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Focal Interictal Positron Emission Tomography Hypermetabolism and Electrical Cortical Stimulation Accurately Localizes the Seizure Onset Zone: A Cohort Study

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Abstract

Objective: To determine the value of interictal Positron Emission Tomography (PET) hypermetabolism and extraoperative electrical stimulation mapping in the location of the Epileptogenic Zone (EZ).

Methods: A retrospective study was conducted on epileptic patients with interictal PET hypermetabolism from January 2007 to December 2017. Fifteen patients underwent cortical resection, and 11 of them underwent subdural electrode placement and extraoperative electrical stimulation mapping.

Results: PET imaging of 15 patients showed that hypermetabolic regions were common in the frontal lobe, followed by the parietal lobe. Eight patients with abnormal brain lesions were found by Magnetic Resonance Imaging (MRI), and seven patients were negative. The EZ was determined by extraoperative electrical stimulation mapping in 11 patients. In nine patients, the hypermetabolic region of PET was identical with the EZ. In eight patients, the EZ was adjacent to the functional area. In the brain lobe with focal hypermetabolism, 182 electrode sites (22.2%) induced after discharges, and the sites that directly produced after Discharges (ADs) were often found in the center of the focal hypermetabolic area. Patients with high metabolic lesions near the functional area were more likely to induce AD than those with non-adjacent functional areas. Pathological results showed eight cases of cortical dysplasia, two cases of cortical malformation, four cases of gliosis, and one case of low-grade glioma. Engel scores in at least 3 years of follow-up were 60% (9) class I, 26.7% (4) class II, and 13.3% (2) class III.

Conclusion: Interictal PET hypermetabolism can locate the epileptic focus. Combined with extraoperative electrical stimulation mapping, it was helpful in accurately locating the EZ to help surgeons make clinical decisions.

Keywords: PET hypermetabolism; Electrical cortical stimulation; Epilepsy; Surgery

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Abbreviations

EZ: Epileptogenic Zone; EEG: Electroencephalography; iEEG: Intracranial Electroencephalographic; PET: Positron Emission Tomography; SE: Status Epilepticus; Ads: After Discharges

Introduction

The current surgical purpose of intractable epilepsy is to completely remove the epileptogenic focus under the premise of functional preservation, while maintaining accurate localization of the Epileptogenic Zone (EZ), which is crucial in surgery. Epileptic surgery involves epileptic foci as well as the cortex functional area, and the location of epileptogenic foci is mostly based on comprehensive noninvasive assessment methods, including clinical symptoms, interictal and ictal Electroencephalography (EEG), functional Magnetic Resonance Imaging (fMRI), magnetic

resonance spectroscopy, Single Photon Emission Computed Tomography (SPECT), Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET), Magnetoencephalography (MEG), and neuropsychology [1,2]. However, some patients fail to provide satisfactory localization information using noninvasive examination methods, especially when the various preoperative results are contradictory or the lesion is adjacent to the functional area. Intracranial Electroencephalographic (iEEG) surveys are currently the most accurate and valuable method to determine clinical seizure onset patterns [2]. Electrical Cortical Stimulation (ECS) is a reliable technique during IEEG monitoring to help identify the EZ. The location of EZ is a combination of multiple localization technologies, including Positron Emission Tomography (PET) to localize epileptic foci and ECS to study important eloquent zones such as the language area, sensorimotor area, and visual area. It is now widely recognized that FDG-PET can be used to accurately locate the EZ in patients with intractable epilepsy. According to previous reports, interictal PET shows asymmetric focal decreased FDG uptake in the EZ, while ictal PET shows asymmetric focal increased FDG uptake at the same site [3-5]. In actual clinical practice, the focal cortical hypometabolism of interictal PET is often used to help determine the location of epileptic foci, because ictal PET scans are difficult to capture, except in special circumstances such as during acute seizures and Status Epilepticus (SE). Some recent studies reported hypermetabolism interictally in the epileptic foci [6]. Glucose metabolism in a dynamic state in the epileptogenic zone, and glucose hypermetabolism may reflect a prodromal pathophysiology of future epileptic cortex demises [7]. For the study of language areas, the Wada test, fMRI, and MEG are commonly used, but ECS is still the gold standard. In addition, some investigations have studied ECS-induced auras in the definition of section boundaries in epilepsy surgery with a lesion [8]. PET hypermetabolism may also prompt an EZ, so we should pay close attention to preoperative epilepsy surgery evaluations. Furthermore, using intraoperative subdural grid electrodes, ECS-induced auras or seizures may help define the EZ. In the present study, we described one of the largest single-center series on surgical treatment of epilepsy patients with PET hypermetabolism. The objectives of this study were to evaluate the efficacy of PET hypermetabolism and ECS-induced After Discharges (ADs) on preoperative epilepsy evaluation, especially for patients with EZ adjacent to functional areas.

Methods

Patient selection and study design

This study was a retrospective analysis of patients with interictal PET hypermetabolism who underwent respective epilepsy surgeries at the tertiary comprehensive epilepsy center between January 2007 and December 2017. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2100043274). Informed consent was obtained from all patients or their guardians. A total of 937 patients who underwent an interictal PET scan underwent a standardized presurgical evaluation by a multidisciplinary specialized epilepsy team (consisting of pediatric and adult epileptologists, neurosurgeons, neuroradiologists, nuclear radiologists, and neuropsychologists). A total of 18 patients had interictal PET hypermetabolism. Fourteen patients underwent subdural electrode placement combined with cortical electrical stimulation to localize the cortical EZ. Three patients were not treated with surgery because the EZ overlapped with functional areas. Fifteen epileptic patients with interictal PET hypermetabolisms were finally enrolled in this study (Figure 1). This study has been reported in line with the STROCSS criteria [9].

Clinical variables and outcome assessments

Clinical data were collected using retrospective chart review. Available data included sex, age, age of seizure onset, frequency of seizure, duration of seizure, seizure subtype, and medications, the Full-Scale Intelligence Quotient (FSIQs), clinical examination, operative report, postoperative pathology, and outpatient follow-up. All patient preoperative examinations included a medical history, physical examination, long-term noninvasive video EEG, cranial fMRI, and cranial PET/CT.

PET/CT imaging and analysis

PET/CT imaging was performed with a Biograph 16 PET-CT scanner (Siemens, Germany). The imaging agent is 18F-FDG, which is produced by the PET trace cyclotron system (GE Healthcare, USA), with a radiochemical purity of >95%, and a dose of (3.70~7.4 MBq/kg). All patients were fasted for 6 h or more, fasting blood glucose ≤ 7.0 mmol/L, and rested in bed quietly for 50 min after injection of 18F-FDG. CT scanning parameters: Tube voltage 140 kV, tube current 200 Ma, slice thickness 3.75 mm. 3D brain PET acquisitions were performed 15 min after whole brain CT scan. Two experienced PET/CT diagnosticians performed double-blind film reading and confirmed that metabolic changes (hypometabolism or hypermetabolism) on two or more consecutive levels were abnormal lesions. These z-scores were calculated by statistically comparing each voxel of the brain between the patients and the normal database. Mean z-scores ≥ 2.00 in brain regions were considered significant.

Intracranial video EEG monitoring

Intracranial Video EEG (IVEEG) monitoring was performed when noninvasive data showed non-concordant clinical findings or assumed that the EZ was adjacent to the functional area. Different combinations of a platinum 1 × 8 strip electrode and an 8 × 8 grid electrode (AdTech Medical Instrument Corporation, Racine, WI, USA) were used to complete the IVEEG. Eleven patients underwent IVEEG monitoring for 5 to 12 days (average: 8 days; EEG: 9,200 K; Nihon Kohden, Tokyo, Japan).

ECS and ADs

ECS was performed after recording more than two habitual seizures. Fifty Hz biphasic stimuli with 0.2 ms pulse duration and 2 mA to 20 mA amperage thresholds were used [10]. At each electrode, electrical pulses were given at an initial intensity of 2 mA, and then increased in increments of 1 mA to 2 mA for each subsequent stimulation until a maximum of 20 mA was reached or a functional response was received from the patient. The trials were repeated 2 to 3 times, depending on the patient's condition. ADs were recorded following stimulation. The ADs were defined as continuous epileptiform discharges lasting longer than 4 s after the cessation of stimulation. The percentage of stimulated electrodes provoking ADs,

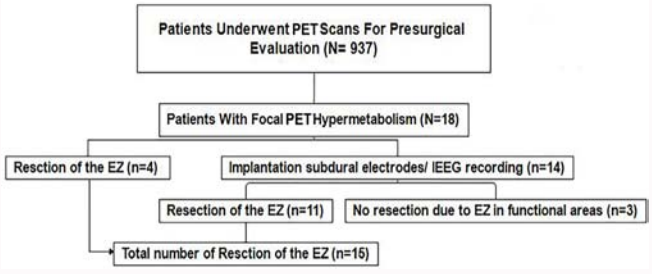

Figure 1: Study profile.

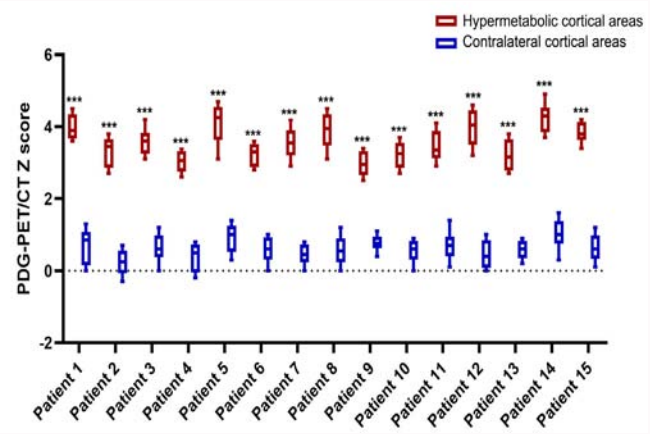

Figure 2: Z-score box plot of glucose metabolism in different cortical regions. Comparisons of standardized z scores between focal cortical hypermetabolic lesions (red) and the contralateral same cortical region (blue) in 15 patients. Box plots with the median for each cortical region. Multiple *t*-tests were used for statistical analyses.
***P<0.0001

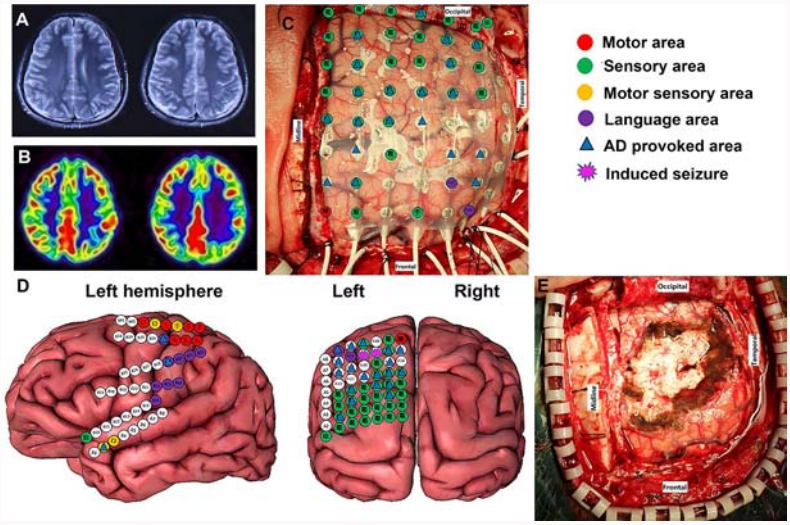

Figure 3: An 18-year-old female with interictal Positron Emission Tomography (PET) hypermetabolism in the left parietal lobe (patient 12). Axial magnetic resonance imaging T2-weighted images were negative in the patient's cortex (A). A PET-computed tomography fusion image showed local hypermetabolism in the left parietal lobe (B). Intraoperative photos showed the position of the subdural electrode used for extraoperative electrical stimulation mapping (C), three-dimensional models showed the structure using preoperative electrical stimulation diagrams to locate motor areas sensory areasmotor sensory areas language areas, and epileptogenic zones (D). After mapping the epileptogenic zone, the second surgery was performed to completely remove the epileptogenic zone (E).

the amperage threshold (mA), amplitude (mV), and duration (s) of ADs in the hypermetabolic and normal cortex were compared and analyzed. Informed consent forms were signed by patients or legal guardians of patients prior to cortical stimulation.

Surgical procedures

Surgical procedures were performed under general anesthesia. After noninvasive investigation, patients with hypermetabolic lesion-related epilepsy were surgically treated according to the location of the hypermetabolic lesion. Resection after invasive study was performed according to the following criteria: (1) The EZ was completely removed when the EZ was adjacent to the functional area of the cerebral cortex; (2) when the EZ and the functional area of the cerebral cortex partially overlapped, if the overlapping cortex was not a fine motor or language area, the EZ was completely removed; if the overlapping cortex was a fine motor or language area, the overlapping cortex was cauterized locally, and the remaining EZ was completely removed; (3) when the EZ and the functional area of the cerebral cortex mostly overlapped, the non-overlapping area was removed and the overlapping cortex was cauterized locally.

Statistical analysis

Data are expressed as the mean ± SD. Statistical analyses were performed using Prism 8.0 (GraphPad, San Diego, CA, USA). Multiple *t*-tests were used to compare the PDG-PET/CT Z scores of different patients (Figure 1). Student's *t*-tests or Fisher's exact test were used to analyze the clinical characteristics and prognosis data of patients with focal PET hypermetabolism (Figure 5). Statistical significance was based on a value of $p<0.05$.

Results

A total of 937 patients with refractory epilepsy underwent FDG-PET scans during preoperative evaluations. A total of 18 patients (2.2%) showed local hypermetabolism using interictal PET. A total of

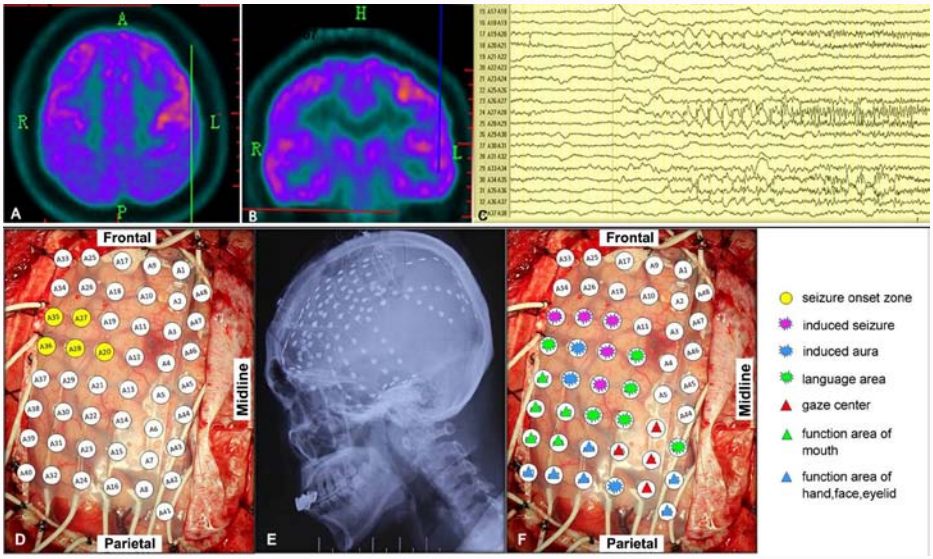

Figure 4: A 12-year-old male with interictal Positron Emission Tomogarphy (PET) hypermetabolism in the left frontal lobe (patient 5). PET imaging (A, axial; B, coronal) showed moderate hypermetabolism in the posterior middle and inferior frontal gyrus of left frontal lobe. Ictal iEEG monitoring (C) demonstrated a very focal seizure onset zone, which was concordant with the PET hypermetabolism zone (sites A20, A27–28, and A35–36). Subdural grids (D), yellow sites represent the seizure onset zone, X-ray film (E), to determine the position of the electrodes, and the result of electrical cortical stimulation (ECS) foci (F), the area with ECS-induced auras and seizures overlapped with the seizure onset zone, and was also adjacent to the Broca area.

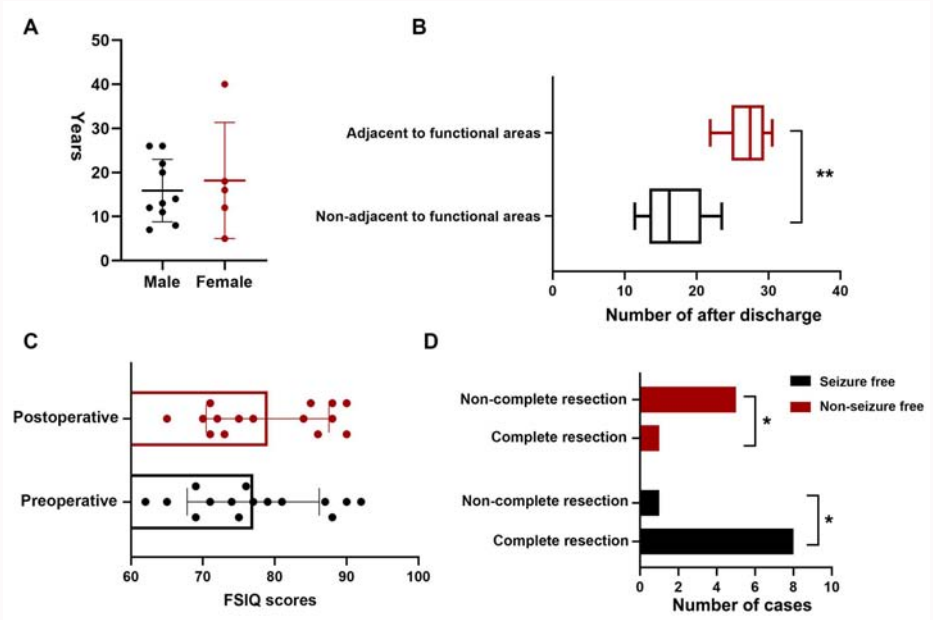

Figure 5: Clinical characteristic and effectiveness outcomes. There was no significant difference in age between patients of different sexes with interictal Positron Emission Tomography (PET) hypermetabolism (A), and there was no difference in the Full-Scale Intelligence Quotient score before and after surgery (C). The probability of inducing AD was higher in patients with PET hypermetabolic lesions adjacent to the functional area than in patients with PET hypermetabolic lesions not adjacent to the functional area (B). The probability of being seizure-free after complete Epileptogenic Zone (EZ) resection was significantly higher than that of the incomplete EZ resection (D).
*p<0.05; **p<0.001

15 epileptic patients who underwent cortical resection were included in this retrospective study (Figure 1). The average age of the study population was 16.67 years (range: 5 to 40 years, Table 1), and the majority of patients were male (n=10, p>0.05, Figure 1A). Fifteen patients had high metabolism in local cortical areas (median Z: 3.55, IQR: 1) compared to the corresponding normal cortical areas (median Z: 0.58, 1, p<0.0001, Figure 2). The preoperative seizure type of 13 patients involved generalized tonic-clonic seizures (86.7%), and two patients showed complicated partial seizures (13.3%) (Table 1). Eight patients had abnormal brain MRI parenchymal signals, and seven patients had negative MRI examinations (Table 2). There was one case with interictal EEG results consistent with abnormal MRI lesions. Ictal EEG results were consistent with MRI abnormal lesions in three patients. Ictal EEG results were consistent with interictal PET hypermetabolic areas in five patient cases (Table 2). Eleven patients underwent intracranial Electroencephalogram (iEEG) monitoring.

Table 1: Presurgical clinical features.

Pat/sex	Age at epilepsy onset	Age at surgery	Duration of epilepsy	Seizure baseline	Seizure semiology	Medication options	FSIQ preoperative
1F	3 years	12	9 years	3-5/week	GTCS Asymmetric tonic	4 AEDs tried	74
2M	7 years	26	19 years	1-3/day	GTCS automatism	6 AEDs tried	90
3F	5 years	40	35 years	4-7/week	GTCS Asymmetric epileptic	7 AEDs tried	79
4F	1st week of life	5	5 years	1-2/day	Asymmetric epileptic	5 AEDs tried	77
5M	2 years	12	10 years	3-6/week	GTCS Head deviation to the R Myoclonic jerks (R arm)	4 AEDs tried	81
6M	2 years	7	5 years	1-3/day	GTCS Asymmetric tonic	4 AEDs tried	69
7M	1st month of life	8	8 years	3-4/week	GTCS Hypermotor	3 AEDs tried	65
8M	2 years, 6 months	26	24 years	4-7/week	Asymmetric tonic Head deviation to the L	6 AEDs tried	88
9F	5 years, 6 months	16	11 years	1-3/day	GTCS Head deviation to the R Myoclonic jerks (R arm)	4 AEDs tried	75
10M	1 year	20	19 years	2-3/week	GTCS Asymmetric tonic	5 AEDs tried	92
11M	2 years	11	9 years	4-5/week	GTCS automatism	4 AEDs tried	71
12F	4 years, 3 months	18	14 years	1-2/day	GTCS automatism	4 AEDs tried	87
13M	2 years, 8 months	14	12 years	3-5/day	GTCS Asymmetric tonic	5 AEDs tried	62
14M	4 years	22	18 years	3-5/week	GTCS Asymmetric tonic	6 AEDs tried	76
15M	1 year, 5 months	13	12 years	2-4/week	GTCS Myoclonic jerks	4 AEDs tried	68

F: Female; M: Male; GTCS: Generalized Tonic-Clonic Seizures; R: Right; L: Left; AEDs: Antiepileptic Drugs

Table 2: MRI, EEG and seizure localizations.

Patient	MRI	Ictal EEG	Interictal EEG	PET hypermetabolism	Intracranial EEG monitoring	Concordance between PET hypermetabolism and EZ	Whether EZ is adjacent to functional areas	Locating the EZ with ADs
1	LFL LHS	Bilateral	LFL	LFL	Yes	Almost	No	Yes
2	RFL	Frontal	N/A	RFL	No	Yes	No	No
3	LHS	Hemispheric	LFL	LFL	Yes	Yes	No	Yes
4	N/A	N/A	ROL	ROL	Yes	Yes	Yes	Yes
5	N/A	Bilateral	LFL	LFL	Yes	Almost	Yes	Yes
6	RFL	Frontal	N/A	RFL	No	Yes	Yes	No
7	N/A	Frontal	RPL	RPL	Yes	Almost	No	Yes
8	N/A	Frontal	RFL	RFL	Yes	Yes	Yes	Yes
9	N/A	Hemispheric	LFL	LFL	Yes	Yes	Yes	Yes
10	RHS	N/A	RFL	RFL	Yes	Almost	No	Yes
11	LPL	Hemispheric	N/A	LPL	No	Yes	Yes	No
12	N/A	Bilateral	LPL	LPL	Yes	Almost	Yes	Yes
13	N/A	Bilateral	RPL	RPL	Yes	Yes	Yes	Yes
14	LHS	Hemispheric	LFL	LFL	Yes	Most	No	Yes
15	LFL	Frontal	N/A	LFL	No	Yes	No	No

LFL: Left Frontal Lobe; HS: Hippocampal Sclerosis; RFL: Right Frontal Lobe; LPL: Left Parietal Lobe; RPL: Right Parietal Lobe; ROL: Right Occipital Lobe; LOL: Left Occipital Lobe

After multiple extraoperative electrical stimulation mapping, the EZ of these patients was determined and secondary surgical resection was performed (Figure 3). The interictal PET hypermetabolic areas and EZs of nine patients were completely consistent. The EZs of eight patients were adjacent to the functional area (Figure 4). A total of 819 electrodes were analyzed in 11 patients who underwent extraoperative electrical stimulation mapping. The process of iEEG and the location of electrodes provoking ADs are shown in Figure 3. In brain lobes with focal hypermetabolism, 182 electrodes (22.2%) induced AD, and the sites directly producing AD were common in the centers of the focal hypermetabolic regions. The percentages of electrodes inducing AD in the hypermetabolic lobes of 11 patients were 16.2%, 23.5%, 26.3%, 30.5%, 17.8%, 29%, 25.8%, 15.4%, 28.6%, 21.9%, and 11.4% (Table 3). Compared with patients with interictal PET hypermetabolic

Table 3: Summary of ADs elicited in PET hypermetabolism regions.

Patient	Total No. of Stimulated Electrodes	No. of Stimulated Electrodes With AD	Amperage Threshold (mean), mA	Mean of duration, s	Mean of amplitude, μV	Percentage of stimulated electrodes provoking AD (%)
1	74	12	11.6	21.36	263.68	16.2
2	N/A	N/A	N/A	N/A	N/A	N/A
3	68	16	11.3	12.08	426.79	23.5
4	72	19	12.3	8.63	232.87	26.3
5	82	25	13	26.67	356.12	30.5
6	N/A	N/A	N/A	N/A	N/A	N/A
7	90	16	13.1	13.6	386.23	17.8
8	62	18	11.2	10.72	153.68	29
9	58	15	14.2	35.24	536.75	25.8
10	84	13	12.8	6.52	417.49	15.4
11	N/A	N/A	N/A	N/A	N/A	N/A
12	77	22	13.5	16.47	126.4	28.6
13	82	18	14.8	9.35	157.36	21.9
14	70	8	12.2	15.82	382.43	11.4
15	N/A	N/A	N/A	N/A	N/A	N/A

Table 4: Surgical Variables, histopathology, and postsurgical findings.

Patient	Surgery	Resection of the EZ	FSIQ postoperative	Histological examination	Follow-Up duration (months)	Surgical Outcome (ILAE)
1	LFR	ACR	75	FCD	49	2
2	RFR	CR	88	FCD	78	1
3	LFR	ACR	72	Gliosis	126	3
4	ROR	CR	85	FCD	60	2
5	LFR	ACR	86	FCD	48	1
6	RFR	CR	73	Gliosis	64	1
7	RPR	CR	77	MCD	58	1
8	RFR	ACR	88	FCD	39	2
9	LFR	SR	71	FCD	36	3
10	RFR	CR	90	Low-Grade Tumors	56	1
11	LPR	ACR	84	FCD	132	1
12	LPR	CR	90	Gliosis	138	2
13	RPR	CR	71	Gliosis	90	1
14	LFR	CR	65	MCD	86	1
15	LFR	CR	70	FCD	59	1

LFR: Left Frontal Resection; RFR: Right Frontal Resection; LPR: Left Parietal Resection; RPR: Right Parietal Resection; LOR: Left Occipital Resection; ROR: Right Occipital Resection; CR: Complete Resection; ACR: Almost Complete Resection; SR: Subtotal Resection; FCD: Focal Cortical Dysplasia; MCD: Malformations of Cortical Development

lesions not adjacent to functional areas, patients with interictal PET hypermetabolic lesions adjacent to functional areas, especially the motor areas, had a higher probability of inducing AD ($p<0.01$, Figure 5B). The ranges of ampere threshold (mA), amplitude (mV), and duration(s) in the PET hypermetabolism regions of 11 patients that induced AD were 11.6–14.8, 126.4–426.79, and 6.52–35.24, respectively (Table 3). Of the 15 epilepsy patients who underwent resection of focal hypermetabolic lesions, 10 were frontal lobectomy, four were parietal lobectomy, and one was occipital lobectomy (Table 4). Among them, the epileptic foci of nine patients were completely resected, five patients were almost completely resected, and one patient was mostly resected. The high metabolism lesions were identified by postoperative pathology involving eight cases of cortical dysplasia, two cases of cortical malformation, four cases of glioma, and one case of low-grade glioma (Table 4). There was no difference between preoperative and postoperative FSIQ scores ($p>0.05$, Figure 5C). After surgery, one patient had a transient decrease of muscle strength of the contralateral limb, and one patient had mixed aphasia, all of which recovered after treatment. Efficacy evaluation of patients followed up for 3 to 11 years involved nine (60%) patients with class I, four (26.7%) patients with class II, and two (13.3%) patients with class III. The seizure-free incidence was significantly higher in the complete resection group than in the incomplete resection group, and the non-seizure-free rate in the incomplete resection group was significantly higher than that in the complete resection group ($p<0.05$; Fisher's exact test) (Figure 5d).

Discussion

During the interictal phase, epilepsy lesions showed reduced radioactivity in 18F-FDG PET brain imaging, while the same region

showed increased metabolism and concentrated radioactivity during the ictal phase [11]. Epilepsy specialists often use the local cortical hypometabolism during the interictal period to determine the location of epileptogenic foci [12], because the images of seizure period are usually difficult to obtain and the epileptogenic foci are highly metabolized only in special cases such as status epilepticus. Intertical PET hypometabolism appears very sensitive in localizing epileptic foci [13]. PET scans are a kind of functional imaging, and its advantage in the presurgical evaluation in epilepsy is obvious compared to structural imaging like MRI. These are sometimes even more sensitive than sEEG in special seizure types [15]. Interictal PET hypermetabolism occupied a very small proportion in different types of pathological epilepsy cases [15]. In our study, seven patients with interictal PET hypermetabolism were negative using MRI. There have only been a small number of cases, and case reports have reported interictal PET hypermetabolism and have been MRI negative [13,16]. In our study, frontal and parietal lobes were the most common sites of hypermetabolism, which were similar to previous studies [17]. We found that the main pathological features of PET hypermetabolic lesions were focal cortical dysplasia and malformations of cortical development. We used a lower spike count cut off of ≥ 10 per min, because this allowed greater sensitivity to assess the relationship of PET hypermetabolism with epileptogenicity. Bansal et al. found that the number of spikes in the interictal period was more than 10 spikes/min in most intractable epilepsy children with interictal PET hypermetabolism [17]. Lee et al. [18] found that some epileptic patients with Rasmussen encephalitis showed hypermetabolic foci in the interictal period, while EEG monitoring showed frequent interictal abnormal discharges during FDG uptake. We speculated that the cause of hypermetabolic foci in the brain was more dependent on the degree of electrical activity of epileptic foci, and not necessarily with clinical seizures. Of course, frequent seizures are the structural basis for the formation of an abnormal electrical activity network. The occurrence of hypermetabolic lesions may be related to frequent episodes, which needs to be confirmed in future studies. In the present study, frequent interictal spikes and polysipkes were found simultaneously by sEEG and iEEG, which may provide a reasonable explanation for the hypermetabolism of the cortex in an active state, and which is consistent with previous studies [19]. It is possible that interictal focal, frequent epileptic discharge and hypermetabolism may sufficiently localize the epileptic foci and may provide more favorable evidence for epilepsy surgery. PET imaging sometimes shows a dynamic state during a period, which may represent an imaging marker of different stages of the pathological process or state [7,20,21]. Hypermetabolism might indicate an early stage of inflammation or structural change, so a series of PET scans and MRIs should be conducted to thoroughly investigate this process. ECS for functional brain mapping is an important tool for neurosurgeons and neurologists in treating perirolandic epilepsy [22]. In our study, the hypermetabolic lesions of eight patients were anatomically proximal to the functional brain (i.e., motor, sensory cortex, and language areas). Removal of the entire epileptogenic focus is critical for the long-term, seizure-free outcome of patients with refractory epilepsy [8,23]. In our study, extraoperative electrical stimulation mapping was used to localize seizure foci and functional areas during the interim between electrode placement and resection, which was consistent with previous reports [8,2324]. Previous studies have shown that no matter if the cortical area causes spontaneous seizures, direct electrical stimulation of sufficient intensity to cause AD will lead to clinical seizures [25,26]. The initial characteristics of AD are similar to spontaneous seizures, but so far, there has been no conclusion on whether the site causing AD can cause seizures. Bernier et al. [27] reported that in 13 epileptic patients with single frontal lobe lesions, the consistency of seizure sites between spontaneous seizures and electrically induced seizures was 92%. Previous studies have also shown that ADs induced by cortical electrical stimulation can be generated inside or outside of focal epileptic foci [27-29]. We found that sites producing AD were common in the center of the PET hypermetabolic lesions, and the incidence of AD was higher when the hypermetabolic lesions were adjacent to the functional areas. ECS-induced auras or seizures can occur inside or near PET hypermetabolic lesions, which may be caused by new facilitatory pathways of hypermetabolic lesions in the surrounding brain areas. ECS-induced auras or seizures can occur inside or near PET hypermetabolic lesions, which may be caused by a new promotion pathway caused by hypermetabolic lesions in the surrounding brain area. Therefore, ECS-induced AD can help to accurately locate the EZ range in patients whose EZ range is larger than the PET hypermetabolic lesions.

In summary, the PET hypermetabolism region was closely related to the EZ. The PET hypermetabolism region combined with ECS accurately located the EZ, language, and motor areas, and provided guidance for the surgical resection range, as well as avoiding language and motor function damage as much as possible, while removing epileptic foci. In our study, iEEG confirmed that focal interictal PET hypermetabolism was concordant with the focal seizure onset zone, and ECS induced habitual auras and seizures also within the area. PET hypermetabolism and ECS-induced auras and seizures can therefore provide favorable evidence for epileptic foci, and help epileptologists make better surgical treatment decisions.

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