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Original Article

Localizing percentages of interictal 18F-fluorodeoxyglucose (FDG)-PET and magnetoencephalography (MEG) in pre-surgical evaluation of 107 consecutive patients with non-lesional epilepsy

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Abstract: Compare with lesional epilepsy, it is very difficult to localize the epileptogenic zone for non-lesional epilepsy. This study was to assess the localizing percentages of interictal 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) and magnetoencephalography (MEG) in non-lesional epilepsy. Eighty-five of one hundred and seven patients who had no detectable lesions via MRIs underwent surgical treatments for intractable epilepsy with good seizure outcomes (Engel class I-III) after a mean postoperative follow-up of 5.22 ± 2.87 (1.5-7.5) years. Most patients underwent several examinations, including invasive monitoring (75 patients), interictal 18F-FDG-PET scans (53 patients), MEG (61 patients), and interictal 18F-FDG-PET with MEG (PET+MEG, 29 patients). A Pearson Chi-square test and Fisher's exact test was applied for the results of location of epileptogenic zone. Compared with interictal 18F-FDG-PET, MEG and PET+MEG, invasive monitoring had the highest diagnostic sensitivity in localizing epileptogenic foci (Pearson Chi-square test, P=0.00). Interictal 18F-FDG-PET localizing epileptogenic foci was significantly higher in a single lobe than in multiple lobes of the brain (Pearson Chi-square test, P=0.004). Similarly, PET+MEG showed a higher diagnostic sensitivity in localizing real epileptogenic foci in a single lobe than in multiple lobes (Fisher's exact test, P=0.008). However, there was no statistical significance in localizing the epileptogenic zone in non-lesional epilepsy among interictal 18F-FDG-PET, MEG, PET+MEG, whether in a single lobe or in multi-lobe brain. PET+MEG had an advantage in localizing the epileptogenic zone in non-lesional epilepsy in a single lobe of the brain. Interictal 18F-FDG-PET showed higher localizing percentages in one lobe than in multi-lobe brain.

Keywords: Non-lesional epilepsy, interictal 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), magnetoencephalography (MEG), epileptogenic zone

Introduction

The absence of a lesion on preoperative magnetic resonance (MR) images is a risk factor for persistent seizures after surgery for epilepsy. Indeed, the worst postoperative seizures have been observed when no foci or lesion was found on MRI [1-4]. Localizing the epileptogenic zone for non-lesional epilepsy is sometimes difficult, and needs a combination of several techniques such as video-EEG monitoring, intracranial electroencephalography (EEG) monitoring, interictal 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and magnetoencephalography (MEG). Although invasive intracranial EEG monitoring is the gold standard for localizing the epileptogenic zone [5], interictal 18F-FDG-PET and MEG may provide valuable preoperative data on epileptogenic foci in cases of non-lesional epilepsy. We previously

assessed the efficacy of interictal 18F-FDG-PET and MEG for localizing the epileptogenic foci in 16 patients with non-lesional epilepsy [6], and found that they can help in determining the surgical eligibility of a patient, especially when foci cannot be localized using MRI or video-EEG monitoring. The two techniques also helped with placement of subdural grids and strips for EEG studies. Despite these findings, the study was limited by its small cohort of patients. Here, we analyzed a larger population with non-lesional epilepsy, and reported the localizing percentages of epileptogenic zones with interictal 18F-FDG-PET and MEG.

Patients and methods

One hundred and seven consecutive patients who had no detectable lesions via MRI underwent surgical treatments for intractable epilepsy in our institution from January 2008 to December 2013. Among the 107 patients, 85 (53 males, 32 females; age: 18.5 ± 4.6 years, range: 15-51 years) with good seizure outcomes (Engel class I-III) were selected for the study. The seizure history covered 9.3 ± 3.7 years. The duration of the follow-up following surgery was 5.22 ± 2.87 (1.5-7.5) years. The seizure types included complex partial seizures, generalized seizures, simple partial seizures, secondary generalized tonic-clonic seizures, and status epilepticus. All the patients underwent basic preoperative 1.5 T MRI and continuous scalp video-EEG monitoring. Interictal 18F-fluorodeoxyglucose (FDG)-PET (53 patients), magnetoencephalography (MEG, 61 patients) or both of them (PET+MEG, 29 patients) were added when the epileptic zones needed further demonstration. When the non-invasive studies remained inconclusive or the epileptic zone close to eloquent cortex, invasive monitoring (75 patients), such as subdual grid or depth electrode recording was used.

Exclusion criteria included the following lesions that can be detected on MRI: vascular malformations, neoplasms, developmental anomalies, hippocampal sclerosis, hypoxic-ischemic changes, and atrophy. The presence of subtle MRI finding was also eliminated, such as poor gray-white matter differentiation.

Magnetic resonance imaging

All MRI studies were carried out using a standard head coil and a 1.5 T magnetic resonance scanner (Philips, Intera Achieva, Amsterdam, The Netherlands) (matrix =256 mm × 256 mm, spatial resolution =1 mm × 1 mm, field of view =25 cm). The imaging sequences included 1 mm axial T1-weighted images, 2 mm axial and coronal T2-weighted images and 3 mm coronal Fluid-attenuated inversion-recovery (FLAIR) images. Coronal imaging was performed perpendicularly to the long axis of the hippocampus. MRIs were analyzed by two reviewers who were blinded to all clinical details.

Video-electroencephalography

Every patient underwent continuous scalp video-EEG recordings while under observation. The electrodes were arranged on the scalp according to the standard international 10-20 system, and recordings were made using a 32-channel electroencephalograph (Nicolet-One, VIASYS NeuroCare Inc., Madison, U.S.A). Field plots of ictal onsets or focal interictal spikes were analyzed to further define the abnormal regions.

Interictal 18F-FDG positron emission tomography

Interictal 18F-FDG-PET scans were performed on a Discovery ST PET/CT (General Electric Healthcare) scanner. The patients fasted from midnight and rested in a darkened, quiet room for 30 minutefs before FDG administration. Depending on body weight, the patients were given an injection of 18F-FDG, intravenously. After resting with eyes closed for 30 minutes, the patients were scanned and PET images of the complete brain were acquired using 3D serial static scanning and the images were reconstructed iteratively. EEG monitoring was not routinely used, however, patients were asked to report any seizures and they were also continuously monitored by trained technicians during the scan. Areas of glucose hypometabolism were then identified through analysis as abnormal regions in the 18F-FDG images (horizontal sections) with reduced radioactivity.

Magnetoencephalography

We used a whole-head, 306-channel Neuromag system (Elekta, Helsinki, Finland) to record the spontaneous MEG activity. Sampling frequency of the MEG was 1000 Hz and band-pass filtered between 0.1 Hz and 333 Hz. Five head

Table 1. Location of epileptogenic foci with invasive monitoring, PET and MEG in 85 patients (Engel class I~III)

L/N-L	Total	L	N-L
IM	75	70 (93.3%)*	5 (6.7%)
PET	53	30 (56.6%)	23 (43.4%)
MEG	61	42 (68.9%)	19 (31.1%)
PET+MEG	29	23 (79.3%)	6 (20.7%)

L, localizing; N-L, non-localizing; IM, invasive monitoring; PET, positron emission tomography; MEG, magnetoencephalography; *: Pearson Chi-square test, P<0.05.

position indicators (HPI) coils were used to monitor the continuous head position. Individual spike analysis using Neuromag software was performed on data segments containing visually identified epileptiform discharges. This analysis was conducted without prior knowledge of the clinical history. A minimum number of six spikes sources were defined as a cluster if the distance between adjacent sources was no more than 1 cm. And the rest of the sources were defined as scatter [7]. The MEG image was then displayed on MR-images to evaluate the anatomic localization.

Invasive monitoring

Subdural grid electrodes, depths electrodes were placed according to the hypothesis of epilepsy localization based on the multiple findings of the pre-surgical evaluation. Different grid sizes were used depending on the size of the region. The sheets in a grid pattern were inserted through either an open craniotomy or a burr-hole. In some cases, the sheets were positioned beyond the borders of the opening to extend the area of investigation. In addition to subdural electrodes, we also use stereo-electroencephalo-graphy (SEEG) with a stereotactic frame and Robotized Stereotactic Assistant (ROSA, Medtech S.A, Parc de Bellegarde, France) in a minority of patients. Intracranial EEG abnormalities were used to define the epileptogenic zone, which included the ictal onset zone defined as the region showing repetitive spiking, bursts of high-frequency discharges, focal transformations into rhythmic activity, or electrodecremental patterns; foci that consistently activated during a seizure [8].

Definition of PET+MEG/single lobe and multi-lobes

29 patients underwent both interictal 18F-FDG-PET and MEG examination. The concordant region of PET+MEG in localizing the epileptogenic zone was defined as the completely or partly overlapping region based on the images of interictal 18F-FDG-PET and MEG, no matter in a single lobe or in multi-lobes of brain. We considered a positive result of PET+MEG in localizing the epileptogenic foci if the resected area which determined by postoperative MRI completely or partly contained the concordant region assessed in the preoperative interictal 18F-FDG-PET and MEG. The epileptic regions in a single lobe of brain defined as follows: frontal lobe, frontopolar, frontal inferior, frontal superior/mesial, parietal lobe, parietal inferior, parietal superior/mesial, occipital lobe, occipital mesial, occipital lateral, temporal lobe, temporopolar, temporomesial, temporolateral and insular lobe. The epileptic regions in multiple lobes of brain defined as the epileptic zones presented in more than two of the five lobes (frontal, parietal, occipital, temporal and insular lobe).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 for Windows (version 20, IBM Corp., Armonk, New York, USA). Variables are expressed as mean ± standard deviation, or number of patients (%). Categorical variables were analyzed by chi-square test and Fisher's exact test. Statistical significance was defined as P<0.05.

Results

Postoperative outcome was graded using the Engel epilepsy surgery outcome scale [9]. Among the 85 patients with good seizure outcomes (Engel class I-III), 75 (88.2%) participated in the invasive monitoring. The localizing percentages for invasive monitoring, interictal 18F-FDG-PET, MEG, and PET+MEG were 93.3%, 56.6%, 68.9%, and 79.3%, respectively. Compared with interictal 18F-FDG-PET, MEG, and PET+MEG, invasive monitoring had the highest diagnostic sensitivity in localizing epileptogenic foci (Pearson Chi-square test, P=0.00; **Table 1**). PET+MEG diagnostic sensitivity tended to be higher than interictal 18F-FDG-PET or MEG, especially for the temporal non-lesional epilepsy (**Figure 1**).

Sometimes the epileptogenic zones found using MEG and interictal 18F-FDG-PET were not limited to a single lobe of the brain (**Figure**

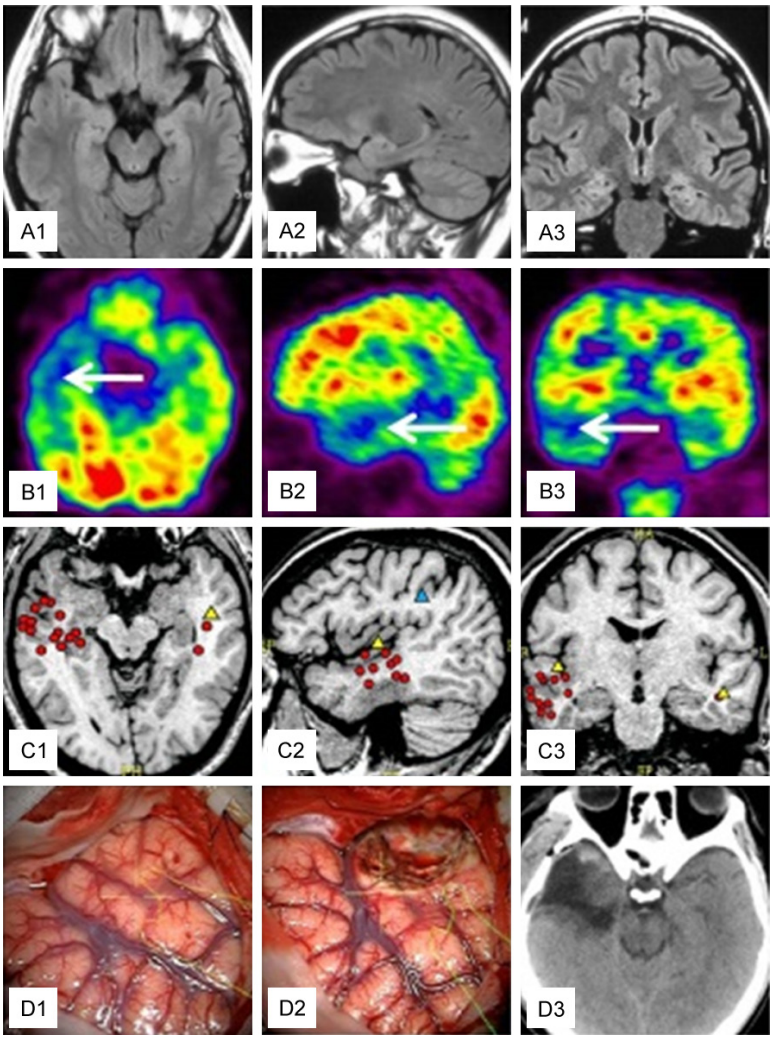

Figure 1. A. Lesions in the right temporal lobe were absent in the axial (A1), sagittal (A2), and coronal (A3) FLAIR sequences. B. Hypometabolism in the right temporal lobe is seen in the axial (B1), sagittal (B2), and coronal (B3) interictal FDG-PET scans (the arrows). C. Epileptogenic foci were localized in the right temporal lobe in the axial (C1), sagittal (C2), and coronal (C3) interictal MEG (red dots). D. (D1) No abnormalities in the right temporal cortex. (D2) The anterior temporal lobe and hippocampus were removed. (D3) The CT scan after operation.

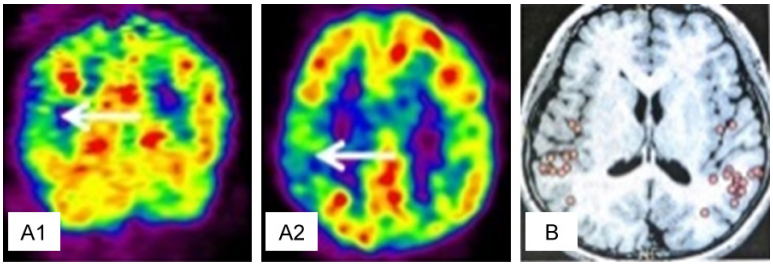

Figure 2. A. Hypometabolism in the right parietal lobe in the coronal (A1) and axial (A2) interictal FDG-PET scans (arrow). B. The epileptogenic foci were localized in the bilateral occipito-temporal area in the axial interictal MEG (red dots).

2). Localization of epileptogenic foci with interictal 18F-FDG-PET had significantly higher sensitivity when it occurred in a single lobe than in multiple lobes (74.1% vs. 34.6%, Pearson Chi-square test, P=0.004; **Table 2**). When localizing epileptogenic foci with MEG, no differences were found between single and multiple lobes (78.6% vs. 60.6%, Pearson Chi-square test, P=0.131; **Table 2**). PET+MEG showed a higher diagnostic sensitivity in localizing real epileptogenic foci in a single lobe than in multiple lobes (91.3% vs. 33.3%, Fisher's exact test, P=0.00; **Table 2**). The percents of cases that were localized to a single lobe using interictal 18F-FDG-PET, MEG, and PET+MEG were 74.1%, 78.6%, and 91.3% respectively (Likelihood Ratio test, P=0.249; **Table 3**). Compared with interictal 18F-FDG-PET, MEG tended to be higher (**Figure 3**). There was no statistical significance among interictal 18F-FDG-PET, MEG, and PET+MEG in localizing epileptogenic foci in multiple lobes of brain in non-lesional epilepsy (Likelihood Ratio test, P=0.103; **Table 4**).

Disscussion

Hypometabolism observed through interictal 18F-FDG-PET is a hallmark of the seizure-onset zone and surrounding areas [10], and is commonly assessed when evaluating patients before epilepsy surgery. Lee et al. found that the diagnostic sensitivity of interictal 18F-FDG-PET was 85% for neocortical epilepsies and medial temporal, even in patients with bilateral sclerosis, ambiguous

Table 2. The results of location of epileptogenic zone (in one brain lobe or multi-lobe of brain) with PET, MEG, and PET+MEG in 85 patients (Engel class I~III)

Examination	Location of epileptogenic foci	Total	L	N-L	*P* value
PET	One brain lobe	27	20 (74.1%)*	7 (17%)	0.004
	Multi-lobe of brain	26	9 (34.6%)	17 (65.4%)	
MEG	One brain lobe	28	22 (78.6%)	6 (21.4%)	0.131
	Multi-lobe of brain	33	20 (60.6%)	13 (39.4%)	
PET+MEG	One brain lobe	23	21 (91.3%)†	2 (8.7%)	0.008
	Multi-lobe of brain	6	2 (33.3%)	4 (66.7%)	

L, localizing; N-L, non-localizing; PET, positron emission tomography; MEG, magnetoencephalo-graphy; *: Pearson Chi-square test, P<0.05; †: Fisher's exact test, P<0.05.

Table 3. The results of location of epileptogenic zone in one brain lobe with PET, MEG, and PET+MEG in 85 patients (Engel class I~III)

Examination	Total	L	N-L
PET	27	20 (74.1%)	7 (25.9%)
MEG	28	22 (78.6%)	6 (21.4%)
PET+MEG	23	21 (91.3%)	2 (8.7%)

L, localizing; N-L, non-localizing; PET, positron emission tomography; MEG, magnetoencephalo-graphy; Likelihood Ratio test, P=0.249.

sclerosis, atrophy, or unremarkable MRI findings [11]. Other studies have reported that the sensitivity of interictal 18F-FDG-PET images in lateralizing temporal lobe epilepsy (TLE) in patients without a discrete neocortical mass lesion was between 60% and 90% [12-16].

Similar to interictal 18F-FDG-PET, MEG is also a non-invasive method used for localizing seizure foci. As reported in Ray et al. [17], MEG can be used to complement EEG for localization of seizure foci, and provides a combination of noninvasiveness with very high spatial and temporal resolutions. They concluded that the overall accuracy of MEG in source localization is better than that of EEG. Other studies comparing the ability of MEG, scalp video-EEG, and brain MRI to localize the epileptic focus have suggested that MEG is a useful technique for pre-surgical evaluation because its sensitivity (approximately 80%) in detecting clinically significant epileptiform activity is relatively high [18]. However, a few studies have investigated which of these two non-invasive methods (interictal 18F-FDG-PET or MEG) is better at localizing seizure foci in non-lesional epilepsy. Here, we found no significant difference in their sensitivities, although MEG trended to be more sensitive (interictal 18F-FDG-PET, 56.6%; MEG, 68.9%).

Although the sensitivities of the two techniques were not significantly different when conducted separately, perhaps combining them together could significantly increase sensitivity. Wong et al. described image coregistration and visualization techniques used to study the relationship between MEG and interictal 18F-FDG-PET metabolism for medical refractory partial epilepsy in a series of 12 patients [19]. They found that MEG and interictal 18F-FDG-PET provided the highest correlation of any combination of non-invasive method, and when concordant could accurately predict the epileptogenic zone. Similarly, Lamusuo et al. evaluated combined interictal 18F-FDG-PET and MEG for preoperative localization of the epileptogenic zone in 9 patients and found concordant interictal 18F-FDG-PET and MEG results in 78% of cases [20]. For non-lesional epilepsy, Knowlton and colleagues obtained localizing values of association between MSI (magnetic source imaging) and interictal 18F-FDG-PET in 51 patients who were free of seizures after surgery [21]. They found that the combined sensitivity of both MSI and interictal 18F-FDG-PET was only 25%, however, the diagnostic specificity was high: 95% for MSI+PET compared with 79% for MSI or interictal 18F-FDG-PET alone. In the present study of non-lesional epileptic patients, we found no significant difference between PET+MEG and interictal 18F-FDG-PET or MEG in localizing epileptogenic foci, though PET+MEG trended to have a higher diagnostic sensitivity. However, PET+MEG was especially helpful in non-lesional temporal lobe epilepsy of our studies. The temporal resection can be determined if both interictal 18F-FDG-PET and MEG localized the epileptogenic zones to the ipsilateral temporal lobe, and if this is consistent with the interictal and ictal scalp EEG, combined with typical types of seizure video monitoring. Ten patients

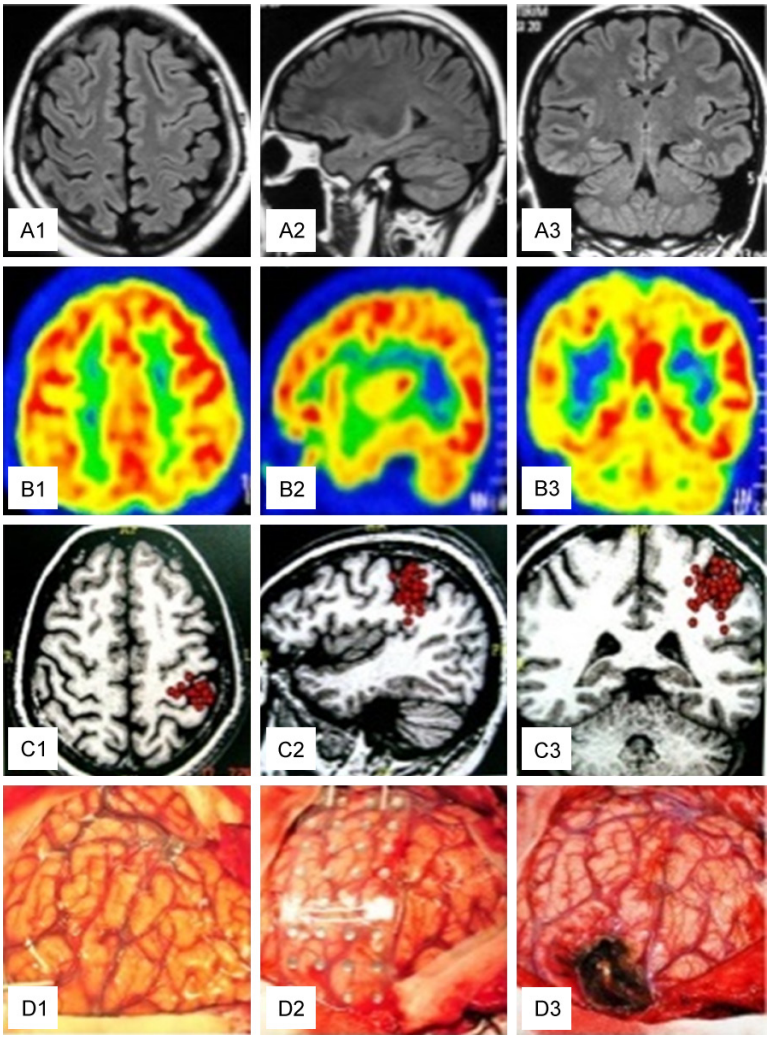

Figure 3. A. Lesions in the left parietal lobe were absent in the axial (A1), sagittal (A2), and coronal (A3) FLAIR sequences. B. Hypometabolism in the left parietal lobe is absent in the axial (B1), sagittal (B2), and coronal (B3) interictal FDG-PET scans. C. The epileptogenic foci were localized in the left central area in the axial (C1), sagittal (C2), and coronal (C3) interictal MEG (red dots). D. (D1) No abnormalities in the left parietal cortex. (D2) The results of invasive monitoring showed epileptogenic foci in the left central area. (D3) The non-functional cortex was removed and the central gyrus was coagulated.

Table 4. The results of location of epileptogenic zone in multi-lobes of brain with PET, MEG, and PET+MEG in 85 patients (Engel class I~III)

Examination	Total	L	N-L
PET	26	9 (34.6%)	17 (65.4%)
MEG	33	20 (60.6%)	13 (39.4%)
PET+MEG	6	2 (33.3%)	4 (66.7%)

L, localizing; N-L, non-localizing; PET, positron emission tomography; MEG, magnetoencephalo-graphy; Likelihood Ratio test, P=0.103.

(11.8%) in our group had good seizures outcomes (Engel class I-III) after temporal resections that were performed directly without intracranial EEG monitoring.

Both interictal 18F-FDG-PET and MEG sometimes located epileptogenic zones in multiple lobes of the brain. For some patients several brain lobes were localized, and we even saw cases in which the two techniques contradicted each other and indicated the epileptogenic zones were in opposite hemispheres. In our study, the highest diagnostic sensitivity in localizing real epileptogenic foci was achieved when both interictal 18F-FDG-PET and MEG localized the epileptogenic zone in the same brain lobe, or the volume of the potential epileptogenic foci partly or completely overlapped. Conversely, locating the real epileptogenic foci was very difficult when both interictal 18F-FDG-PET and MEG localized multiple epileptogenic zones in different lobes of the brain, or when the potential epileptogenic foci provided by the two methods did not overlap. In these cases, the epileptogenic foci appear to be constantly multi-focal, even with invasive monitoring. We also found that when interictal 18F-FDG-PET and MEG located epileptogenic zones in a single lobe, most cases turned out to be temporal lobe epilepsy, and a smaller number were frontal lobe epilepsy. Additionally, the results for interictal 18F-FDG-PET and MEG among patients with multi-lobes non-lesional epilepsy were always inconsistent.

With regard to the interictal 18F-FDG-PET and MEG used in isolation, interictal 18F-FDG-PET showed a higher diagnostic sensitivity in the

localization of epileptogenic foci in a single brain lobe than in multiple brain lobes (74.1% vs. 34.6%, P=0.004), while localization of epileptogenic foci with MEG did not differ between single and multiple brain lobes (78.6% vs. 60.6%, P=0.131). Compared with interictal 18F-FDG-PET, our findings suggest that MEG localized zones were more diffuse and were located more extensively throughout the cortex. Although interictal 18F-FDG-PET showed a higher diagnostic sensitivity for single-lobed localization, this could be explained by the epilepsy types, for example, this study included more cases of temporal lobe non-lesional epilepsy. As Henry reported that in pure temporal lobe epilepsy, regional glucose hypometabolism was typically presented in the temporal lobe ipsilateral to the EEG seizure onset location [22].

Additionally, in the present study, we found that there was no statistical significance among interictal 18F-FDG-PET, MEG, and PET+MEG in localizing non-lesional epileptogenic foci in a single lobe of brain and in multiple lobes of brain. Compared with interictal 18F-FDG-PET or MEG, PET+MEG had the highest diagnostic sensitivity in the localization of epileptogenic foci in a single brain lobe, while in multiple lobes, MEG trended to be higher. This could be explained that both interictal 18F-FDG-PET and MEG had their own interpretations of the epileptic zone and their limitations. For example, for the epileptogenic zones located in mesial temporal lobe epilepsy with interictal 18F-FDG-PET and MEG, when most of the two volumes overlapped, the interictal 18F-FDG-PET usually showed hypometabolism in the temporal pole, while the MEG showed epileptic-form discharges on the outer side of the medium temporal lobe. The latter can be attributed to the limitations of MEG, which is insensitive to exclusively radially oriented sources, such as those found at the depth of sulci or top of gyri [23, 24]. Nevertheless, both interictal FDG-PET and MEG (either in isolation or combination) were helpful in localizing non-lesional epileptogenic zone, the main role of which were to help doctors determine where to place subdural grids and strips.

Several limitations of this study should be considered. First, this is a single center study with a retrospective design. Second, the positive results of localizing non-lesional epileptogenic zone by interictal 18F-FDG-PET, MEG, or PET+MEG are evaluated in qualitative, not in quantitative. Further studies are necessary to accurately calculate the volume of the epileptogenic zone by MEG images and precisely delineate the epileptogenic foci by interictal 18F-FDG-PET images.

We found that combining interictal 18F-FDG-PET with MEG had an advantage in localizing the epileptogenic zone in non-lesional epilepsy, especially in a single lobe of the brain. Additionally, when interictal 18F-FDG-PET analysis showed hypometabolism in single lobes of the brain, it had a higher diagnostic sensitivity in localizing epileptogenic foci than when hypometabolism was seen in multiple lobes. However, despite these positive results, the two techniques consistently revealed a minority of patients who could have resections directly performed without intracranial EEG monitoring.

Disclosure of conflict of interest

None.

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