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# Utility of hybrid PET/MRI multiparametric imaging in navigating SEEG placement in refractory epilepsy

Miao Zhang [a,1], Wei Liu [b,1], Peng Huang [b], Xiaozhu Lin [a], Xinyun Huang [a], Hongping Meng [a], Jin Wang [a], Kejia Hu [b], Jian Li [c], Mu Lin [d], Bomin Sun [b], Shikun Zhan [b,**], Biao Li [a,*]

[a] Department of Nuclear Medicine, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
[b] Department of Neurosurgery, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
[c] Clinical Research Center, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
[d] MR Collaborations, Siemens Healthcare Ltd., Shanghai, China

A R T I C L E I N F O

*Keywords:*
Hybrid PET/MRI
Epilepsy
Seizure onset zone (SOZ)
Stereo-Electroencephalography (SEEG)
Surgical outcome

A B S T R A C T

*Purpose:* Stereo-electroencephalography (SEEG) implantation before epilepsy surgery is critical for precise localization and complete resection of the seizure onset zone (SOZ). Combined metabolic and morphological imaging using hybrid PET/MRI may provide supportive information for the optimization of the SEEG coverage of brain structures. In this study, we originally imported PET/MRI images into the SEEG positioning system to evaluate the application of PET/MRI in guiding SEEG implantation in refractory epilepsy patients.
*Materials:* Forty-two patients undergoing simultaneous PET/MRI examinations were recruited. All the patients underwent SEEG implantation guided by hybrid PET/MRI and surgical resection or ablation of epileptic lesion. Surgery outcome was assessed using a modified Engel classification one year (13.60 ± 2.49 months) after surgery. Areas of SOZ were identified using hybrid PET/MRI and concordance with SEEG was evaluated. Logistic regression analysis was used to predict the presence of a favorable outcome with the coherence of concordance of PET/MRI and SEEG.
*Results:* Hybrid PET/MRI (including visual PET, MRI, plus MI Neuro) identified SOZ lesions in 38 epilepsy patients (90.47 %). PET/MRI showed the same SOZ localization with SEEG in 29 patients (69.05 %), which was considered to be concordant. The concordance between the PET/MRI and SEEG findings was significantly predictive of a successful surgery outcome (odds ratio = 20.41; 95 % CI = 2.75–151.4, $P = 0.003$**).
*Conclusion:* Hybrid PET/MRI combined visual PET, multiple sequences MRI and SPM PET helps identify epilepsy lesions particularly in subtle hypometabolic areas. Patients with concordant epileptic lesion localization on PET/MRI and SEEG demonstrated a more favorable outcome than those with inconsistent localization between modalities.

## 1. Introduction

Epilepsy is one of the most common neurological disorders, with an estimated worldwide prevalence of 6.38 per 1000 persons [1]. Approximately one-third of patients are resistant to epileptic drugs, and in these patients, surgical intervention is the only viable treatment option. To date, however, the safety and efficacy of reported neurosurgical procedures for focal epilepsy have varied widely. The rate of postoperative seizure freedom after at least one year of follow-up ranges from 53 to 84% in patients with temporal lobe epilepsy (TLE) to 36–76 % in patients with localized neocortical epilepsy [2]. The success of epilepsy surgery depends on the precise localization and complete resection of the seizure onset area without the production of neurological consequences [3].

The application of stereo-electroencephalography (SEEG) for the pre-surgical assessment of patients with refractory epilepsies is

* Corresponding author at: Department of Nuclear Medicine, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin Er Road, Shanghai, China.
** Corresponding author at: Department of Neurosurgery, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin Er Road, Shanghai 200025, China.
*E-mail addresses:* zsk10715@rjh.com.cn (S. Zhan), lb10363@rjh.com.cn (B. Li).
[1] These authors contributed equally to this work.

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increasing, particularly for those with deep epileptic zones or foci distributed in both hemispheres [4]. SEEG can be regarded as the gold standard for SOZ localization, and a positive finding on SEEG recordings is usually indicative of a good outcome of surgical resection [5]. However, SEEG has limitations and entails risks for complications because of its invasive nature. Successful SOZ identification by SEEG depends upon correct planning and placement of intracerebral electrodes. The hypothesis regarding the SOZ location used for electrode placement needs to be focused, since SEEG coverage of brain structures is limited and the risk of complication rises with increasing number of electrodes implanted. Additional information from non-invasive studies is needed to improve SEEG placement and to reduce the number of required electrodes.

Hybrid PET/MRI imaging is a newly developed non-invasive technology that allows for the simultaneous acquisition of an illustration of glucose metabolism provided by PET imaging and various morphological and functional parameters measured by MRI under the same physiological and psychological conditions [6]. Multiparametric MRI brain scans are required for focus localization, and the precise fusion of PET and MRI images is important for planning surgery. The combination of PET and fMRI may also allow for the detection of functional brain areas and topographic association with epileptogenic material [7]. In previous studies, PET and MRI images were obtained separately and co-registered in the same coordinate system. However, the co-registered PET and MRI images may be suboptimal for the detection of seizure foci because these two examinations were performed on different machines and at different times. Mis-registration or various motion artifacts may introduce errors [8].

Previous studies have shown increased accuracy of hybrid PET/MRI imaging compared to separate MRI imaging and PET/CT for SOZ localization with less radiation exposure [9–11]. However, until now, very few hybrid PET/MRI data have been available for navigating SEEG electrode implantation in MRI-negative refractory epilepsy. In this study, we integrated hybrid PET/MRI imaging into the SEEG planning system to navigate SEEG electrode implantation.

Our hypothesis is that hybrid PET/MRI with multiparametric imaging would be of great help for SEEG precisely to locate the seizure focus and to predict the surgery outcome in MRI-negative refractory epilepsy. In this study, we evaluated the application of PET/MRI in precisely localizing the SOZ and originally navigating SEEG implantation in 42 patients. Furthermore, we conducted long-term follow-up to evaluate outcomes after surgery and analyzed the relationship between seizure outcomes and the concordance between PET/MRI and SEEG results.

## 2. Material and methods

### *2.1. Participants*

This study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (No. 2016-128). All procedures performed in this study involving human participants were in accordance with the ethical standards of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine research committee and with Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from each individual participant or his/her legal guardian.

A total of 82 epilepsy patients underwent hybrid PET/MRI examination at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China) between December 2017 and October 2019. Among them, 42 patients (51.2 %) completed SEEG implantation guided by PET/MRI, surgery, and postsurgical follow-up.

The inclusion criteria of the epilepsy patients were as follows: 1) diagnosis of epilepsy based on International League Against Epilepsy (ILAE) criteria and comprehensive clinical examinations, including a comprehensive neurologic evaluation, video EEG recordings, diagnostic MRI, PET, MEG, and SEEG; 2) diagnosis of refractory epilepsy with persistence of seizures after treatment with at least two antiepileptic drugs at their maximal tolerated doses; and 3) provided written informed consent for PET/MRI examination. The exclusion criteria were as follows: 1) posttraumatic epilepsy, progressive brain tumor, or other nervous system lesions; 2) structural abnormalities on MRI other than hippocampal atrophy or T2 signal hyperintensity which was evaluated by two radiologists in our hospital or other medical center; 3) pregnancy or lactation. 4) Generalized epilepsy syndromes. 5) With serious head movement artifacts and difficulty in PET/MR imaging interpretation.

### *2.2. PET/MRI acquisition protocol*

Scanning was performed on a hybrid PET/MRI scanner (Biograph mMR, Siemens Healthcare, Erlangen, Germany) using the vendor-supplied 8-channel phase-array head coil. The PET ring was integrated into a 3 T MRI scanner, between the shielded radio-frequency body coil and the gradient coils. After fasting for at least 6 h, patients received an IV injection of $^{18}F^{-}$FDG at a mean dose of (184.56 ± 41.19) MBq. Simultaneous FDG PET/MRI acquisition started 40 min after the injection. No patients had experienced an ictal event <6 h before or during the PET scan.

Static FDG PET data were acquired in sinogram mode for 15 min covering the whole brain with the following parameters: 128 slices per slab, gap =0.5 mm; and matrix size = 344 × 344, reconstructed with OSEM iterative reconstruction (subsets = 21, iterations = 4) and post-filtered with an isotropic full-width half-maximum (FWHM) Gaussian kernel of 2 mm. Attenuation correction (AC) was performed using advanced PET attenuation correction with unique 5-compartment model including bones [12].

MRI imaging was performed simultaneously to PET data acquisition. MRI scan based on standard epilepsy magnetic resonance imaging (MRI) protocols [13–16]. First, we performed three dimensional T1-MPRAGE and FLAIR sequences followed by axial two dimensional T2 and SWI, coronal T2 and coronal FLAIR. Coronal slices were angulated perpendicular to the hippocampal long axis. s The total duration of MRI is about 30 min and MRI protocol detailed information is displayed in Supplementary Table S1.

### *2.3. SEEG electrode implantation navigated by hybrid PET/MRI imaging*

Following hybrid PET/MRI imaging and pre-surgical evaluation with a multi-disciplinary team (MDT) to indicate the possible position of the epileptic focus, the SEEG electrodes were implanted, guided by PET/MRI imaging. The flow diagram of pre-surgical hybrid PET/MRI evaluation of epilepsy localization and SEEG electrodes implanting guided by PET/MRI imaging was shown in Fig. 1.

PET/MRI DICOM data was imported into the SEEG positioning system by Ruijin hospital PACS server and Network system, DICOM-SERVER process. Under local anesthesia, the patient's head was fixed using a stereotactic frame (Elekta Inc, Stockholm, Sweden), and CT scans were obtained. PET/MRI imaging was co-registed with CT imaging using Leksell Surgiplan system software (Elekta Inc., Stockholm, Sweden). After the X, Y, Z values were precisely coordinated, electrodes were subsequently implanted stereotactically as indicated by PET/MRI. The exact number and configuration of electrodes varied among the patients and were individually tailored based on the conclusions of the MDT. After implantation, all the patients underwent CT to confirm the localization of each contact before SEEG monitoring and to ensure there was no hemorrhage in the brain.

SEEG recording and data analysis: Intracranial SEEG data were recorded for 72–264 h (3–11 days) and a minimum of 3 seizures in each patient had to be recorded. A positive SEEG result indicates that there is sufficient evidence to define the seizure-onset zone. In this study, evidence included the first clear SEEG change, such as a low-voltage fast activity in the beta and gamma bands, or recruitment and periodic fast discharge of spikes that occurred before the clinical onset of the seizure.

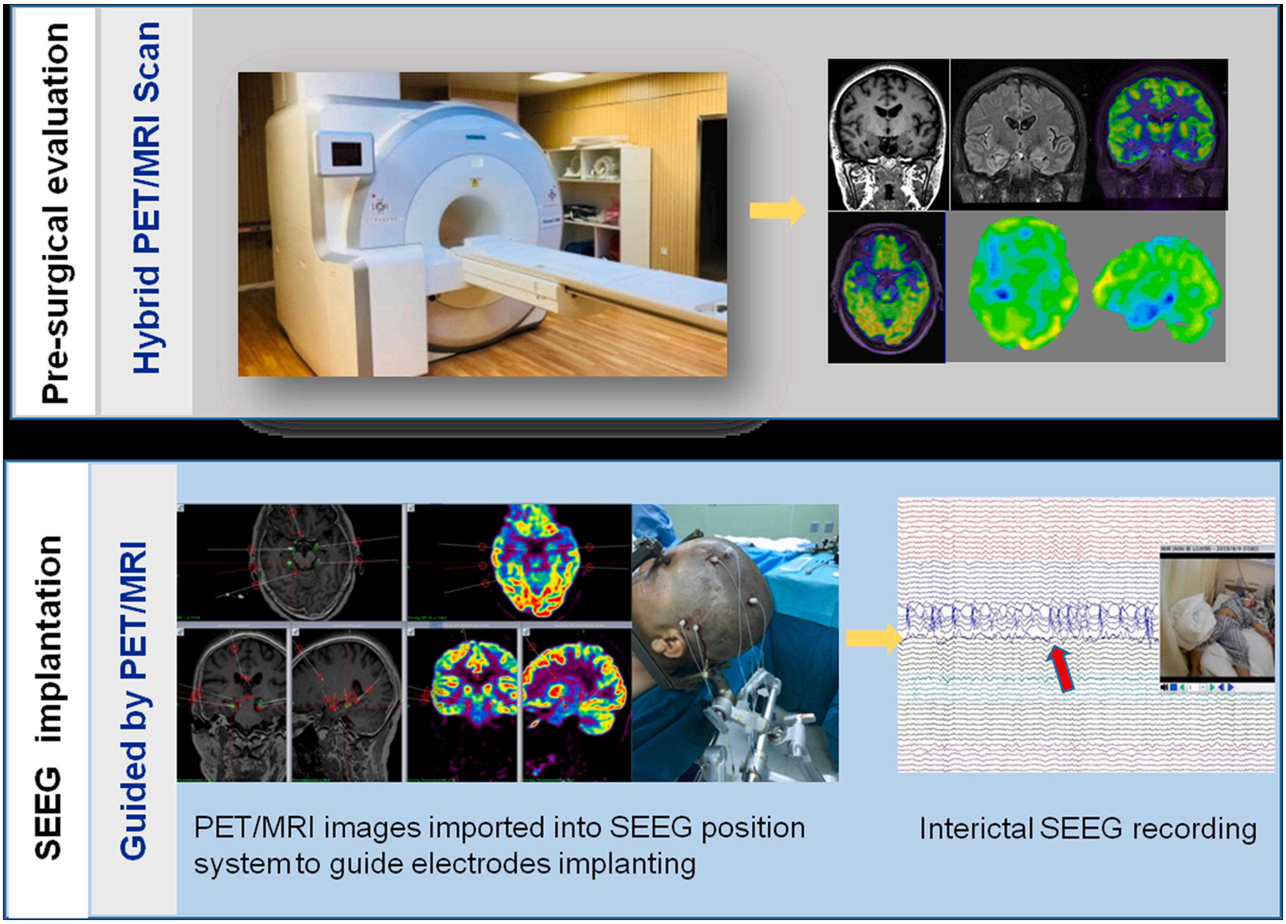


**Fig. 1.** The flow diagram of SEEG electrodes implanting guided by PET/MRI imaging.

Interictal epileptiform discharges were also considered to be relevant when they consisted of spikes, polyspikes, spike-and-wave, or poly spike-and-wave complexes. [17]

### 2.4. Hybrid PET/MRI imaging analysis for localization of the SOZ

Before analysis of the conventional visual inspection of the MRI and PET images, hybrid PET/MRI images were independently performed by three imaging experts (detailed in author contributions) who were blind to the presumed location of the epileptogenic zone based on clinical, EEG, and MRI findings. All the physicians have been certified by two boards (nuclear medicine and radiology) including two senior physicians have more than 20 years' working experience. All discrepancies were resolved through discussion. All separate images were analyzed using the MR Oncology package (Syngovia, version VB10, Siemens Healthcare).

PET studies were visually interpreted, using PET Rainbow grading (white as highest metabolism followed by red, orange, yellow, green, blue, and with black as lowest). Each cerebral PET image was divided into eight zones (left and right frontal, temporal, parietal, and occipital), and every zone with at least one well-defined hypometabolic focus was classified as clearly positive. Areas of the brain showing only poorly defined hypometabolism, that is, a mildly decreased uptake or too small an area to be clearly reported visually, were classified as subtle positive. Areas with completely normal and symmetric distribution of cortical metabolism were classified as negative. Each study was globally considered positive if it showed at least one positive (clear or subtle) hypometabolic area. Areas with abnormal glucose metabolism were identified as the SOZs [18,19].

We fused PET and MRI imaging after simultaneous PET/MRI scanning. Under the help of PET, we applied multiple MR sequences imaging Combined with PET, we analyzed multiple sequences MRI imaging (including 3D T1, 3D FLAIR, T2WI and SWI, Cor T1WI, Cor FLAIR) to increase diagnosis confidence of subtle changes. MRI-criteria indicative of epileptogenic SOZ includes: 1) Abnormal morphology abnormalities on T1, Flair, T2 or SWI; 2) Abnormal MRI signal abnormalities on T1, Flair, T2 or SWI; 3) Hyperintensity of hippocampus or amygdale on Flair or T2; 4) Volume alterations of hippocampus.

### 2.5. Statistical parametric mapping (SPM) analysis

The fused PET/MRI images were analyzed using the MI Neurology package (Syngo.via, version VB10, Siemens Healthcare). For the PET images, each individual was compared with a reference set of age-matched normal brains in the database of the MI Neurology package. The standard deviation from the mean value was achieved from MI Neuro SPM analysis by converting the individual cerebral PET image to a standardized uptake value ratio image and comparing it voxel-by-voxel with an age-matched normal database of healthy subjects by using a two-sample *t*-test. Hypometabolic clusters were described quantitatively in terms of their size (slices number of hypometabolic zone) and severity (Z-score decreasing in the hypometabolic zone).

### 2.6. Concordance analysis between PET/MRI and SEEG findings

Based on the degree of concordance between the PET/MRI and SEEG findings, the epileptogenic hypometabolic areas were classified as one of three types: 1) fully concordant, with PET/MRI showing the same location as SEEG; 2) partially concordant, with the locations almost matching, but PET showing an extended area compared to SEEG; and 3) inconsistent, with PET/MRI showing a different location than SEEG.

### 2.7. Surgical procedure and outcome assessment

Surgical resection was performed according to PET/MRI and SEEG SOZ localization if they were concordant. When PET/MRI and SEEG results were partially concordant or inconsistent, surgical resection following SEEG findings was prioritized. Guided by the positive SEEG results, resection or lesion ablation was performed at the same time the intracranial electrodes were removed. For patients identified with TLE, resection surgery was performed using a standardized protocol of anterior temporal and hippocampus lobectomy immediately after the intracranial electrodes were removed. For patients identified with ETLE, surgical resection or lesion ablation was tailored according to the SEEG monitoring results. All 42 surgically treated patients were assessed postoperatively. Seizure outcomes were classified by independent neurologists and neurosurgeon according to Engel classification [20].

### 2.8. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (version 25.0; SPSS, IBM, Chicago, IL, USA). Continuous variables were expressed as mean ± SD or median (range) as per the distribution type, and categorical data were expressed as frequency and percentages. For continuous variables, independent-sample *t*-test analysis was conducted, as appropriate. For categorical variables, $X^2$ tests were performed. Logistic regression analysis was used to predict the presence of a favorable outcome with the coherence of concordance of PET/MRI and SEEG, seizure frequency, age, sex, location, duration of epilepsy, and age at epilepsy onset being the independent variables, using a backward stepwise multivariate logistic regression model (entry and removal probability were 0.05 and 0.10, respectively). A *p*-value of less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. Demographics and clinical characteristics

The main characteristics and demographic data of 42 patients (including 17 females) are shown in Table 1. The mean age of the patient group was 30.24 ± 9.22 years (range 10~53 years). The mean age at epilepsy onset was 19.90 ± 9.40 years (range 3~42 years). Thirty-one patients had temporal lobe epilepsy (including 11 with hippocampus sclerosis), whereas seizure onset was extra-temporal in the other 11 patients (6 with frontal lobe, 3 with occipital lobe, and 2 with parietal lobe epilepsy). Eight patients were identified by pathology to be focal cortical dysplasia (FCD) including 3 patients with FCD type IIA and 5 patients with type IIB. Three cases had multi-centric FCD lesions (Detail in supplementary Table S2, case 12, case 13 and case 15), one of which was shown in Fig. 2 (case 12 detail in supplementary Table S2). The mean follow-up period was 13.60 ± 2.49 months (range, 12–21 months). Thirty-one patients (including 25 TLE) who met criteria of Engel class I were classified as being seizure-free. Eleven patients (including 6 TLE) who met the criteria for Engel Class II, III, or IV (one or more recurrent complex partial or secondarily generalized seizures) were classified as not being seizure-free. The SEEG electrode number was 7.07 ± 1.85 (range, 6–14) electrodes in each patient.

Patient demographics, clinical characteristics were summarized in Table 1. Seizure frequency in the seizure-free group (Engel Class I) was statistically lower than that in the non-seizure-free group ($P = 0.007$). There are more patients (25 patients) with concordance of PET/MRI and SEEG in the seizure-free group than in the non-seizure-free group (2 patients).

**Table 1**
Demographic data of the total epilepsy, temporal, and extratemporal lobe epilepsy patients.

| | Total patients | Engel Class I | Engel Class II–IV | p value |
|---|---|---|---|---|
| Number of subjects, n (%) | 42 | 31 (73.81) | 11 (26.19) | NA |
| Female, n (%) | 17 (40.5) | 13 (41.94) | 4(36.36) | 0.75 |
| Age, y, mean (SD) | 30.24 (9.22) | 30.35 (9.40) | 29.91(9.13) | 0.42 |
| Age,y,Range | 10~53 | 10~53 | 16~47 | NA |
| Age at epilepsy onset, y, mean (SD) | 19.90 (9.40) | 20.81 (9.75) | 17.36(8.23) | 0.57 |
| Age at epilepsy onset, y, Range | 3~42 | 3~42 | 5~27 | NA |
| Duration of epilepsy, y, mean (SD) | 9.98 (7.01) | 9.55(6.24) | 11.18(9.09) | 0.11 |
| Seizure frequency(SD, per year) | 42.64 (75.64) | 33.26 (54.95) | 69.19 (115.58) | 0.007** |
| Side of epilepsy SOZ | | | | 0.49 |
| Left-sided, n% | 19 (45.24) | 15(48.39) | 4(36.36) | NA |
| Right sided, n% | 23 (54.76) | 16(51.61) | 7(63.64) | NA |
| Location of epilepsy SOZ | | | | 0.09 |
| TLE, n% | 31(73.81) | 25(80.65) | 6(54.55) | NA |
| ETLE, n% | 11(26.19) | 6(19.35) | 5(45.45) | NA |
| Number of implanted SEEG, n | 7.07 (1.85) | 7.13(1.94) | 6.91(1.64) | 0.63 |
| Follow up duration, mo, mean (SD) | 13.60 (2.49) | 13.61 (2.68) | 13.55(1.97) | 0.49 |
| FDG injection dose(MBq) | 184.56 (41.19) | 191.92 (41.98) | 163.81 (32.05) | 0.48 |
| Concordance PET/MR& SEEG, n% | 29(69.04) | 27(87.10) | 2(18.18) | 0.00** |

(Abbreviations: SOZ = seizure onset zone; TLE = temporal lobe epilepsy; ETLE = extratemporal epilepsy. The age of the subjects, age at epilepsy onset, duration of epilepsy, seizure frequency, and follow-up duration were reported as the mean ± standard deviation (SD). For continuous variables between the Engel Class I and Engel Class II—IV groups, independent-sample t tests analysis was conducted, as appropriate. For categorical variables, $X^2$ tests were conducted. $^{**}P < 0.01$).

### 3.2. Value of hybrid PET/MRI in localizing the SOZ and navigating SEEG

Hybrid PET/MRI (including visual PET, MRI, plus MI Neuro) localized 38 (90.47 %) SOZ lesions. The conventional visual PET analysis identified 26 (61.90 %) hypometabolic regions which were presumed to be the SOZ after the SEEG data review. Hybrid PET/MRI (including visual PET, MRI, plus MI Neuro)identified 12 subtle hypometabolic areas that were overlooked by conventional visual PET analysis. The hypometabolic, visual PET-negative areas involved fewer slices and had slighter Z-score decreasing than the positive hypometabolic areas. Images of one case with hybrid PET/MRI-positive and visual PET-negative areas are shown in supplementary Figure S1.

Second, hybrid PET/MRI guided the second MRI reading. Initially, all MRI studies were reported as no lesion on traditional single MRI exam other than hippocampal atrophy or T2 signals hyper intensity which was evaluated by two experienced radiologists in our hospital or other medical center. Combined with PET, we identified subtle abnormalities on MRI in 13 patients (34.2 %), and the diagnosis was thus changed. The guided second reading changed the MRI report as follows: Three hypometabolic areas were identified as FCD type IIA, showing subtle pathologic abnormalities that were detectable in a hybrid PET/MRI-driven second reading; five hypometabolic areas were identified as FCD type IIB that showed subtle MRI abnormalities, which were initially reported as not being specific in the first reading;; five patients' hippocampus showed subtle high signal on the FLAIR sequence without morphologic changes. Combined PET with multiple sequences MRI, hybrid PET/MRI proved more confident to identify multi-centric subtle epilepsy lesions (an example as Fig. 2).

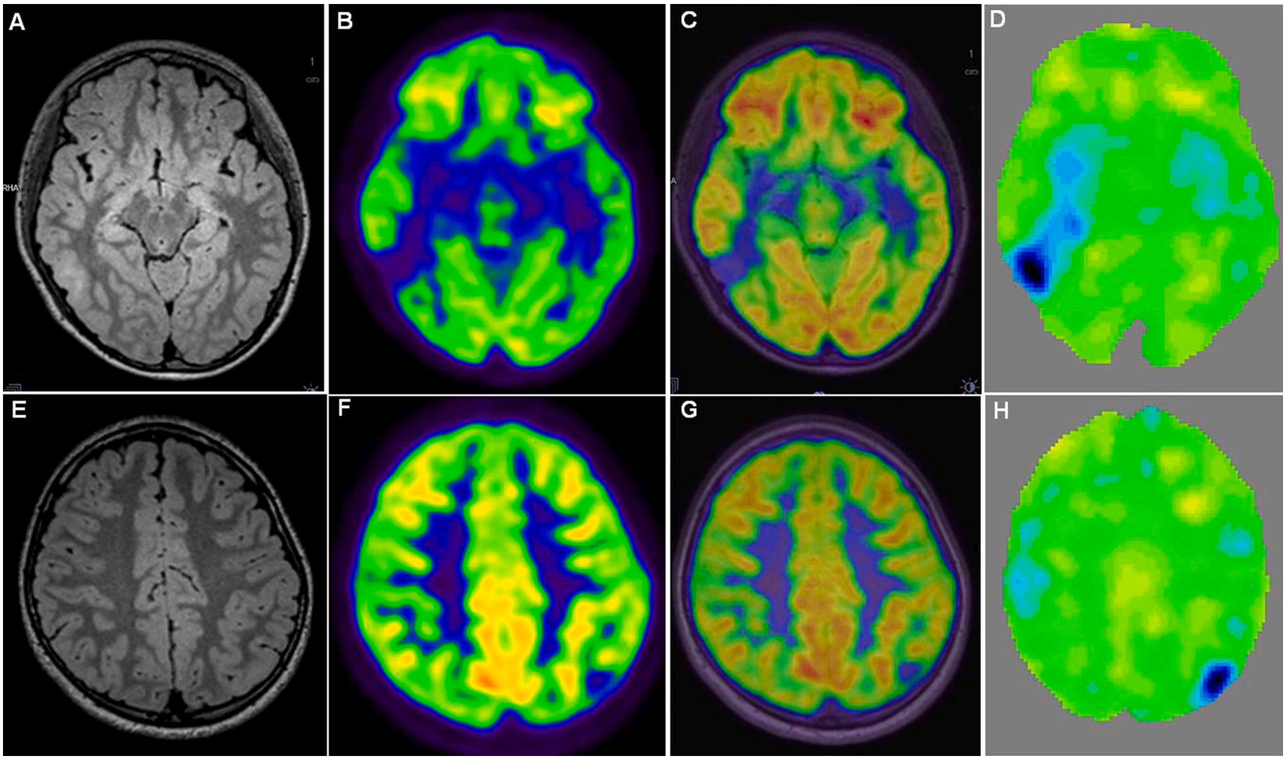


**Fig. 2.** Hybrid PET/MRI increase in viewer confidence of multi-centric subtle epileptic lesions.
A female juvenile patient, 10 years old, with a history of seizures, onset at 7 years of age. This patient underwent MRI scanning in another medical center but the epileptic lesions can't be confirmed. Then the patient was suggested to take PET/MRI scanning in our hospital. Combined PET with multiple sequences MRI, hybrid PET/MRI proved more confident to identify the two lesions (one in right temporal and another in left parietal lobe) which were proved by pathology to be focal cortical dysplasia (FCD) type IIB after surgery. SEEG was performed guided by the PET/MRI image and the same SOZ was confirmed with PET/MRI. The patient achieved seizure-free status (Engel Class I) after surgery. **A~2D** Axial hybrid PET/MRI images show epileptic lesion in right temporal lobe. Fig. 2**A** T2 Flair axial image shows a slightly higher MR signal lesion on the right temporal lobe. Fig. 2**B** PET visual imaging shows hypometabolic lesion in the right temporal lobe. Fig. 2**C** Hybrid PET/MR fusion axial image supply more precise positioning information. Fig. 2**D** SPM image analyzed by Syngovia MI neurology software, which shows a slighter Z-score decreasing lesion, compared with the normal database. **E~2H** Axial hybrid PET/MRI images confirm another subtle epileptic lesion in left parietal lobe. Fig. 2**E** T2 Flair axial image shows no obvious signal abnormal in left parietal lobe. Fig. 2**F-H** Combined PET imaging, hybrid PET/MRI images can help to confirm this subtle lesion in left parietal lobe.

### *3.3. Predictive value of PET/MRI in surgically treated patients*

After a detailed evaluation, we imported PET/MRI images into the SEEG positioning system, and the coordinates of the hypometabolic areas were precisely localized. The electrodes were then stereotactically implanted, as indicated by PET/MRI (Fig. 3). Forty-two patients fulfilled SEEG implantation with 7.07 ± 1.85 electrodes per patient (ranging from 6 to 10 electrodes). As shown in Table 1, PET/MRI helped to navigate SEEG to localize the SOZ in 35 patients (83.33 %). As shown in Table 2, complete seizure-free status (Engel I) was achieved in 31 (73.81 %) patients, including 25 TLE patients and 6 ETLE patients. In 25 patients, lesion localizations using hybrid PET/MRI and SEEG methods were fully concordant (one case, as Fig. 2 showed). In four patients, lesion localizations by the two methods were partially concordant, and in another two patients, lesion localization was inconsistent. Eleven patients (26.19 %), including six TLE and five ETLE patients, had epileptic seizures persisting after surgery (Engel Class II–IV). In nine of these patients, lesion localizations were either partially concordant or inconsistent between the PET/MRI and SEEG methods. Fig. 4 shows one case with extensive hypometabolic areas on PET/MRI, which were regarded as being partially concordant with SEEG. This patient achieved an unfavorable outcome (Engel class III) after surgery.

Supplementary Table S3 showed the results of logistic regression analysis used to predict the presence of a favorable outcome with the coherence of concordance of PET/MRI and SEEG, seizure frequency, age, sex, location, duration of epilepsy, and age at epilepsy onset as independent variables. The concordance between the PET/MRI and SEEG findings was significantly predictive of a successful surgery outcome (odds ratio = 20.41; 95 % CI = 2.75–151.4, $P$ = 0.003**). Gender, age, age at onset, course of disease (years) and seizure frequency showed no predictive value for determining favorable outcomes.

## 4. Discussion

In this study, we originally imported PET/MRI images into the SEEG positioning system to evaluate the application of PET/MRI in guiding SEEG implantation. Our study demonstrated three main findings: 1) Hybrid PET/MRI combined visual PET, multiple sequences MRI and SPM PET helps identify epilepsy lesions particularly in subtle hypometabolic areas. 2) Concordant epileptic lesion localization between the PET/MRI and SEEG methods predicted more favorable outcomes compared with inconsistent lesion localizations.

### *4.1. Hybrid PET/MRI showed advantage in SOZ precise localization*

MRI is a first-line imaging modality for the identification of an epileptogenic focus prior to epilepsy surgery. However, some patients show no structural lesions on MRI or discordant findings between MRI and EEG. Thus, aberrant brain function needs to be assessed using other noninvasive imaging modalities such as MEG, Single Photon Emission Computed Tomography (SPECT), and PET [18,21–23]. Interictal $^{18}$F-FDG PET scans contribute to the functional deficit zone definition by

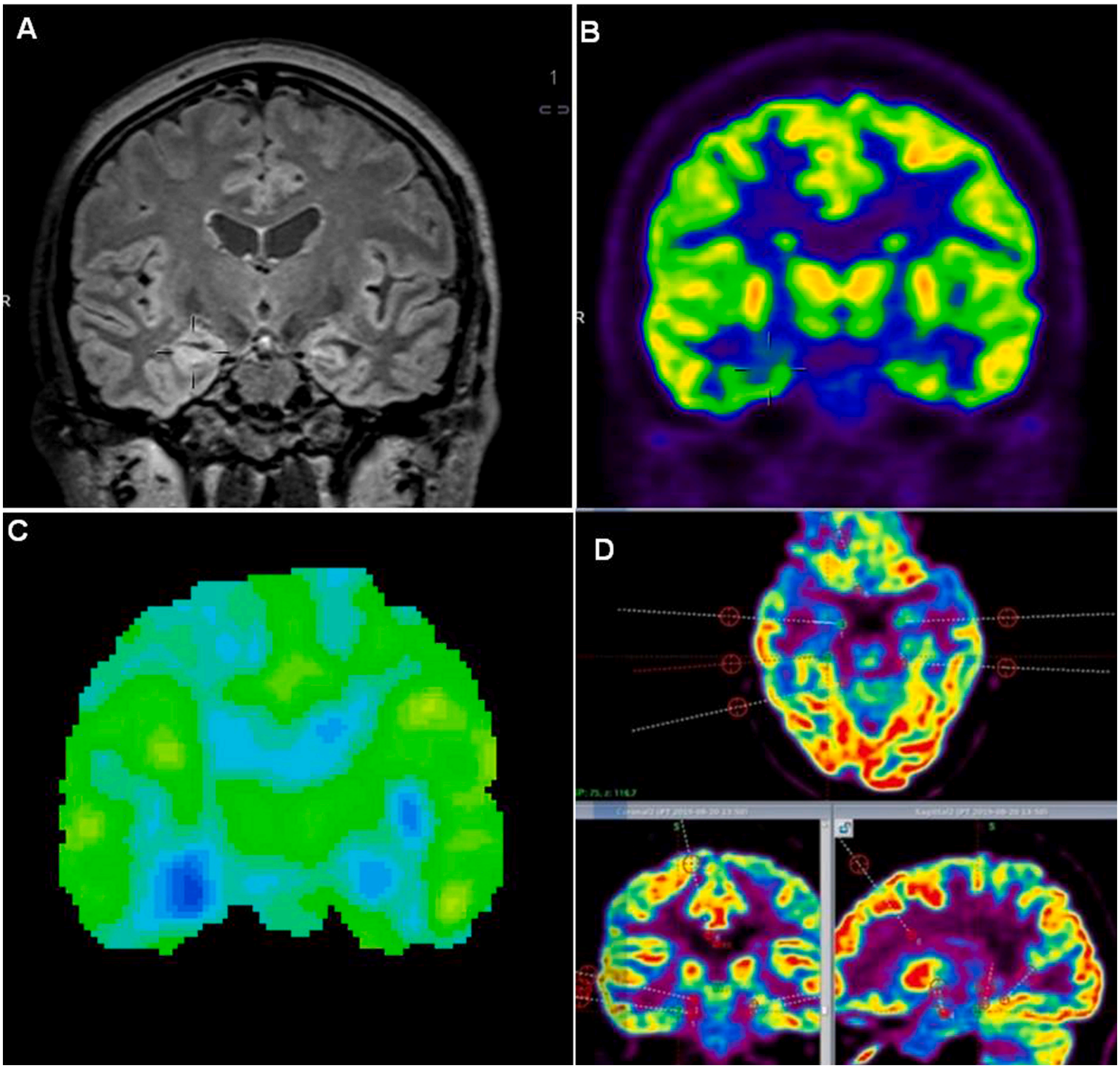


**Fig. 3.** Hybrid PET/MRI navigate SEEG electrodes implanting.
A female patient, 53 years old, with a history of seizures, onset at 36 years of age. Fig. 3**A** Coronal T2 Flair image shows a slightly higher MR signal lesion on the right hippocampus, amygdale and temporal lobe. Fig. 3**B** With MR supplying anatomic localization, coronal PET imaging shows hypometabolic lesion in the right hippocampus, amygdale precisely. Fig. 3**C** SPM image analyzed by Syngovia MI neurology software analysis, which shows Z-score decreasing lesion in right hippocampus, amygdala. Fig. 3**D** PET/MR images were imported into the SEEG positioning system, and the X, Y, and Z values were precisely coordinated. The electrodes were then stereotactically implanted for coverage of the right hippocampus, amygdala, and temporal lobe, navigated by PET/MR images. Ictal data show seizures originating from the right hippocampus, amygdala, and temporal lobe. After surgical resection, the patient achieved a favorable outcome (Engel Class I).

**Table 2**
Concordance of PET/MRI and SEEG methods in epileptic lesion localization among the different Engel classes.

| Concordance of PET/MR and SEEG | Engel Class | | | | | |
|---|---|---|---|---|---|---|
| | Class I | | | Class II–IV | | |
| | TLE | ETLE | Total | TLE | ETLE | Total |
| Total | 25 | 6 | 31 | 6 | 5 | 11 |
| Concordant | 22 | 3 | 25 | 1 | 1 | 2 |
| Partial concordant | 2 | 2 | 4 | 2 | 2 | 4 |
| Inconsistent | 1 | 1 | 2 | 3 | 2 | 5 |

(Abbreviations: SEEG = stereoelectroencephalography; TLE = temporal lobe epilepsy; ETLE = extratemporal epilepsy.).

revealing areas of reduced glucose metabolism, which is of great help in localizing the SOZ [4]; however, PET scans have low structural resolution. PET/MRI co-registration can improve PET sensitivity for the detection of SOZ hypometabolic areas [24,25]. However, co-registered PET and MRI obtained with separate PET/CT and MRI imaging presents difficulty for precise registration and additional exposure to radiation by CT. Recently, some studies showed that a hybrid PET and MRI system minimized patient discomfort while maximizing clinical information and optimizing the use of both modalities [6,8,10,26].

Hybrid PET/MRI systematically offers a complementary combination of two modalities that have often proven to be superior to the single modality approach in the diagnostic work-up of many neurologic and psychiatric diseases. Moreover, simultaneous PET/MRI is well-suited for complex brain function studies in which fast brain signal fluctuations need to be monitored on multiple levels in combination with fMRI [21,27–29]. Initial simultaneous studies have already demonstrated that these complementary brain function measures can provide new insights into the functional and structural organization of the brain [6–8,10,30,31]. Deuschl and coworkers [15] showed integrated PET/MRI may enable a dual platform for improved diagnostic confidence and overall detection of TLE. PET/MRI provides additional diagnostic information

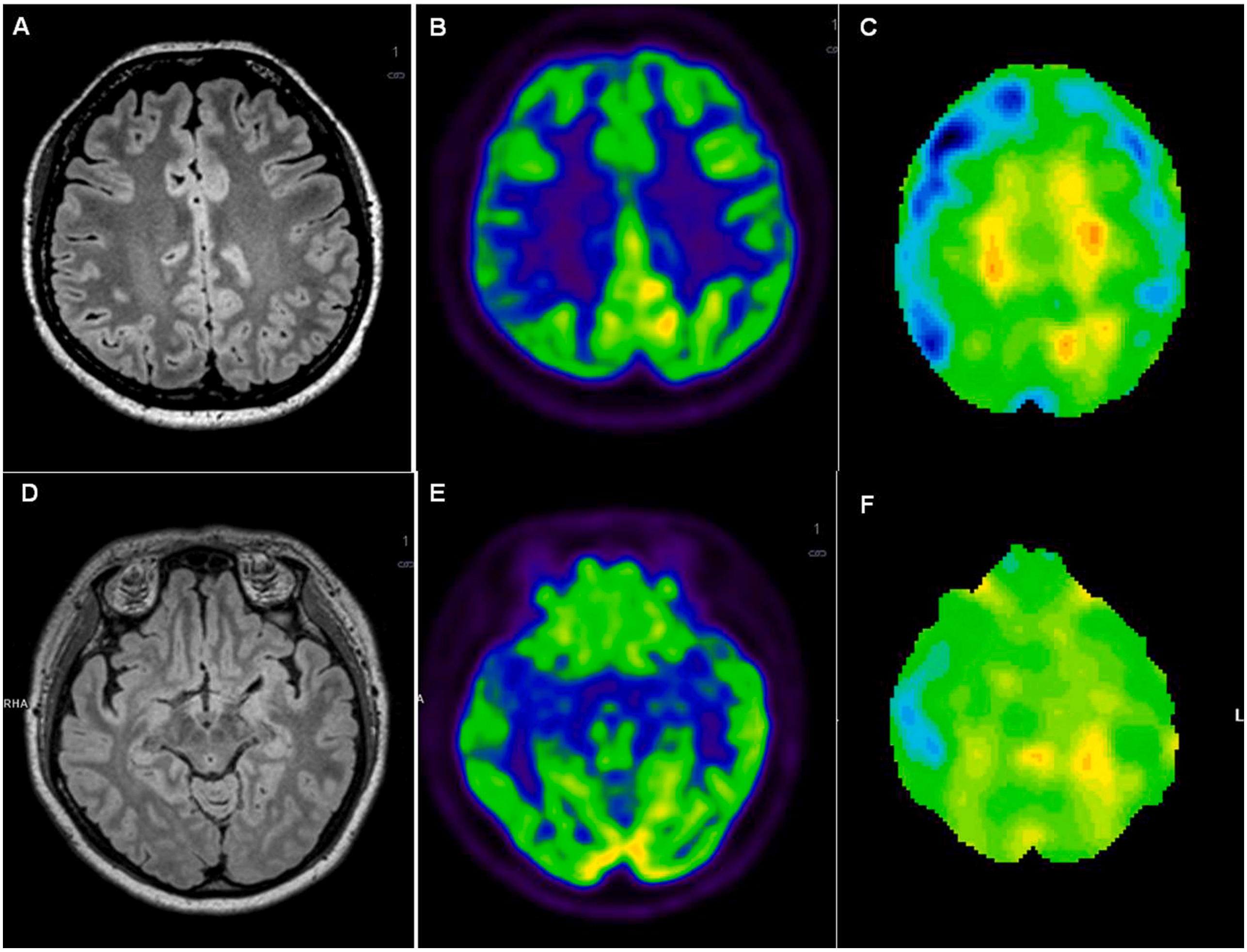


**Fig. 4.** Extending hypometabolic predict unfavorable outcome.
A female patient, 42 years old, with seizure onset at 12 years. Fig. 4**A and 4D** Axial T2 Flair image shows no obvious structurally abnormal hypometabolic areas. Fig. 4**B and 4E** Axial visual PET image. Fig. 4**C and 4 F** MI Neuro SPM image. PET/MRI imaging shows extending hypometabolic areas in the right temporal bilateral frontal and parietal lobes. SEEG confirmed the SOZ located in the right temporal lobe. Lesion localizations using hybrid PET/MR and SEEG methods were partially concordant. The patient underwent temporal resection surgery. Unfortunately, the patient achieved an unfavorable outcome (Engel Class IV) after surgery.

for infantile epilepsy or infantile spasms and improves etiologic classifications and the predication of therapy efficacy [11,32].

Hybrid PET/MRIidentified 12 subtle hypometabolic areas (with fewer slices and slighter Z-score decreasing) that were overlooked by conventional visual PET analysis. Subtle hypometabolic areas with limited involved slices and slighter Z-score decreasing were difficult to identify using conventional visual PET (Figure S1). Hybrid PET/MRI plus MI Neurology SPM analysis was helpful to confirm subtle hypometabolic seizure areas which were difficult to identify on visual PET. Second, hybrid PET/MRI helps to identify subtle hypometabolic areas, which were vague on MRI imaging alone. The cost of PET/MRI is higher than MRI, so most patients chose to take PET/MR exam because MRI can't confirm epilepsy SOZ. In this study, most inclusion subjects were MRI negative or difficult to define epilepsy SOZ by MRI. Thus the frequency of abnormal MR finding is low. And for MRI negative subjects, hybrid PET/MRI increase in viewer confidence of subtle epileptic lesions.

Attenuation correction is critical for the quantitative accuracy of PET imaging for PET/MRI [33,34]. In this study, we employed an advanced Dixon-based 5-compartment attenuation correction method [15]. The inclusion of model-based bone compartment was proved to have good accuracy for the quantification of brain lesions [12,35]. Despite the demonstrated advantages, this attenuation correction method was not systematically evaluated on epilepsy lesions, which may be improve in future studies.

### 4.2. Utility of hybrid PET/MRI in navigating SEEG electrode implantation

Although SEEG provides essential information for the surgery of selected patients, it also has some disadvantages, such as high costs, risks for infection, the patient burden involved in implantation of the electrodes and long-term invasive monitoring. In addition, SEEG fails to reveal the SOZ in some cases, despite using conventional non-invasive imaging modality, such as video-EEG and MRI. In this study, we originally imported PET/MRI images into the SEEG positioning system to guide SEEG implantation. Additional information from hybrid PET/MRI improved the SEEG placement and limited the number of required electrodes.

We imported PET/MRI into the SEEG positioning system and placed SEEG electrodes using PET/MRI navigation. With PET/MRI guidance, we were able to localize hypometabolic epileptic areas more precisely, and therefore could reduce the number of SEEG electrodes needed. The number of SEEG electrodes was reduced to $7.07 \pm 1.85$ (range, 6–14) electrodes for each patient, which had two main advantages: reduced brain injury and decreased patient financial burdens. Hybrid PET/MRI helped to navigate SEEG to localize the SOZ in 35 patients (83.33 %) and showed the same SOZ localization with SEEG in 27 patients (64.29 %), values that were defined as being concordant. In another 8 patients

(19.05 %), PET/MRI showed hypometabolic areas extending beyond the SOZ confirmed by SEEG, which was regarded as being partially concordant. Only in 7 patients (16.67 %) did PET/MRI show a different SOZ location than SEEG or fail to identify hypometabolic areas.

### 4.3. The role of concordance of PET/MRI/SEEG in predicting the surgical outcomes of epilepsy patients

The number of patients without seizures after surgery in this study compared favorably with previous reports [2,36–38]. We found that patients with concordant findings between PET/MRI and SEEG had a more favorable outcome than those with inconsistent results. Importantly, gender, age, age at onset, and course of disease had no additional predictive value.

In 31 seizure-free patients, 25 patients (80.65 %) showed a concordant SOZ location between PET/MRI and SEEG. Eleven patients still had epileptic seizures after surgery, four of whom showed partially concordant or inconsistent results between PET/MRI and SEEG. In these patients, hypometabolism extended to both the frontal and temporal lobes (Fig. 4), and PET/MRI failed to precisely localize hypometabolic epileptic areas. This was consistent with previous reports indicating that patterns of hypometabolism on PET carry predictive information, with more severe hypometabolism in the SOZ and the absence of hypometabolism beyond the SOZ associated with a better prognosis [39,40].

There were five patients, in whom the PET/MRI locations were inconsistent with the SEEG locations. These patients finally underwent resection surgery but had no worthwhile improvement after surgery (Engel class IV). Therefore, the concordance of PET/MRI with SEEG can be predictive of surgical outcomes. In the patients where PET/MRI localizations are partially concordant or inconsistent with that of SEEG, more unfavorable post-surgical outcomes are probable, and these patients need to undergo more careful evaluations and surgical planning before the resections are performed.

There were several limitations in this study. In this study, we included relatively limited patient population from only one medical center, which may introduce potential biases in statistically comparing seizure-free to not seizure-free patients. Secondly, follow up is already more than one year in this study, but still limited and longer following-up is expected to give us more confident results in the future study.

## 5. Conclusion

Hybrid PET/MRI combined visual PET, multiple sequences MRI and SPM PET helps identify epilepsy lesions particularly in subtle hypometabolic areas, which improves SEEG placement and limits the number of required electrodes. Furthermore, patients with concordant epileptic lesion localization on PET/MRI and SEEG demonstrated a more favorable outcome than those with inconsistent localization between modalities.

## Authors' contributions

B.L. and S.K.Z. contributed to the study concept and critically revised the manuscript. M.Z. and W.L. drafted the manuscript. W.L., S.K.Z. and B.S. performed SEEG and the resection surgeries. P.H., K.H. contributed to clinical evaluation and follow-up. X.H., X.Z.L. and B.L. contributed to interpretation of the imaging data and clinical data analysis. H.P.M. and J.W. contributed to patients' PET/MR scanning. M.L. contributed to PET/MRI protocol optimization and imaging technique support. M.Z. and J.L. contributed to the statistical analysis.

## Declaration of Competing Interest

Mu Lin is employed by the company Siemens Healthcare Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as being potential conflicts of interest.

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