2 and B patients, the extent of resection included the ictal onset zone (IOZ) on the extraoperative iVEEG and part of ictal symptomatogenic zones, and active interictal zones adjacent to the ictal onset zone.[44] In six cases, the IOZs were related to motor or language functional regions. We only delineated the part of the IOZs preventing damage of eloquent cortex in order to minimize neurological deficits post surgery. Intraoperative navigation system was used if necessary. Surgical procedures consisted of lobectomy, corticectomy, multiple subpial transaction (MST) or a combination. All of the patients had MRI scans within 24 h after their operation. A neuroradiologist and a radiologist with great experience in MEG data, who were both blinded to the surgical procedures and outcomes, examined the relationship between volume of surgical resection and evSAM (g2) only for the group B patients. We defined "concordance" as the majority of evSAM (g2) ($\geq$2/3) being in the volume of resection and "discordance" as the majority of evSAM (g2) ($>$1/3) being outside of the volume of resection. This criteria was based on a previous study.[45] According to this, the nonlesional NE patients were divided into 2 sub groups made up of the group B1 (concordance) and the group B2 (discordance).

All patients were regularly followed up with for more than a year (mean: 26.9 ± 11.7 months; range: 12–52 months). Surgical outcome was classified using a modified Engel classification[46]: (1) seizure freedom for more than a year post-surgery (Engel class IA); (2) favorable operative outcome: seizure free or significantly improved seizures rare (Engel class I or II: more than 90% reduction in seizure frequency) and (3) unfavorable operative outcome: worthwhile or no worthwhile improvements (Engel class III or IV: less than 90% reduction in seizure frequency).

2.6. Statistical analysis

The χ^2 test was used to evaluate whether there were significant differences between group A and group B. To demonstrate the relationship between MEG localization and surgical outcome, the patients were divided into two sub groups within the group. For

Table 1
Clinical profiles, MRI, MEG, EEG, surgical procedures, pathology, and outcomes of lesional epilepsy.

No.	Age (year)/gender	Seizure duration (year)	Seizure type	MRI (lesion location)	Interictal MEG		EEG		Surgical procedures	Pathology	Outcomes follow up (months)/ Engel
					SAM (g2)	ECD	Scalp	Intro/extraoperation			
1	31/Male	2.5	CP	LT (lat, mid-ant)	LT (lesion-ant)	Clusters	LFT	LT (lesion-ant, sup)	Lesionectomy + corticectomy (lesion-ant) + MST (perilesion)	Angiomalformation	52/IA
2	20/Female	11	Aura, CP, 2G	RPO	RPO	Scatters	Nonlaterlized	RP (perilesion)	Lesionectomy + corticectomy (perilesion)	Ganglioneuroma	43/IA
3	3/Female	2	CP	RF (lat, mid-sup)	RF (lesion-ant)	Clusters	Bilaterial F	RF (lesion-ant)	Lesionectomy + corticectomy (lesion-ant)	Ganglioneuroma	40/IA
4	22/Female	6	CP	LT (lat, mid-inf)	LT (lesion-pos, sup)	Clusters	Nonlaterlized	LT (perilesion)	Lesionectomy + corticectomy (lesion-pos, sup)	Gliosis	47/IA
5	39/Male	4.5	SP, 2G	Rprecentral (lat, inf)	RFC	Scatters	RFCT	RF (lesion-ant)	Lesionectomy + corticectomy (lesion-ant)	Gliosis	26/IIB
6	22/Female	4	Aura, CP, 2G	LT (lat, ant)	LT (lesion-pos)	Clusters	NA	LT (lesion-pos)	Lesionectomy + corticectomy (lesion-A)	Pilocytic Astrocytoma	46/IA
7	19/Female	3	Aura, CP	RTO	RTO (lesion-pos, sup)	Scatters	Bilaterial T,P,O	RTO (perilesion)	Lesionectomy + corticectomy (lesion-p,s) + MST (visional area)	Heterotopia	37/IA
8	17/Male	8	Aura, CP	RT (bas-lat, mid)	RT (perilesion)	Clusters	RT	RT (perilesion)	Lobectomy (anterior T)	Ganglioneuroma	30/IC
9	12/Male	3	SP	RF (precentral, inf)	RF (perilesion)	Clusters	NA	RF (perilesion)	Lesionectomy + corticectomy (perilesion)	Gliosis	35/IA
10	5/Male	3	SP	RC (lat, inf)	RF (lesion-ant)	Clusters	Nonlaterlized	RF (lesion-ant)	Lesionectomy + corticectomy (lesion-ant) + MST (hand motor area)	CD	28/IA
11	28/Female	26	SP, 2G	RF (operculum)	RF (lesion)	Clusters	Nonlaterlized	NA	Lesionectomy	Heterotopia	24/IA
12	42/Female	20	CP	LT (lat, pos-sup)	LT (lesion-ant)	Clusters	NA	LT (perilesion)	Lesionectomy	Cavernous hemangioma	19/IIIC
13	28/Female	10	Aura, CP	LTF (sylvian, sup-inf)	LTF (perilesion)	Clusters	L-hemispheric	LTF (perilesion)	Lesionectomy + cortical cxcision (lesion-ant) + MST (lesion-pos)	Malacoma cyst	19/IA
14	17/Male	8	CP, 2G	LTO (lat)	LTO (lesion-ant)	Scatters	LPTO	LO (perilesion)	Lesionectomy+cortical cxcision	CD	16/IA
15	26/Male	12	SP, CP	LFC (lat, inf)	LF,T (perilesion)	Clusters	Nonlaterlized	LF.T (perilesion)	Lesionectomy + corticectomy (perilesion)	Malacoma cyst	13/IA
16	36/Male	4.5	CP, 2G	LT (lat, ant-mid)	LT (perilesion)	Clusters	NA	LT (perilesion)	Lesionectomy	Meningeal angiomatosis	14/IA
17	22/Female	7	CP	RT (lat, ant)	Bilateral T	Scatters	RTF	IOZ: RT (perilesion)	Lesionectomy + MST (perilesion)	Gliosis	52/IIB
18	13/Male	4	CP, 2G	RFT (sylvian sup-inf)	Bilateral P,RT	Clusters	Nonlaterlized	IOZ: RP (lesion-pos)	corticectomy (RP) + MST	Malacoma cyst	48/IVB
19	16/Male	5	SP, 2G	RF (lat, mid-sup)	RF (lesion-pos)	Clusters	R F	IOZ: RF (lesion-pos, inf)	Lesionectomy + corticectomy (lesion-pos) + MST (hand motor area)	Malacoma cyst	32/IID
20	6/Male	2.5	CP	LT (ant)	Bilateral P,O	Clusters	NA	IOZ: LT (lesion-P)	Lesionectomy + corticectomy (lesion-pos)	Malacoma cyst	20/IIC
21	16/Male	7	CP	LF (precentral, inf)	RFT, LF	Clusters	L-hemispheric	IOZ: LF (bas-lat, mid-sup)	Lobectomy (ant F)	CD	20/IIC
22	7/Female	6	AA, CP, 2G	LT (lat, inf)	RF, LFT	Scatters	NA	IOZ: LT (lat, mid-sup)	Lobectomy (ant T)	CD	15/IA
23	15/Male	4	SP, 2G	LF (sylvian, sup)	LFT, RF	Clusters	Nonlaterlized	IOZ: LF (perilesion)	Lesionectomy + corticectomy (lesion-ant) + MST (hand motor area)	Gliosis	18/IA

AA: atypical absence; ant: anterior; bas: basal; CD: corticaldysplasia; CP: complex partial seizure; F: frontal; 2G: secondarily generalized seizure; inf: inferior; IOZ, ictal onset zone; L: left; lat: laterial; mid: middle; MST: multiple subpial transections; NA: not available; O: occipital; P: parietal; pos: posterior; R: right; SP: simple partial seizure; sup: superior; T: temporal.

categorical variables within the group, Fisher's exact test was used for analysis of whether the proportion of those with seizure free/favorable outcome differed between the concordance and the discordance groups (i.e. between A1 and A2 or B1 and B2). For all tests, statistical significance level was set at $P < 0.05$.

3. Results

We summarized clinical profiles, MRI, MEG (SAM (g2) and ECD), EEG (scalp, intracranial), surgical procedures, pathology, and postsurgical outcomes for all 23 patients with lesional NE in Table 1 and for all 20 patients with nonlesional NE in Table 2. Both SAM (g2) and ECD results showed high agreements for both lesional (87%) and nonlesional NE (85%). Although there were some cases which showed scatters of ECD results, the ECD scatters findings were still similar to the SAM (g2) results (see Fig. 2).

The routine scalp EEG (interictal and ictal) was valuable for localizing epileptic discharges in 43.5% of the patients (10/23) with lesional NE, while MEG findings proved to be crucial for providing additional information for resection in 39.1% of the patients (9/23) and for intracranial electrodes implantation in 17.4% of the patients (4/23) with lesional NE. The routine scalp EEG (interictal and ictal) was helpful in localization of epileptic discharges in 50% of the patients (10/20) with nonlesional NE, while MEG supplied additional critical information for intracranial electrodes implantation in 30% of the patients (6/20) with nonlesional NE (see Table 2: Nos. 5, 8, 11, 17, 18, 20).

The mean follow-up period was 30.2 ± 13.1 months (range: 13–52 months) for lesional NE patients and 23.2 ± 8.7 months (range: 12–47 months) for nonlesional NE patients. Favorable operative outcomes were 91.3% in lesional NE and 75% in nonlesional NE, whereas seizure freedom rate was 65.2% for lesional NE and 35.0% for nonlesional NE (see Table 3). There was no statistically significant difference in favorable operative outcomes between the lesional and nonlesional NE group ($\chi^2 = 2.08$, $P > 0.05$). However, the seizure free rate showed a statistically significant difference ($\chi^2 = 5.24$, $P < 0.05$) between these two groups of patients. This might indicate that nonlesional NE is associated with seizure free outcomes much less often compared with lesional NE.

A 69.6% of the patients (16/23) with lesional NE (see Table 1 Nos. 1–16) had concordance between interictal MEG and MRI findings, while 65% of the patients (7/23) with nonlesional NE showed concordance between interictal MEG and iVEEG findings (see Table 2 Nos. 1–13). Our postsurgical outcomes for the lesional NE patients were very encouraging. 65.2% of the patients (15/23) were seizure free and 91.3% of the patients (21/23) (including seizure free cases) showed favorable outcomes after surgery (see Table 3). Only one patient (see Table 1 No. 12) did not have a favorable outcome (Engel class IIIC). This patient only underwent a lesionectomy operation in order to avoid neurological deficit of language because the lesion (cavernous hemangioma) was in the left posterior–superior temporal lobe.

In the lesional NE group with concordant MEG and MRI findings, 81.3% of the patients (13/16) were seizure free post surgery (see Fig. 1: a representative patient No. 14 in Table 1), and 93.8% of the patients (15/16) had favorable operative outcomes. In the lesional NE group without concordant MEG and MRI findings, only 28.6% of the patients (2/7) were seizure free, and 85.7% of the patients (6/7) had favorable outcomes. The seizure free rate showed a statistically significant difference (Fisher's $P = 0.024 < 0.05$) between the subgroups within the lesional NE group, which indicated better surgical outcomes associated with the concordance between MEG and MRI findings.

In the nonlesional NE group with concordant MEG and iVEEG findings, 46.2% of the patients (6/13) were seizure free post surgery (see Fig. 2: a representative patient No. 5 in Table 2), and 76.9% of the patients (10/13) had favorable outcomes. In the nonlesional NE group without concordant MEG and iVEEG findings, 14.3% of the patients (1/7) were seizure free, and 71.4% of the patients (5/7) had favorable outcomes. There was no statistically significant difference in either favorable operative outcomes (Fisher's $P = 0.62 \gg 0.05$) or the seizure free rate (Fisher's $P = 0.177 > 0.05$) between the subgroups within the nonlesional NE group.

4. Discussion

This is the first clinical epilepsy research which evaluates whether interictal MEG concordant with other modalities could be a reliable predictor for surgical outcomes in both lesional NE and nonlesional NE. MEG, as one of the most important neurophysiological techniques, has rapidly influenced the management of epilepsy patients in the past two decades and has been widely used in presurgical evaluation to delineate epileptogenic zones and eloquent cortex. In the last few years, several studies suggest that MEG is more sensitive for some areas of the brain compared with EEG, such as the superficial frontal lobe.[10] Thus, MEG is a valuable technique to assess presurgical epilepsy for NE patients and improve postsurgical outcomes. Our findings indicated that including MEG in the presurgical evaluation increased the likelihood of successful surgery and reduced seizure reoccurrences, which is consistent with other studies.[12,47,48]

To localize the interictal MEG spikes, there are two popular methods including conventional ECD and SAM (g2). Previous studies compared these two methods and found SAM (g2) had more advantages versus ECD.[11,49] The drawbacks of ECD modeling are that it is highly dependent on good SNR of the data, and that it is labor intensive and time consuming, as it requires the manual identification of spikes and considerable skill to minimize human errors.[13,34,50,51] Although SAM (g2) has not yet been extensively applied to symptomatic epilepsy, the automated SAM (g2) analysis of spikes appears to offer better detection of irritative zones and more information of volumetric frequency characteristics than conventional ECD modeling.[52] However, ECD has its strengths when trying to localize the interictal onset zone since SAM (g2) yields a stationary distribution of the source strength which could make it hard to distinguish the interictal onset (irritative) zone and the subsequent propagation areas. Therefore, we employed both conventional ECD and this relative new method SAM (g2) to localize the interictal spikes in our MEG data. Our results showed strong agreements between SAM (g2) and ECD results. In addition, 67.4% of the patients had concordant SAM (g2) results with other modalities (MRI or iVEEG). Our findings were consistent with other studies,[34] which suggests that SAM (g2) analysis is valuable to localize the epileptogenic foci.[31,32,35,49,53]

At our epilepsy center, we defined nonlesional findings as normal findings or nonfocal abnormalities, such as diffuse brain atrophy, nonspecific white matter signal changes and periventricular leukomalacia, because these features are less likely to provide useful clues regarding the localization of the potential epileptogenic zone during the presurgical evaluation. We applied MRI criteria which have also been used in other studies.[37,38] The discordance between MEG and MRI finding may be due to developmental lesions such as cortical dysplasia or gliosis where epileptiform discharges extend up to several centimeters away from the MRI-visible lesion.[54] In some cases, the discordance between MEG findings and the scalp EEG results would eliminate the patients from surgery. For example, MEG showed evidence for focal discharges, while the routine scalp EEG had generalized or bilaterally synchronous discharges. In these patients, the alternatives include placement of long-term subdural electrodes with attendant risks, resection based on structural abnormalities with

Table 2
Clinical profiles, MEG, EEG (scalp, intracranial), surgical procedures, pathology, and outcomes of nonlesional epilepsy.

No.	Age (year)/ gender	Seizure duration (year)	Seizure type	Interictal MEG		EEG (ictal onset zones)		Surgical procedures	Pathology	Outcomes follow up (months)/Engel
				SAM (g2)	ECD	Scalp EEG	Intracranial EEG			
1	21/Female	7	CP	RT (lat mid-inf)	Clusters	RTPO	RT (restricted lat mid-inf)	Focal corticectomy	Gliosis	40/IA
2	7/Male	6.5	AA, CP, 2G	LF (lat mid-sup)	Scatters	Nonlaterlized	LF (extensive lat mid-sup)	Lobectomy (L F ant) + MST	Normal	34/IVB
3	36/Male	24	SP, 2G	RF (lat precentral)	Clusters	RFTC	RF (restricted lat, precentral)	Focal corticectomy	NA	26/IIC
4	20/Male	11	CP	RF (precentral sup)	Clusters	Bilateral FC	RF (restricted precentral, sup)	Focal corticectomy	CD	21/IA
5	16/Male	14	SP	LP (lat postcentral)	Clusters	Nonlaterlized	LP (restricted lat, postcentral)	Focal corticectomy	CD	23/IA
6	21/Male	18	CP	LF (lat ant-mid)	Scatters	Nonlaterlized	LF (restricted lat, ant-mid)	Focal corticectomy	CD	26/IA
7	24/Female	10	CP, 2G	RT (lat mid-inf)	Scatters	R F T	RT (extensive lat, ant, mid-inf)	Lobectomy (ant T) + MST	Gliosis	47/IIIB
8	9/Male	2.5	Aura, SP	LF (operculum)	Clusters	Nonlaterlized	LF (extensive operculum)	Focal corticectomy + MST	Normal	16/IB
9	15/Male	6	CP	LF (lat ant-sup)	Clusters	LF	LF (extensive lat, ant-sup)	Lobectomy (ant F)	Gliosis	16/IA
10	20Male	16	CP	LF (lat mid-sup)	Scatters	Bilateral F	LF (restricted lat, mid-sup)	Multiple corticectomy (lat mid-sup)	CD	25/IIB
11	13/Male	8.5	CP	RF (bas-lat ant)	Clusters	Nonlaterlized	RF (extensive lat, ant-sup)	Lobectomy (ant F)	Gliosis	20/IA
12	25/Female	9	CP	LF (lat mid-inf)	Clusters	Bilateral F,T	LF (restricted lat mid-inf)	Focal corticectomy (lat mid-inf)	CD	16/IIIB
13	36/Male	18	CP, 2G	RF (precentralsup-mid)	Clusters	Bilateral FC	RF (extensive precentral sup-mid)	lobeectomy (SMA)	Gliosis	13/IIA
14	15/Female	10	SP, AA, CP, 2G	LFT RF	Scatters	Nonlaterlized	LF, insular lobe (extensive)	Multiple corticectomy (LF insular lobe)	Normal	25/IVA
15	15/Male	6	SP, 2G	LF (bas)	Clusters	L-hemispheric	LF (restricted lat mid-inf)	Focal corticectomy (lat mid-inf)	Gliosis	20/IIA
16	15/Male	8	CP	LT (lat mid-sup)	Scatters	Nonlaterlized	LF (extensive lat ant-inf)	Focal corticectomy LF (lat ant-inf)	Normal	23/IC
17	17/Male	12	CP, 2G	Bilateral F (precentral)	Clusters	Nonlaterlized	RP (extensive poscentral)	Multiple corticectomy RP + MST (central)	CD	22/IIC
18	12/Female	11	AA, CP, 2G	Bilateral F, LT	Clusters	Nonlaterlized	LF (extensive operculum-precentral)	Focal corticectomy (LF operculum) + MST (precentr)	NA	20/IIB
19	24/Female	10	Aura, CP, 2G	LT (lat mid-sup)	Scatters	Bilateral F,T	LF (extensive bas-lat, inf)	Multiple corticectomy LF (bas-lat, inf)	Normal	18/IVA
20	33/Female	16	CP	RTPO	Clusters	Nonlaterlized	RT (restricted lat, pos)	Focal corticectomy (RT pos)	CD	12/IA

AA: atypical absence; ant: anterior; bas: basal; CD: corticaldysplasia; CP: complex partial seizure; F: frontal; 2G: secondarily generalized seizure; inf: inferior; L: left; lat: laterial; mid: middle; MST: multiple subpial transections; NA: not available; O: occipital; P: parietal; pos: posterior; R: right; SP: simple partial seizure; sup: superior; T: temporal.

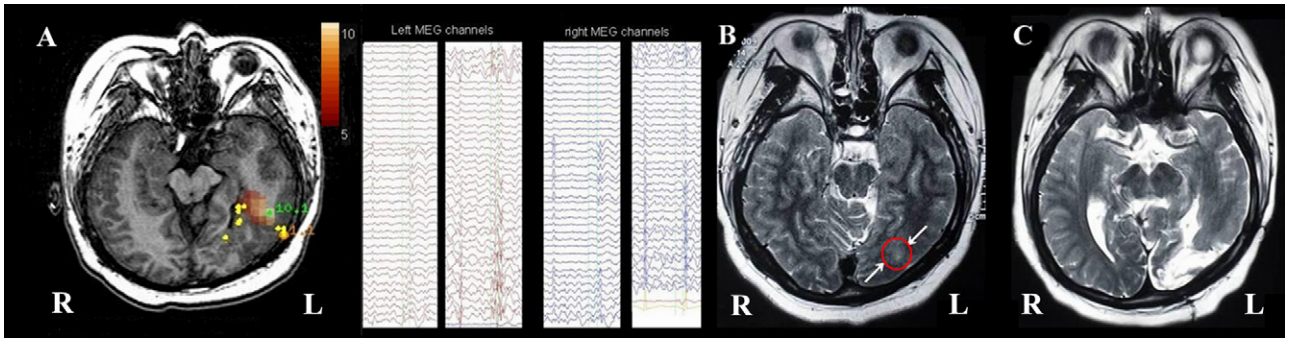

Fig. 1. (Table 1: Patient No. 14) A 17-year-old boy presented with 8-years CP and 2G seizures. (A) Interictal spike localization from MEG SAM (g2) and ECD results demonstrated a frequent high-amplitude spike was found in the left tempo-occipital lobe. The color bar shows the corresponding kurtosis value and color scale. (B) Pre-surgical MRI revealed a cortical dysplasia in the left tempo-occipital lobe. (C) Post-surgical MRI showed the extent of resection. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the possibility of subtotal resection of the epileptogenic foci, or resection with intraoperative ECoG that might be affected by anesthesia and limited to the relative short operation time frame.

Our study showed that the routine scalp EEG (interictal and ictal) was helpful for localization of epileptic discharges in 46.5% of the patients (20/43) with NE, while there were 67.4% of the patients (29/43) with NE who had concordant MEG findings with other modalities (MRI or iVEEG). From our results, although the agreements between MEG findings and other modalities suggested that the high concordance associated with better surgical outcomes, it still remains unclear whether interictal MEG also turns out to be a good predictor of the epileptogenic zone or if there is no a priori knowledge regarding the IOZ.

Recent studies[55,56] have reported that advanced MEG techniques can possibly identify the origin of spike propagation that appears synchronous on standard clinical EEG. In our future study, we would systematically analyze the spatiotemporal information of MEG spikes using the new approach in,[55,56] which may provide more accurate information relating to spike propagation than EEG and may be clinically useful in the presurgical evaluation.

Our findings strongly suggested the important role of MEG in presurgical evaluation to the patients with NE. When the interictal irritative zone based on the MEG was localized around the lesion, resection of the lesion and irritative zone would bring seizure freedom to the majority of patients. The use of intraoperative ECoG was necessary to further investigate the surgical outcome, whereas

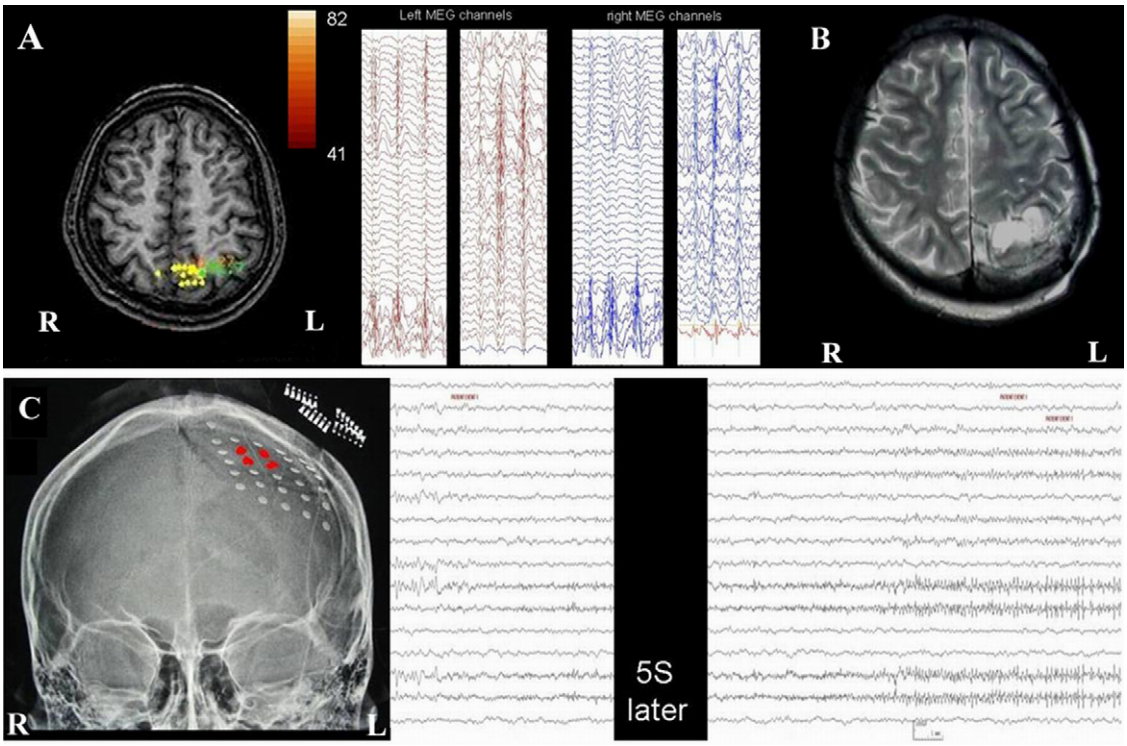

Fig. 2. (Table 2: Patient No. 5) A 16 year-old boy presented with 14-years SP. (A) Interictal spike localization from MEG SAM (g2) and ECD demonstrated a frequent high-amplitude spike was found in the left lateral parietal lobe. The color bar showed the corresponding kurtosis value and color scale. (B) Post-surgical MRI (T2 weighted) showed the extent of resection. (C) Skull X-ray film was obtained after placement of intracranial electrodes over the left parietal (post-central) lobe and displayed the location of the ictal onset zone (red) from the results of iEEG recordings. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Summary of EEG, MEG and surgical outcomes.

		Scalp EEG (interictal and ictal)		EEG (intraoperation)		MEG (dipole)		I–II	III–IV	Total	Favorable outcomes (%)	IA	Seizure free rate (%)
		Available	Not available	Available	Not available	Clusters	Scatters						
Lesional NE		10	13			17	6	21	2	23	91.3	15	65.2*
	A1	7	9	15	1	12	4	15	1	16	93.8	13	81.3**
	A2	3	4			5	2	6	1	7	85.7	2	28.6
Nonlesional NE		10	10			13	7	15	5	20	75.0	7	35.0
	B1	8	5			9	4	10	3	13	76.9	6	46.2
	B2	2	5			4	3	5	2	7	71.4	1	14.3

Group A1: concordance between MEG and MRI findings; group A2: discordance between MEG and MRI findings; group B1: concordance between MEG and iVEEG findings; group B2: discordance between MEG and iVEEG findings; I, II, III, IV represents the Engel classification level; Engel IA is treated as serizure free, Engel I + Engel II is treated as favorable outcomes.

* $P < 0.05$ comparison between lesional and nonlesional NE groups.

** $P < 0.05$ comparison between groups A1 and A2.

the extraoperative iVEEG monitoring seemed to be unnecessary because it has less impact on the surgical outcomes, especially for seizure freedom. Several other studies have reported the important role of MEG in preoperative workup of epilepsy surgery.[18,57] Fischer et al.[18] applied a novel technique designed to generate an ellipsoidal volume from the scattering of single MEG source localizations to represent MEG results in 33 adult patients who underwent surgery for epilepsy. This volume was compared voxel wise with the resection volume generated from pre and postoperative MR images. A high coverage of the MEG results ellipsoid by the resection volume and a low distance between the mass centers of both volumes correlated to a favorable outcome.

In our study, of the 16 patients with lesional NE whose MEG results were concordant with MRI findings (<2 cm), who did not undergo the placement of intracranial electrodes for iVEEG and who underwent the surgery with the assistance of ECoG, 81.3% (13/16) were seizure free post surgery and 93.8% (15/16) had favorable operative outcomes. The extent of resection included the lesion and SAM (g2) regions. Although MEG SAM (g2) included both interictal onset zone and subsequent propagation, our highly favorable operative outcomes suggested that the subsequent propagation could possibly be active interictal zones or potential IOZ post-surgery.

This was very crucial to patients in developing countries such as China, because the attendant risks of placement of long-term subdural electrodes and the great expense may delay the surgery procedure when it is actually needed. On the other hand, the use of iVEEG was necessary and could be more helpful than ECoG, when MEG results were discordant with MRI findings.

Although MEG has been reported to be a valuable component of presurgical evaluation, the on-going debates still exist. Lau et al.[58] performed a statistical meta-analysis of the data reported in English from 1996 to 2006 including a minimum of four patients with at least 6-month follow-up. They correlated surgical outcome (seizure freedom) with the concordance between the MEG source localization and the resection areas and concluded that there was insufficient evidence in the current literature to support the relationship between the use of MEG in surgical planning and seizure-free outcome after epilepsy surgery. Therefore, additional studies are needed to provide sufficient evidence. However, Lewine[59] reclassified all cases that were listed in Lau's literature, and he reached the opposite conclusion. In our study, 20 patients with nonlesional NE were divided into two sub groups according to the spatial correlation between SAM (g2) results and volume of surgical resection. All patients in group B underwent resection mainly according to extraoperative iEEG findings. There was no statistically significant difference either in favorable operative outcomes or in seizure freedom rate between the two sub groups. Our results support Lau's opinion that the use of MEG cannot obviously improve the seizure freedom rate for these NE epilepsy patients. However, the concordance between MEG and iVEEG results (group B1) indicated a higher seizure freedom rate according to our data (46.2% in group B1, 14.3% in group B2), though the difference was not statistically significant, which might be due to the limited number of patients. Further investigation is needed.

In summary, this study suggested that MEG should play a different role in lesional NE patients and nonlesional NE patients. A good postsurgical outcome is highly associated with concordant results from MEG and MRI presurgical findings in lesional NE patients, and is related with concordant results from MEG and iVEEG findings in nonlesional NE patients. However, we found that the value of MEG for the nonlesional NE patients was inferior. MEG cannot substitute for iVEEG, but may be useful tool to guide the placement of intracranial electrodes for iVEEG.

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