Prognostic value of high-frequency oscillations combined with multimodal imaging methods for epilepsy surgery

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Abstract

Background: The combination of high-frequency oscillations (HFOs) with single-mode imaging methods has been proved useful in identifying epileptogenic zones, whereas few studies have examined HFOs combined with multimodal imaging methods. The aim of this study was to evaluate the prognostic value of ripples, an HFO subtype with a frequency of 80 to 200 Hz is combined with multimodal imaging methods in predicting epilepsy surgery outcome.

Methods: HFOs were analyzed in 21 consecutive medically refractory epilepsy patients who underwent epilepsy surgery. All patients underwent positron emission tomography (PET) and deep electrode implantation for stereo-electroencephalography (SEEG); 11 patients underwent magnetoencephalography (MEG). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in predicting surgical outcome were calculated for ripples combined with PET, MEG, both PET and MEG, and PET combined with MEG. Kaplan-Meier survival analyses were conducted in each group to estimate prognostic value.

Results: The study included 13 men and 8 women. Accuracy for ripples, PET, and MEG alone in predicting surgical outcome was 42.9%, 42.9%, and 81.8%, respectively. Accuracy for ripples combined with PET and MEG was the highest. Resection of regions identified by ripples, MEG dipoles, and combined PET findings was significantly associated with better surgical outcome ($P < 0.05$).

Conclusions: Intracranial electrodes are essential to detect regions which generate ripples and to remove these areas which indicate good surgical outcome for medically intractable epilepsy. With the assistance of presurgical noninvasive imaging examinations, PET and MEG, for example, the SEEG electrodes would identify epileptogenic regions more effectively.

Keywords: High-frequency oscillations; Ripples; PET; MEG; Epileptogenic zone

Introduction

Resection surgery is essential to control seizures in patients with medically intractable epilepsy. The key principles of epilepsy surgery are precise localization and complete removal of epileptogenic zones (EZs). Noninvasive examinations, such as magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET),[1] and magnetoencephalography (MEG), can provide useful EZ information and are the first step in pre-operative epilepsy surgery evaluation.[2,3] If these modalities indicate that the same area is responsible for seizure onset, seizure freedom is likely after resecting the abnormal brain tissue. However, in complex cases, such as those with negative MRI findings or dispersed abnormal zones detected by different modalities, stereo-electroencephalography (SEEG) is often required for precise EZ localization.[4]

High-frequency oscillations (HFOs) are a promising EZ biomarker. These oscillations range from 80 Hz to 500 Hz and are classified into two subtypes according to frequency namely ripples (80–200 Hz) and fast ripples (200–500 Hz).[5] Ripples are considered clinically useful in localizing seizure onset zone, and scalp ripples are good prognostic biomarkers for pediatric epilepsy patients.[6-8] Although the efficacy of using HFOs combined with single-mode imaging methods to locate epileptogenic foci has been examined in several previous studies[9-11] few studies have examined HFOs combined with multimodal imaging methods. Moreover, these few only included a small number of surgical patients. Therefore, we exam-

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ined and compared seizure localization using HFOs combined with different imaging modalities in patients with drug-resistant epilepsy who required presurgical SEEG evaluation. In addition, we investigated the effect of the different combinations on surgical outcome.

Methods

Ethical approval

The present study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (No. [2020]079). Written informed consent was obtained from all participants.

Patients

This study included 21 consecutive medically refractory epilepsy patients who were treated at our epilepsy center between February 2017 and September 2019 and met the following criteria: (1) epilepsy resection surgery was performed; (2) SEEG was performed because noninvasive examinations failed to localize the EZ; (3) routine presurgical investigations including electroencephalography (EEG), video-EEG, and MRI were performed; (4) positron emission tomography (PET) and/or MEG were performed; (5) follow-up >12 months. Board-certified neurophysiologists, epileptologists, neuroradiologists, and neuropathologists reviewed all clinical data, including medical history, neurological examination, video-EEG monitoring, and imaging, to provide treatment to each patient.

SEEG recording and identification of HFOs

Based on pre-operative evaluation, SEEG electrodes with 8, 10, 12, or 16 contacts (0.8 mm diameter, 2 mm length, 1.5 mm between contacts; Beijing Huakehengsheng Healthcare Co., Ltd., Beijing, China) were implanted in the putative epileptogenic region. Intracranial EEG was performed using a 256-channel recording system (Nicolet; Natus Medical, San Carlos, CA, USA) with a sampling rate set at 2048 Hz and a 128-channel EEG system (DaVinci; Micromed, Treviso, Italy) with a sampling rate set at 1024 Hz. All segments were selected from interictal periods during the slow sleep period and were at least 2 h before or after seizures. To detect HFOs, we selected 5-min segments in which the delta band (1–3 Hz) measured >25% of all delta bands in a 30 s epoch; automated measurement was used as described previously.[12] HFO recording requires a sampling rate of at least four times the upper limit of the desired frequency.[13] Because fast ripples cannot be analyzed in EEG recording systems with a sampling rate <2000 Hz, only ripples were analyzed. Contact-displayed dense HFOs (>10 times during the 5-min segment) were considered strongly associated with the EZ.

Image acquisition and analysis

Positron emission tomography

Patients fasted for at least 6 h before PET examination, and blood glucose was checked before ^{18}F-PDG administration to ensure concentration <8 mmol/L. PET images were acquired with patients in the supine position after an intravenous injection of ^{18}F-PDG at a dose of 3.7 to 7.4 MBq/kg. Low-dose computed tomography was used for attenuation correction during imaging, followed by acquisition of PET data in a three-dimensional mode. The PET scanning parameters were as follows: matrix, 128 × 128; layer thickness, 2.44 mm; and time, 15 min. No seizures occurred during PET scanning or within 6 h before scanning. PET images were analyzed by two experienced nuclear medicine physicians blinded to the clinical data.

Magnetoencephalography

MEG was performed using a 306-channel whole-head system (Neuromag, Helsinki, Finland) for 60 min. Patients were instructed to rest during the examination. The MEG sampling frequency was 1200 Hz, and EEG signals were recorded at the same time. An experienced neurologist used the single equivalent current dipole method to analyze the MEG signal. The MEG spike sources were overlaid on a T1 magnetization-prepared rapid acquisition with gradient echo MRI. A cluster was defined as at least five MEG spike sources within a 1-cm region. Regions without a cluster were regarded as unclear MEG results.[14]

Post-operative outcome assessment

Patients were followed up at 3, 6 months, 1 and 2 years after surgery. Surgical outcome was evaluated using the Engel classification system[15] and confirmed by both telephone interviews and chart review.

Statistical analysis

To compare the prognostic value among combinations of HFOs with different imaging modalities, patients were divided into four subgroups according to the imaging examination they underwent: group 1, combination of HFOs and PET; group 2, combination of HFOs and MEG; group 3, combination of PET and MEG; and group 4, combination of HFO, PET, and MEG. The abnormal area identified by the combined examinations was considered the presumed EZ and classified as completely resected or incompletely resected. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy in predicting surgical outcome were calculated for each group. Sensitivity was defined as the proportion of patients who had incomplete resection of the presumed EZ with postsurgical seizures. Specificity was defined as the proportion of patients who achieved seizure freedom post-operatively with complete resection of the presumed EZ. PPV was defined as the proportion of patients with retained presumed EZ who developed seizures after surgery. NPV was defined as the proportion of patients with complete resection of the presumed EZ who achieved seizure freedom. Accuracy was defined as the proportion of all patients who (1) achieved seizure freedom with complete resection of the presumed EZ and (2) developed seizures with incomplete resection of the presumed EZ detected by each method [Table 1]. Survival analyses were conducted using the Kaplan-Meier method. $P < 0.05$ was considered significant. Statistical analyses

Table 1: Explanation on how to calculate sensitivity, specificity, PPV, NPV, and accuracy.

Group	Complete-resection		Incomplete-resection		Sensitivity	Specificity	PPV	NPV	Accuracy
	Seizure-free	Seizures	Seizure-free	Seizures					
HFO+PET (*n*)	a	b	c	d	d/(b+d)	a/(a+c)	d/(c+d)	a/(a+b)	(a+d)/*n*

HFO: High-frequency oscillation; NPV: Negative predictive value; PPV: Positive predictive value; PET: Positron emission tomography.

Table 2: Characteristics of 21 consecutive medically refractory epilepsy patients who underwent epilepsy surgery.

No.	Gender	Age of onset (years)	Disease course (years)	Side of surgery	Outcome (Engel)	Follow-up (months)	Resection area	Ripple findings	PET findings	MEG findings
1	M	6	12	R	I	44.17	R-F posterolateral	R-F, T	R-T	R-F
2	F	21	8	R	I	40.97	R-T anteromesial	L-T, R-T, P	R-T	–
3	F	10	10	L	II	37.43	L-F lateral	L-F	L-F	L-F, R-T
4	M	5	25	R	I	36.77	R-F posterolateral	R-F, I	L-F, T	R-F
5	M	28	20	R	I	35.30	R-F basal	R-T	R-F, T	–
6	M	18	4	L	I	34.43	L-T anteromesial	L-T, I, F	L-F, T	–
7	M	6	14	L	II	27.20	L-F basal, L-T	L-F, T, R-T	L-F, T	L-T, L-T
8	F	2	20	L	II	32.27	L-T anteromesial	R-T, F, L-T	R-L, L T	L-T, L-T
9	F	15	1	L	III	31.73	L-T posterior	L-F	L-F, T	L-T, L-T
10	F	2	33	R	II	31.53	R-T posterior	R-F, I, T	R-P, O, T	–
11	M	9	21	R	II	31.40	R-F anterior	R-F, T, P	R-T	–
12	M	7	11	L	I	29.27	R-F posterolateral	L-T	L-F, T	–
13	M	5	9	R	I	28.37	R superior and middle frontal gyrus	R-F, L-T	R-P; L-T	R-F
14	F	20	14	L	III	25.00	L-T anteromesial	L-T, P	R-T	L-T, L-T
15	M	1	20	L	I	22.77	L-T anteromesial	L-T, F	L-T	L-T
16	M	9	4	R	IV	21.57	R-P lateral	R-P	R-P	–
17	M	9	7	L	III	26.03	L-T anteromesial	L-T, F, P	L-F, T, P;R-P	L-F
18	M	2	23	L	III	24.87	L-T anteromesial	L-T, I	L-P, T	L-T
19	F	7	5	R	I	14.83	R-F anterior	R-F, T, P	R-F, P, T	–
20	M	13	9	R	I	15.53	R-F basal, pole, mesial, T anteromesial	R-F, T, P	R-F, P, T	–
21	F	6	3	R	I	32.77	R-F posterior, T posterior	R-F	L-T, P, R-T	–

F: Female; F: Frontal; I: Insula; L, Left; M: Male; MEG: Magnetoencephalography; O: Occipital; PET: Positron emission tomography; P: Parietal; R, right; T: Temporal.

were performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Among the 21 patients, 13 were men and 8 were women. Mean age with standard deviation at seizure onset was 9.6 ± 7.2 years. Mean disease duration with standard deviation was 13.0 ± 8.5 years. All patients underwent deep electrode implantation. Most had negative MRI findings, and only four achieved seizure freedom by resecting regions detected by MRI. PET was performed in all patients; 11 underwent MEG. Focal cortical dysplasia was the most common pathology (12 patients), followed by ulegyria (1 patient), glial scar (1 patient), and hippocampal sclerosis (1 patient). No clear pathological findings were found in the remaining six. Follow-up duration ranged from 13.37 to 42.70 months. Eleven patients (52.4%) became seizure-free (Engel class I). Examination findings, demographic characteristics, and follow-up outcomes are shown in [Table 2].

Single modality analysis

SEEG and ripple analysis

The intracranial electrode implantation plan was designed to cover the presumed EZ according to the pre-operative examinations; 12 patients underwent bilateral implantation, and 9 patients underwent unilateral implantation. The median number of SEEG electrodes was seven (interquartile range [IQR]: 6–8), and the median number of SEEG contacts was 92 (IQR: 75–112). The origin of the abnormal discharge is described as follows: nine in temporal lobe, eight in frontal lobe, 1 in insula and parietal lobe, respectively, and three from the junction of temporal and front lobe.

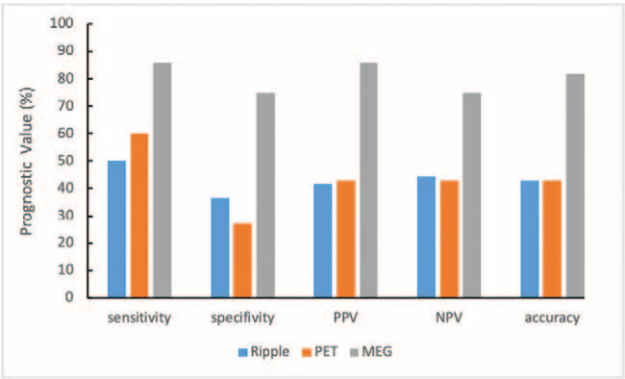

Figure 1: Prognostic characteristics of each modality. MEG: Magnetoencephalography; NPV: Negative predictive value; PPV: positive predictive value; PET: Positron emission tomography.

HFO data were recorded sufficiently in all patients. The ripples findings matched the resection area in nine patients. Sensitivity, specificity, PPV, NPV, and accuracy in predicting surgical outcome were 50.0%, 36.4%, 41.7%, 44.4%, and 42.9%, respectively [Figure 1]. Survival analyses showed that time to first post-operative seizure was not associated with incomplete resection of the region detected by ripples ($P < 0.05$; Figure 2).

PET analysis

All patients underwent PET. The resection area matched the hypometabolic zone in seven patients. Sensitivity, specificity, PPV, NPV, and accuracy in predicting surgical outcome were 60.0%, 27.3%, 42.9%, 43.0%, and 42.9%, respectively [Figure 1]. There was no significant association between PET findings and postsurgical outcome [Figure 2].

MEG analysis

Eleven patients underwent MEG. Four patients achieved seizure freedom post-operatively, and MEG findings matched the surgical area in 3 patients. Sensitivity, specificity, PPV, NPV, and accuracy in predicting surgical outcome were 85.7%, 75.0%, 85.7%, 75.0%, and 81.8%, respectively [Figure 1]. Although MEG had the highest accuracy in detecting the EZ compared with other modalities, patients with resection of the MEG findings did not demonstrate a strong association with good postsurgical outcome ($P < 0.05$; Figure 2).

Multimodality analysis

Group 1 (HFOs and PET) contained all 21 study patients. By integrating the two approaches, the results matched the surgical zone in 10 patients and four achieved seizure freedom. Sensitivity, specificity, PPV, NPV, and accuracy in predicting surgical outcome in this group were 40.0%, 36.4%, 36.4%, 40.0%, and 38.1%, respectively [Figure 3]. Identification of resection areas by ripples and PET examination was not significantly associated with good surgical outcome ($P = 0.259$; Figure 4).

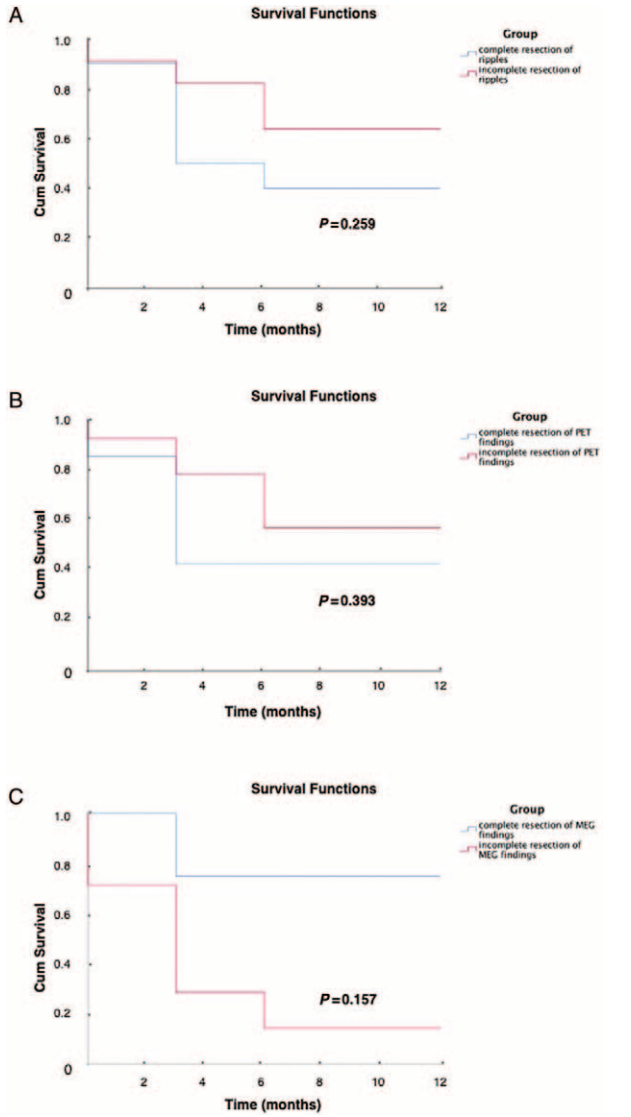

Figure 2: Survival analyses for single modality. (A-C) represent the impact of incomplete resection of ripples, PET, and MEG findings on postoperative seizure freedom, respectively. MEG: Magnetoencephalography; PET: Positron emission tomography.

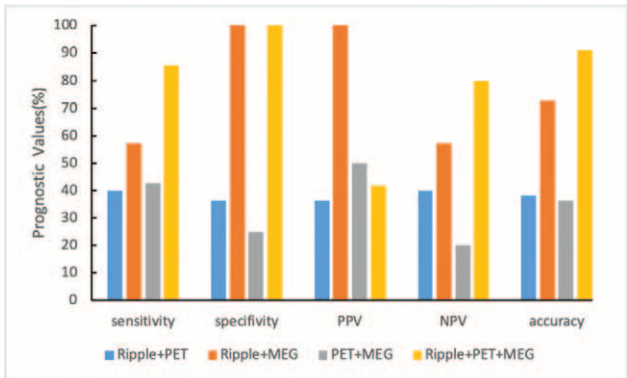

Figure 3: Prognostic characteristics of multimodality. MEG: Magnetoencephalography; NPV: Negative predictive value; PPV: Positive predictive value; PET: Positron emission tomography.

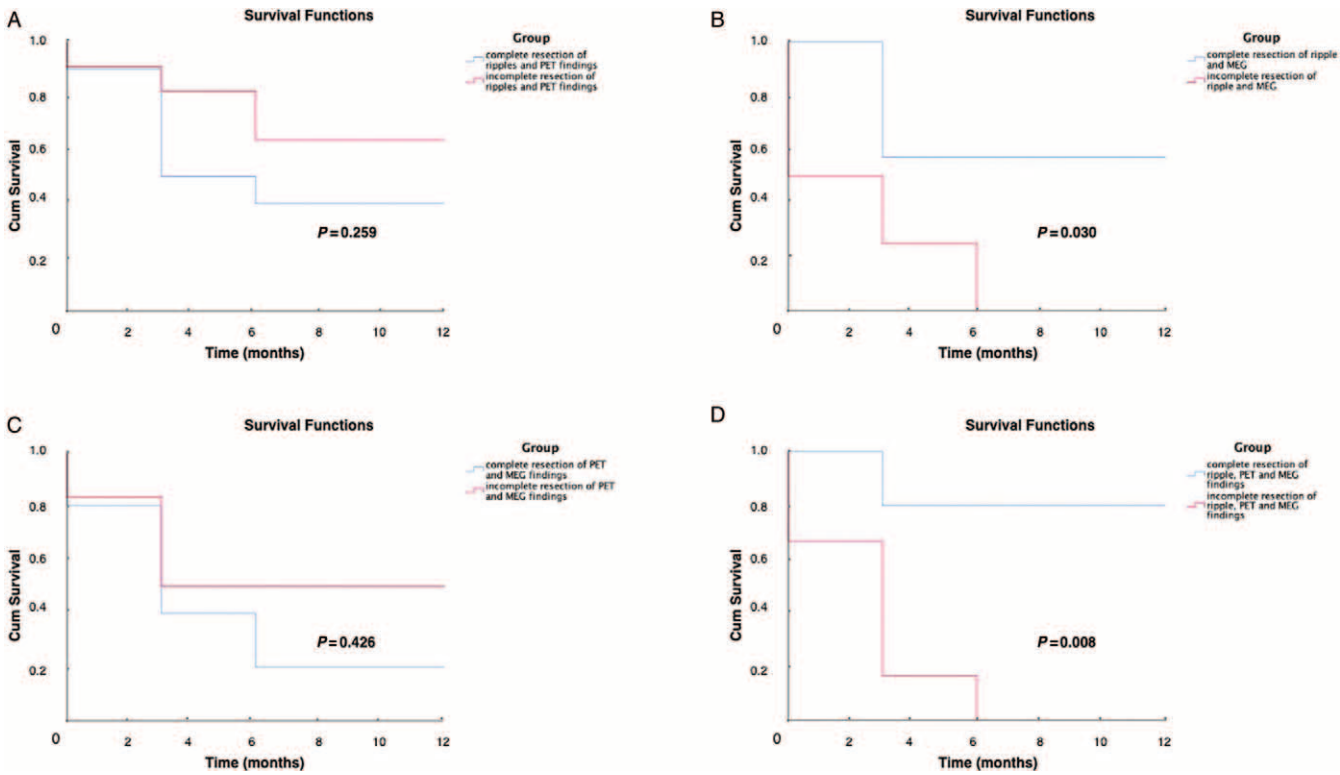

Figure 4: Survival analyses for multimodality. (A-D) represent the Impact of incomplete resection of ripples combined with PET, ripples combined with MEG, PET combined with MEG, and ripples combined with both PET and MEG findings on postoperative seizure freedom, respectively. MEG: Magnetoencephalography; PET: Positron emission tomography.

Group 2 (HFOs and MEG) contained 11 patients. EZs located in 4 and these patients had a better outcome after surgery ($P = 0.03$; Figure 4). Sensitivity, specificity, PPV, NPV, and accuracy in predicting surgical outcome in this group were 57.1%, 100.0%, 100.0%, 57.1%, and 72.7%, respectively [Figure 3].

Group 3 (PET and MEG) contained 11 patients; sensitivity, specificity, PPV, NPV, and accuracy in predicting surgical outcome in this group were 42.9%, 25.0%, 50.0%, 20.0%, and 36.4%, respectively [Figure 3]. This group had an unsatisfying surgical outcome ($P = 0.43$; Figure 4).

Group 4 (HFOs, PET, and MEG) contained 11 patients. The presumed EZ matched the surgical area in five patients and four achieved seizure freedom. The remaining six patients continued to have seizures because the presumed EZ was not completely removed. Sensitivity, specificity, PPV, NPV, and accuracy in predicting surgical outcome in this group were 85.7%, 100.0%, 41.7%, 80.0%, and 90.9%, respectively [Figure 3]. Identification of resection areas by ripples, PET, and MEG findings was significantly associated with good surgical outcome ($P = 0.008$; Figure 4). Examples of patients who underwent evaluation with these modalities are shown in Figures 5 and 6.

Discussion

This study examined the efficacy of combining ripples with different imaging methods to localize the EZ in patients with medically refractory epilepsy in whom noninvasive localization examinations failed. HFOs provided valuable additional information that led to better outcomes. We recommend routine recording of HFOs in patients undergoing pre-operative SEEG for EZ localization.

Previous studies have shown that HFOs are a serviceable biomarker of EZs.[5,9,16,17] We elected to evaluate SEEG recording of HFOs rather than scalp EEG for several reasons: SEEG is appropriate for patients of all ages, whereas scalp EEG is more suitable for pediatric patients. In addition, SEEG has a higher signal-to-noise ratio than scalp EEG and is less susceptible to myoelectric artifacts and interference from power frequencies. It also provides a more accurate depiction of the EZ than scalp EEG. Furthermore, SEEG illustrates the propagation of abnormal discharges, aids in functional mapping of the network, and can easily monitor electrical activity in deep areas.

The clinical value of ripple generating areas is still under debate.[16,18,19] Ripples are found more widely and commonly than fast ripples in patients with epilepsy.[20,21] Although most epilepsy patients undergo surgery that is limited to one brain lobe, ripples were confined to one brain lobe in only six patients in our study. One possible explanation for this is that ripples located outside the epileptogenic focus may respond to normal physiological mechanisms; as mentioned earlier, the surgical decision was decided by a group of certified experts, and only ripples related to the presumed EZ would be removed

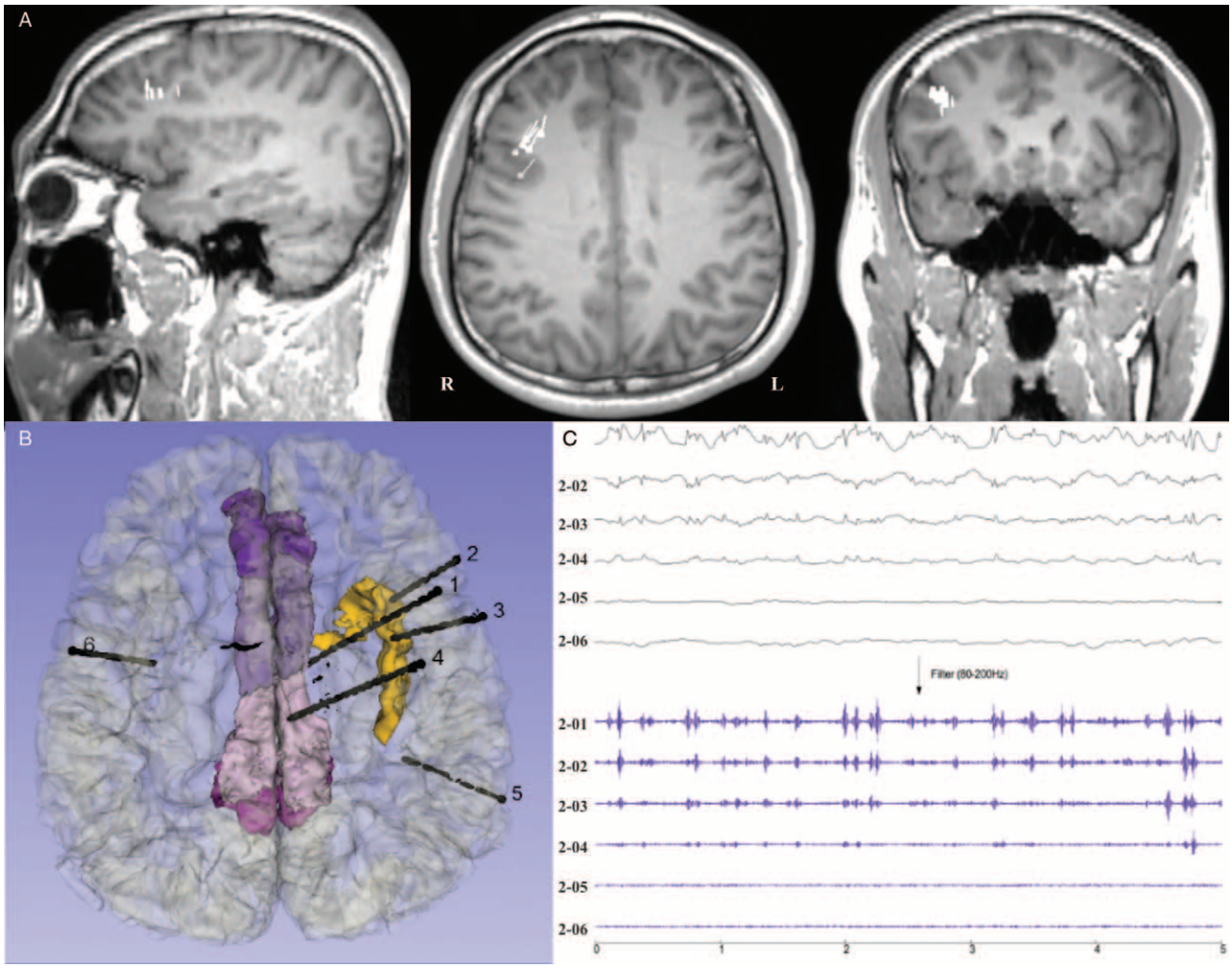

Figure 5: Examples of patients who underwent ripple and MEG analysis. Clinical data of patient 1,6-year-old boy with nocturnal epilepsy, reported an aura of dysphoria before seizures. The MEG demonstrated interictal spike dipoles located in right frontal lobe (A). Intracranial electrodes were mainly implanted for coverage of the right frontal lobe, left frontal lobe, and right insular lobe was also implanted by electrodes (B). Ripples were recorded in the right frontal lobe and parietal lobe (C). The posterior part of right middle and inferior frontal gyrus were removed, and the patient was seizure-free through the last follow-up at 44 months; the pathological finding was FCD IIb. FCD: Focal cortical dysplasia; L: Leftside; MEG: Magnetoencephalography; R: Right side.

eventually. Alternatively, if ripples are pathological and arise from the spread of epileptogenic discharges, removing the EZ may have blocked ripple propagation.

PET is useful in evaluating patients with drug-resistant epilepsy and was used routinely in our patients. In temporal lobe epilepsy, PET identifies the seizure onset zone with a sensitivity up to 90%; however, in extratemporal lobe epilepsy, sensitivity is only 45 to 60%.[22,23] Whether the electrical anomalies share the same physiological mechanism as the metabolic anomalies detected by PET is under debate.[24,25] Some studies have demonstrated a relationship between metabolic anomalies and low-frequency abnormal electrical activity but not HFOs[26,27]; however, Lamarche *et al*[28] found that hypometabolic areas correlate with the presence of HFOs only in temporal lobe epilepsy. In our study, metabolic imaging and HFOs did not show agreement but the number of temporal lobe epilepsy patients was low. Future studies with a larger number of patients are warranted to verify whether hypometabolic areas generate HFOs.

In group 2, patients with the resection of regions identified by ripples and MEG dipoles eventually achieved seizure freedom. MEG noninvasively measures the magnetic field generated by neurons and is useful in pre-operative epilepsy surgery evaluation.[29] Owing to its high spatial and temporal resolution, MEG can provide essential EZ information and guide electrode implantation for SEEG.[30-32] We mainly focused on epileptic spikes for localizing epileptic foci, like previous studies.[14,33] Although MEG and recording HFOs both measure abnormal neuronal electrical activity, HFOs mainly record high-frequency rhythmic activity (>80 Hz) and MEG mainly records spikes. In our study, the accuracy of MEG in detecting the EZ was relatively high, but MEG findings alone are inadequate to predict a better surgical outcome ($P = 0.157$). One reason for that is MEG can demonstrate a broader area, both epileptic and normal, than ripples; further identification of these two areas is needed. When combined with ripples, accuracy was equally satisfactory. These results support previous studies that found

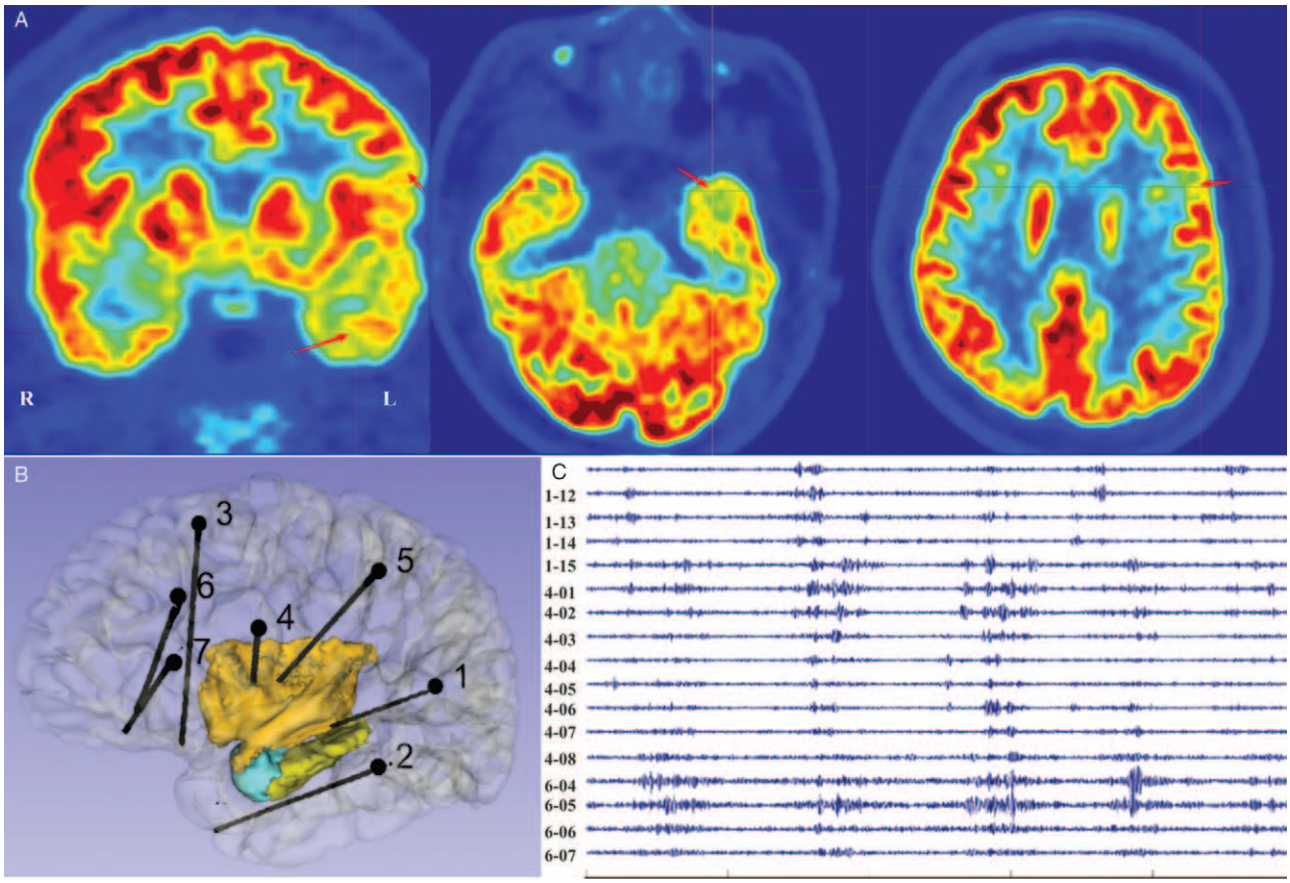

Figure 6: Examples of patients who underwent ripple and PET analysis. Clinical data of patient 6, an 18-year-old men with an aura of uprising sensation. PET demonstrated hypometabolic areas in left temporal and frontal lobe (A). Intracranial electrodes were implanted in lest temporal and frontal lobe(B). Ripples were recorded in left temporal, frontal, and insular lobe (C). After resection of left temporal lobe, the patient was seizure-free through the last follow-up at 34 months. L: Left side; PET: Positron emission tomography; R: Right side.

resection of regions generating interictal spikes and correlating with ripples often translates to a better outcome.[34-37] Therefore, we suggest that MEG be used as a routine preoperative examination in patients who require SEEG for localization, as MEG findings can provide useful information.

When ripples, PET, and MEG findings were combined, the results were quite satisfying. All patients with resection areas where combined findings did not match eventually experienced seizure recurrence. Group 3 had the highest accuracy, sensitivity, and specificity for predicting surgical outcome. Furthermore, the results of group 3 were more significant compared with group 2. Given that PET and MEG can provide useful information, we analyzed the relationship between resection and outcome with PET and MEG findings and found no association ($P = 0.424$). This suggests that ripples data provided useful information beyond PET and MEG and played a role in achieving better outcomes.

Based on our study, combining ripples, PET, and MEG findings was the most effective approach to predict surgical outcome. We therefore recommend MEG, PET, and recording of HFOs as routine examinations for patients with drug-resistant epilepsy. Intracranial SEEG electrodes can be implanted more rationally based on MEG and PET results. Several recent studies have used MEG to record high-frequency neuronal electrical activity other than spikes, as well as other low-frequency electrical activity. Moreover, noninvasive recording of HFOs is showing efficacy for accurate presurgical evaluation and postoperative outcome prediction.[36,37] Although this approach is worth promoting, it is not yet ready for routine clinical use.

Our study has several limitations. First, the number of patients was small. Second, we did not analyze fast ripples because of the difficulty in recording them and the low sampling rate of one of our intracranial EEG recording systems. Although some researchers have demonstrated that fast ripples are more local than ripples, they can also provide valid EZ information. In future studies, we intend to analyze more pre-operative investigational modalities, including fast ripples.

In conclusion, recording of HFOs is also recommended to allow joint application of ripples, PET, and MEG for localization, which we found particularly effective. However, clinicians should still use other clinical data as well, including EEG results, symptoms, and other imaging findings, as "abnormal" findings on recording of HFOs, PET, and MEG may be physiologically or spatially distant from the epileptic foci.

Intracranial electrodes are essential to detect regions which generate ripples and to remove these areas which indicate good surgical outcome for medically intractable epilepsy. PET and MEG results should also be considered for the SEEG implantation to locate epileptogenic focus. By the assistance of presurgical noninvasive imaging examinations, PET and MEG, for example, the SEEG electrodes would identify epileptogenic regions more effectively. Further study would focus on the fast ripples, another subtype of HFOs, which we did not include in the study due to the low sampling rate, and other imaging examination method and image post-processing technology, such as fluid and white matter suppression and voxel-based morphometry.

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Conflicts of interest

None.

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