RESEARCH ARTICLE

Patterns of hypometabolism in frontal lobe epilepsy originating in different frontal regions

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Abstract

Objectives: Analysis of FDG-PET imaging commonly shows that hypometabolism extends into extra-epileptogenic zones (extra-EZ). This study investigates the distribution patterns of hypometabolism in frontal lobe epilepsy (FLE) originating in different frontal regions. **Methods:** Sixty-four patients with FLE were grouped by EZ localization according to Brodmann areas (BAs): Group 1 (the frontal motor and premotor area), BAs 4, 6, and 8; Group 2 (the inferior frontal gyrus and opercular area), BAs 44, 45, and 47; Group 3 (the dorsal prefrontal area), BAs 9, 10, 11, and 46; and Group 4 (the medial frontal and anterior cingulate gyrus), BAs 32 and 24. Regions of extra-EZ hypometabolism were statistically analyzed between FLE groups and healthy controls. Correlation analysis was performed to identify relationships between the intensity of hypometabolism and clinical characteristics. **Results:** Significant hypometabolism in the ipsilateral (Groups 1 and 4) or bilateral (Groups 2 and 3) anterior insulae was found. Groups 1 and 4 presented with limited distribution of extra-EZ hypometabolism, whereas Groups 2 and 3 showed widely distributed extra-EZ hypometabolism in the rectus gyrus, cingulate gyrus, and other regions. Additionally, the intensity of hypometabolism was correlated with epilepsy duration in Groups 2 and 3. **Conclusions:** All FLE groups showed hypometabolism in the anterior insula. In addition, distinct patterns of extra-EZ hypometabolism were identified for each FLE group. This quantitative FDG-PET analysis expanded our understanding of the topography of epileptic networks and can guide EZ localization in the future.

Introduction

Frontal lobe epilepsy (FLE) is characterized by rapid and complex seizure propagation,[1] accounting for nearly 22.5% of the focal epilepsy[2,3] and is the second most common focal epilepsy.[4] There are abundant structural and functional connections both within the frontal lobe and projecting into other brain regions.[5–7] Seizures originating in the same area of the frontal lobe can propagate multidirectionally, resulting in the expression of various semiologic phenotypes.[8] However, highly similar semiologic manifestations can be produced by seizures originating from different frontal regions.[9,10] Therefore,

localization of the epileptogenic zone (EZ) in FLE based purely on electroclinical features can pose a considerable challenge without supporting imaging findings.[11] Moreover, a range of 43%–55% of FLE patients show normal MRI findings despite the utility of advanced MRI post-processing techniques,[12–15] thus increasing the difficulty of accurately localizing the EZ.

Analysis of interictal hypometabolism using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is routinely performed in preoperative evaluations of intractable epilepsy for MRI-negative or inconclusive patients and is an informative tool for identifying potential EZs in conjunction with other findings.[16] Previous studies

have revealed that hypometabolism can extend beyond the boundary of the EZ (i.e., extra-EZ hypometabolism),[17–19] regardless of whether it originated in the frontal, temporal,[20] parietal, or occipital lobes.[21] In cases of widely distributed extra-EZ hypometabolism, the difficulty of EZ localization considerably increases with negative or inconclusive MRI findings, leading to misdiagnosis. In addition, the distribution patterns of this extra-EZ hypometabolism can differ greatly among different categories of localization-related epilepsy. For example, mesial[22,23] and neocortical temporal lobe epilepsies[19,24] show different patterns of extra-EZ hypometabolism. Specifically, mesial temporal lobe epilepsy is more likely to present with ipsilateral anteromesial temporal hypometabolism, whereas in lateral temporal lobe epilepsy, hypometabolism displays in the ipsilateral temporal lobe avoiding the mesial temporal cortex.[24] Thus, distinct hypometabolic patterns can be clinically useful to differentiate mesial temporal lobe epilepsy from lateral temporal lobe epilepsy.

It should be noted that previous studies investigating the distribution of hypometabolism in FLE have shown inconsistent findings.[18,19] These discrepancies are likely due to an inability to distinguish between FLE originating in different frontal regions. Previous interictal FDG-PET studies, validated by stereoelectroencephalography (SEEG), have reported that temporal lobe epilepsies with EZs localized in different temporal regions are associated with specific patterns of extra-EZ hypometabolism, suggesting that the topography of interictal hypometabolism may be related to the specific neuronal networks involved in ictal discharge and spread pathways.[24] Hence, we speculate that epilepsies originating from different frontal regions also have different patterns of extra-EZ hypometabolism, and the characterization of the distinct hypometabolic patterns associated with EZs localization may provide insight into networks which may be responsible for FLE. Additionally, clinical characteristics, such as duration of epilepsy, can also potentially impact hypometabolic patterns,[19] and several studies have shown that extra-EZ hypometabolism is a consequence of prolonged seizure attacks and reflects extension of the epileptic network.[25,26] Here, we used quantitative FDG-PET analysis to explore the distribution of hypometabolism in a cohort of patients with focal epilepsy localized in different frontal regions. The relationship between the extra-EZ hypometabolism and clinical characteristics was also investigated.

Materials and Methods

Study design and participants

We retrospectively reviewed 406 consecutive patients with focal pharmaco-resistant epilepsy from our epilepsy center

between January 2012 and December 2019. A total of 64 patients fulfilled the following inclusion criteria: (a) negative or inconclusive abnormalities in conventional MRI; (b) focal epilepsy with well-localized EZ in the frontal lobe, based on seizure history, electroclinical findings, and neuroimaging information. The exclusion criteria included: (a) generalized epilepsy, multifocal epilepsy, or non-localizable epilepsy; (b) the presence of extensive cerebral lesions such as multiple cortical dysplasia, explicit tumor, or vascular malformations which were directly referred to surgery, and FLE with stroke or encephalitis lesions in the frontal lobe; (c) FDG-PET images with artifacts due to head movement or insufficient uptake of glucose; (d) FLE cases in which FDG-PET scanning was not performed. This study was approved by the Human Subject Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University and was registered in the ClinicalTrials.gov Protocol Registration and Result System (No. NCT04642573).

Long-term video-EEG monitoring was performed using digital EEG systems (Nicolet, VIASYS, USA and Biologic, NATUS, USA) with scalp electrodes placed according to the international 10/20 system. Medications were reduced or stopped (if necessary) to capture habitual seizures. We analyzed the clinical semiology patterns of each individual based on seizures recorded during Video-EEG. All seizures were categorized according to Bonini et al.'s semiologic classification[27]: Type 1, elementary motor signs; Type 2, elementary motor signs and nonintegrated gestural motor behavior; Type 3, integrated gestural motor behavior with distal stereotypies; and Type 4, integrated gestural motor behavior with fearful behavior (Table 1). The video-EEG data were interpreted by at least two experienced electroencephalographers. Interictal epileptiform discharges were classified as regional (restricted to a single lobe or in two contiguous regions, such as the centroparietal region) or non-regional (multi-lobar, hemispheric, or generalized)[28] according to video-EEG findings.

Weekly multidisciplinary patient management conferences included discussion of seizure localization and treatment strategy, and recommendations were made for resective surgery, SEEG evaluation, neuromodulation, and/or continuing pharmacological treatment. Surgical outcomes were scored using Engel classification[29] if the patients' follow-up duration was more than 2 years.

FDG-PET acquisition and image processing

Brain FDG-PET images were acquired by a PET/CT scanner (Biograph mCT, Siemens Medical Solutions; Malvern, PA, USA) at 30 min after intravenous (i.v.) injection of ^{18}F-fluorodeoxyglucose (3.7 MBq/kg). Patients were fasted

Table 1. Demographic and clinical information of the patients.

Clinical characteristics	Total	Group 1 (*n* = 20)	Group 2 (*n* = 19)	Group 3 (*n* = 18)	Group 4 (*n* = 7)	*p*
Gender (M/F)	35/29	14/6	11/8	8/10	2/5	0.198
Onset age (median; IQR, years)	8;3–14	6;3–15	9;4–12	5;2–10	17;8–19	0.100
Epilepsy duration (median; IQR, years)	5;2–12	6;2–11	5;2–23	5;1–13	3;1–10	0.678
PET scanning age (median; IQR, years)	14;9–24	16;8–27	12;9–34	12;6–20	18;12–24	0.439
Semiologic types	Type 1:2:3:4	19:0:1:0	5:7:3:4	4:4:8:2	0:1:1:5	
FBTCS (Yes/No)	19/45	6/14	6/13	4/14	3/4	0.747
EEG interictal discharges	53	16	19	13	5	0.070
Regional	42	10	16	11	5	
Non-regional	11	6	3	2	0	
EEG normal	11	4	0	5	2	
Seizure frequency						0.297
Daily/weekly	43	12	12	14	5	
Monthly	21	8	7	4	2	
Pathology	41	16	10	9	6	0.367
FCD I	8	3	2	2	1	
FCD II	25	9	8	5	3	
Other pathology	8	4	0	2	2	
Engel classification						0.226
Ia	37	15	10	8	4	
II–IV	4	1	0	1	2	

IQR, interquartile range, 25%–75%; PET, positron emission computed tomography; FBTCS, focal to bilateral tonic–clonic seizures; FCD, focal cortical dysplasia; EEG, electroencephalography.

for 6 h and had no seizures for at least 24 h prior to the scans. The same protocol was used on 30 age- and sex-matched healthy volunteers who served as control subjects. The images of patients whose EZ located on the left hemisphere were flipped to the right side to provide a uniform data set, as described in previous FDG-PET studies.[30,31] Spatial preprocessing was performed as previously described, using the Statistical Parametric Mapping software package (SPM 12 version, Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB. Individual FDG-PET scans, including healthy control (HC) scans, were normalized to the PET MNI (Montreal Neurological Institute, McGill University, Canada) brain template and smoothed by convolution with a 10 mm full width half-maximum Gaussian kernel.

Group analysis of FDG-PET images

We then classified all recruited patients into four groups by EZ localization within Brodmann areas (BAs)[32,33] (Fig. 1). Group 1 included BAs 4, 6, and 8 (the frontal motor and premotor area); Group 2 included BAs 44, 45, and 47 (the inferior frontal gyrus and opercular area); Group 3 included BAs 9, 10, 11, and 46 (the dorsal prefrontal area); Group 4 included BAs 32 and 24 (the medial frontal gyrus and anterior cingulate gyrus). Statistical Parametric Mapping (SPM) analysis was then applied to

all patient groups (i.e., Groups 1 through 4) and the HC group to screen for extra-EZ hypometabolic patterns in each FLE group,[19] using age and gender as covariates. We further generated regions of interest (ROIs) for statistical analysis based on the AAL template,[34] and the average intensity of hypometabolism was quantified in each selected ROI for all patient groups.

Statistics

Basic statistical analyses were performed in SPSS 23 for Kruskal–Wallis tests (ordered data or non-normally distributed continuous variables), Pearson chi-square tests (non-ordered categorical data), or the Fisher's exact probability method. We set the consecutive significant hypometabolic cluster size above 60 voxels in SPM-t map imaging and corrected for family-wise error (FWE) with $p < 0.05$. Correlation analysis was used after group comparison to identify significant associations between hypometabolism in the ROIs and clinical information.

Results

Demographic information

Sixty-four patients (M/F: 35/29) met the inclusion criteria. The median age at seizure onset was 8 (IQR, 3–14)
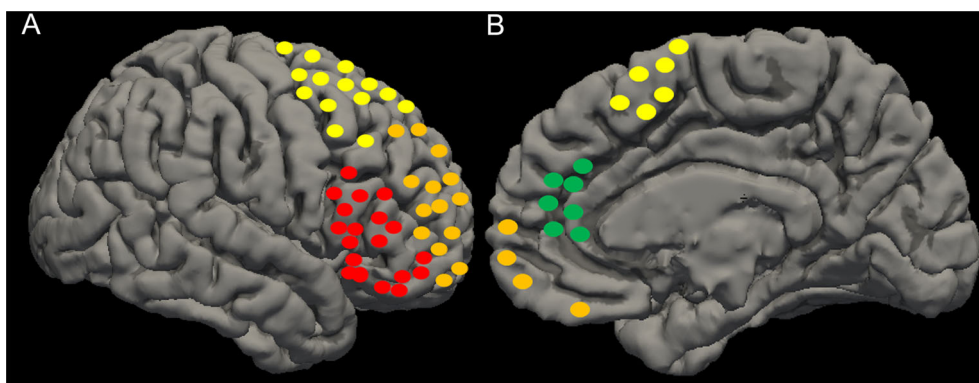
Figure 1. Localization of the epileptogenic zones in different frontal regions (A: lateral, B: medial). Group 1, the frontal motor and premotor areas (*n* = 20; BAs 4, 6, and 8; yellow); Group 2, the inferior frontal gyrus and opercular area (*n* = 19; BAs 44, 45, and 47; red); Group 3, the dorsal prefrontal area (*n* = 18; BAs 9, 10, 11, and 46; orange); Group 4, the medial frontal gyrus and anterior cingulate gyrus (*n* = 7; BAs 32, 24; green).

years; the median duration of epilepsy was 5 (IQR: 2–12) years. The median age of FDG-PET scan was 14 (IQR: 9–24) years. The patients in Group 1 and Group 4 predominantly demonstrated semiologic types 1 and 4, respectively, whereas the patients in Group 2 and Group 3 showed multiple semiologic types (Table 1). No significant differences were found among groups in the age at seizure onset, the age at FDG-PET scanning, epilepsy duration, the history of focal to bilateral tonic–clonic seizures (FBTCS), presence of interictal discharges, or seizure frequency. Post-surgical pathology included focal cortical dysplasia in 33 cases, non-specific findings in five patients, low-grade glioma in two patients, and encephalomalacia in one patient. The median post-surgical follow-up duration was 2.5 (IQR:1–7) years. Thirty-seven patients had an Engel class Ia outcome, four patients were classified into Engel class II-IV.

Distribution of hypometabolism in different FLE localizations

Group-level SPM analysis indicated that all four FLE groups presented with hypometabolism in the anterior insula (Fig. 2). Hypometabolism was present in the ipsilateral anterior insula in Group1 and Group 4, and in the bilateral anterior insulae in Group 2 and Group 3. Notably, the hypometabolic clusters in bilateral anterior insulae of Group 2 and Group 3 were 4–7 times larger than those in Group 1 and Group 4. The largest anterior insula hypometabolic cluster was found in Group 2 (Table 2).

Group 1 and Group 4 presented with limited extra-EZ hypometabolism. Group 1 exhibited only one cluster of extra-EZ hypometabolism in the ipsilateral anterior insula. Group 4 had a limited number of extra-EZ hypometabolic clusters in the bilateral orbital superior frontal gyri (oSFG) and ipsilateral anterior insula. By contrast,

Group 2 and Group 3 showed a wider extra-EZ distribution of hypometabolic clusters, including in the bilateral anterior insulae, bilateral anterior cingulate gyri (ACG), and rectus gyri (Fig. 2, Table 2). Additionally, Group 2 showed hypometabolism in the bilateral middle frontal gyri (MFG), superior frontal gyri (SFG), supplementary motor areas (SMA), medial cingulate gyri (MCG), and the precentral gyri (preCG). In Group 3, hypometabolic clusters were also observed in the bilateral orbital inferior frontal gyri (oIFG) and the ipsilateral putamen. The largest extra-EZ hypometabolic cluster was found in the ipsilateral MFG in Group 2 (Fig. 2, Table 2).

Correlation between intensity of hypometabolism and clinical features

We examined the relationships between clinical features and the average intensity of extra-EZ hypometabolism in the ROIs (as listed in Table 2) in each group. Epilepsy duration was significantly correlated with the average intensity of hypometabolism in several ROIs (Fig. 3), including the ipsilateral preCG, bilateral medial SFG, and MFG in Group 2, and bilateral IFG, contralateral ACG, and bilateral anterior insulae in Group 3. No significant correlations were identified between epilepsy duration and intensity of hypometabolism in any ROIs in Group 1 and Group 4. In addition, hypometabolic intensity in the ROIs was not significantly correlated with any other clinical features, including age at seizure onset, age at FDG-PET scanning, seizure frequency, interictal discharge, or FBTCS history.

Discussion

FDG-PET is a sensitive method for localizing EZs and provides relevant information to complement MRI.[9]
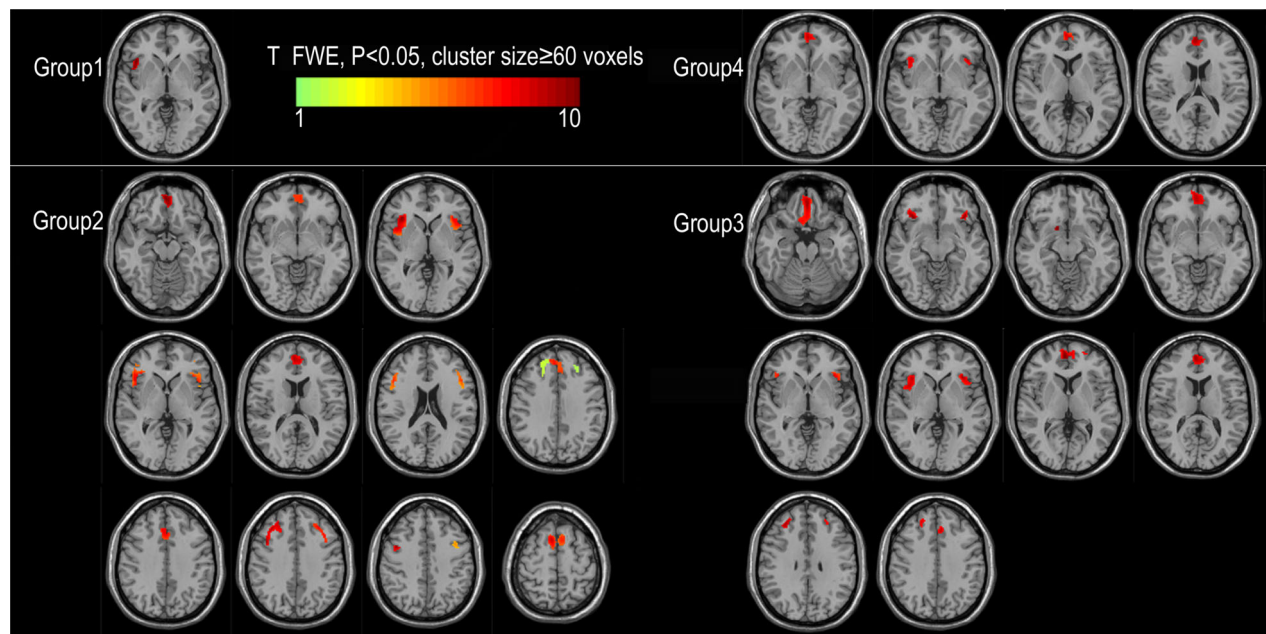
Figure 2. Characteristics of extra-EZ hypometabolism in FLE groups (Groups 1 to 4) compared with healthy controls. Extra-EZ hypometabolism in the anterior insula is commonly found in all four FLE groups. Groups 1 and 4 presented with limited extra-EZ hypometabolism, whereas the hypometabolic distribution was extensive in Groups 2 and 3.

Table 2. Distribution of extra-EZ hypometabolism in FLE patient groups compared with healthy controls.

Group	Hypometabolic brain regions	Cluster ke (voxels)	Peak *t* valve
Group 1	ipsi INS[2]	64	6.0901
Group 2	ipsi/cont MFG[1,3]	703/325	6.8578/7.065
	ipsi[2]/cont INS	445/185	9.4694/7.5755
	ipsi/cont mSFG	361/432	8.4259/6.3249
	ipsi/cont oSFG	378/128	8.4259/6.2782
	ipsi/cont SMA[3]	373/364	8.7916/6.833
	ipsi/cont SFG	252/64	8.4259/5.8705
	ipsi/cont ACG	177/176	7.2042/6.2076
	ipsi/cont MCG[3]	137/60	8.2807/6.0388
	ipsi/cont RECT	67/88	6.303/6.3264
	ipsi/cont preCG[3]	67/85	6.9401/6.3522
Group 3	ipsi[2]/cont INS	306/174	6.9015/7.5262
	ipsi/cont RECT	213/255	7.6968/7.4819
	ipsi/cont ACG	224/241	7.1405/6.2215
	ipsi/cont oIFG	153/111	6.9016/7.5227
	ipsi putamen[3]	60	6.3188
Group 4	ipsi/cont oSFG	61/67	5.7917/4.8583
	ipsi INS[2]	60	5.855

ipsi, ipsilateral; cont, contralateral; INS, insular; MFG, middle frontal gyrus; SMA, supplementary motor area; SFG, superior frontal gyrus; mSFG, medial superior frontal gyrus; oSFG, orbital superior frontal gyrus; ACG, anterior cingulate gyrus; MCG, median cingulate gyrus; RECT, rectus; preCG, precentral gyrus; oIFG, orbital inferior frontal gyrus; PUT, putamen.
[1]The largest cluster across groups.
[2]The hypometabolic region common to all groups.
[3]Affected brain regions unique to a group.

Hypometabolism often extends into extra-EZ regions, which may cause overestimation of EZ and even false localization.[19,20,23] However, the EZ and extra-EZ hypometabolic regions may both participate in the epileptic network.[19,26] In FLE, the ictal semiology is complex and the corresponding seizure propagation

The significant correlation between intensity of hypometabolism in ROIs and epilepsy duration
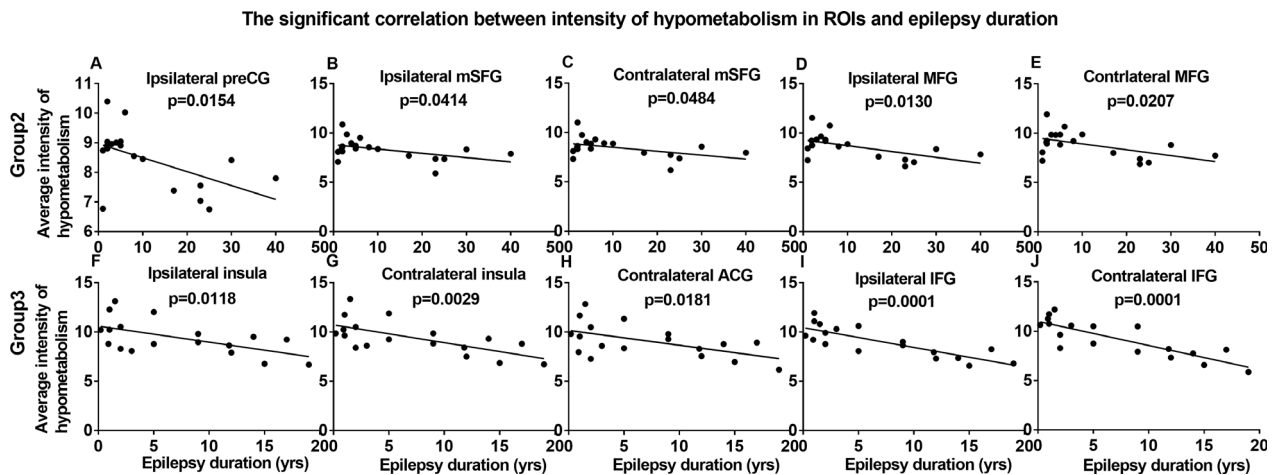

Figure 3. Analysis of regions of interest (ROIs) shows a significant correlation between average intensity of extra-EZ hypometabolism and epilepsy duration in Groups 2 and 3. Statistical significance was determined by Pearson correlation test at a significance level of $p < 0.05$. preCG, precentral gyrus; mSFG, medial superior frontal gyrus; MFG, middle frontal gyrus; ACG, anterior cingulate gyrus; IFG, inferior frontal lobe.

pathways are diverse, reflecting potentially distinct epileptic networks.[27] Hence, hypometabolic patterns in FLE can differ depending on the frontal region in which they originated. However, visual analysis, which is routinely applied in clinical settings and in many studies,[16–18] can be subjective based on personal experience and not sufficiently sensitive to detect subtle metabolic changes. Ozdem et al. found that quantitative analysis of hypometabolism in FLE could more accurately characterize hypometabolism in the EZ areas versus extra-EZ areas compared with visual assessments.[35] Quantitative analysis of our data showed that epilepsy originating from different frontal regions had distinct extra-EZ hypometabolic patterns, and that hypometabolism intensity was correlated with the duration of epilepsy originating from the inferior frontal gyrus and opercular area (Group 2) and the dorsal prefrontal area (Group 3). Our study, therefore, expands our understanding of the epileptic networks in FLE and facilitates individualized analysis of metabolic changes in the future.

Hypometabolism is common in the anterior insula

In the current study, all FLE groups consistently exhibited hypometabolism in the anterior insula. In previous studies of insular epilepsy, the insular seizure semiology[36] could mimic that in either temporal lobe epilepsy[37] or FLE.[38] Additionally, in mesial temporal lobe epilepsy, the insula is also commonly involved; and hypometabolism in the anterior insula was found to be a predictive factor for long-term persistence of disabling seizures after anterior temporal lobectomy.[37,39] The anterior insula is also

closely involved in the generation of hyperkinetic and fearful behaviors, which are classical semiologic manifestations in FLE.[40,41] Here, the common hypometabolic region in the anterior insula shared among all FLE groups indicates a tight structural connection between different frontal regions and the anterior insula.[42] Diffusion tensor imaging study showed that the SFG, MFG, and IFG are connected to the bilateral dorsal anterior insulae, while the pars triangularis and pars operculum are connected to the ventral anterior insula.[43] In agreement with our findings, Rei et al. found close functional connections between different frontal regions and the anterior insula using cortico-cortical evoked potential and functional MRI.[44,45] Hence, the tight structural and functional connections between anterior insula and different frontal regions provide the bases for hypometabolism in the insula in each of the FLE groups. In addition, the opercular region, which is highly connected with the insula, is often involved in early seizure spreading in insular epilepsy,[46] which may explain why the largest anterior insular hypometabolism cluster was identified in Group 2 (defined by FLE originating in the inferior frontal gyrus and opercular area).

Different hypometabolism patterns associated with different FLE localizations

Extra-EZ hypometabolism outside of the anterior insula was also found in various cortical and subcortical regions. Previous research using integrated analysis of ictal SEEG and interictal FDG-PET has shown that different semiology types could be correlated with different hypometabolism patterns.[47–49] We found that epilepsy originating

from the frontal motor and premotor area (Group 1) mainly presented as elementary motor signs and only showed minimal extra-EZ hypometabolism in the ipsilateral anterior insula. Similarly, EZs in the medial frontal gyrus and anterior cingulate gyrus (Group 4) mainly manifested as integrated gestural motor signs with fearful behavior; in these cases, extra-EZ hypometabolism was limited to the oSFG and the ipsilateral anterior insula. In contrast, EZs in the inferior frontal gyrus and opercular area (Group 2) and in the dorsal prefrontal area (Group 3) presented with more widely distributed extra-EZ hypometabolism in the frontoparietal areas and subcortical region (the putamen). Correspondingly, multiple semiologies were found in Group 2 and Group 3. These semiologic manifestations in FLE were determined by localization of primary seizure propagation areas and epileptic networks using ictal SEEG analysis.[27] Similarly, other FLE studies showed that different epileptic networks are associated with different changes in interictal hypometabolism.[40,48] In patients with orbital frontal lobe epilepsy, SEEG recordings indicated that ictal seizures mainly propagating to the frontal region exhibit extra-EZ hypometabolism involving the ipsilateral ACG and anterior insula, while ictal seizures mainly propagating to the temporal region show extra-EZ hypometabolism only in the anterior insula.[48] Hence, different semiology types which reflect the different underlying seizure propagation and epileptic networks could be associated with distinct patterns of hypometabolism in FLE.

A relationship between the intensity of hypometabolism and epilepsy duration

Hypometabolic changes were also previously shown to be associated with various clinical factors.[19,25,26] For example, extensive cortical hypometabolism was demonstrated to be associated with frequent seizures in neocortical epilepsy.[50] History of FBTCS has been reported as an important predictor of more widespread hypometabolic changes in extratemporal lobe epilepsy.[19] In the current study, we recruited patients who were devoid of mass lesions in MRI to exclude the influence of hypometabolic changes induced by structural damage. Different from previous studies, we found that the intensity of hypometabolism was not significantly correlated with seizure frequency or FBTCS history in our FLE patients, although average intensity of hypometabolism was correlated with epilepsy duration in Group 2 and Group 3. This correlation has also been identified in mesial temporal lobe epilepsy patients.[23,50] Furthermore, an intracranial EEG study found that more areas with elevated epileptogenic index were involved as the epilepsy progressed in a cohort of temporal lobe epilepsy patients.[25] These clinical findings

suggest that pharmaco-resistant epilepsy is a progressive disorder in that the epileptic network gradually expands with prolonged epilepsy duration.

Limitations

Our study was retrospective and included a limited number of patients with accurately localized EZ; future work will examine these patterns in a broader cohort and potentially epilepsy involving other brain regions. Furthermore, the analytical method used here to identify different patterns of extra-EZ hypometabolism does not provide dynamic functional information, and further evidence in functional MRI and/or SPECT data is necessary to identify the underlying mechanisms for these patterns.

Conclusions

Hypometabolism in the anterior insula is common in all FLE patient groups. In addition, epilepsy originating from different frontal regions shows different patterns of extra-EZ hypometabolism. Our study expands the scope of our understanding of the epileptic networks involved in FLE originating in different regions. The current study can aid individualized analysis of hypometabolism helping for localization in FLE.

Author Contributions

Y.D and S.W contributed to the conception and design of the study. Z.X.Z, C.C, and C.M.H collected and analyzed the original data. H.L and S.W analyzed and interpreted the FDG-PET data and revised the manuscript. J.M.Z and Z.Z collected the surgical data. M.P.D provided the technique and material support. All authors contributed to drafting the paper and were involved in the approval of the final version.

Conflict of Interest

The authors declare no conflicts of interest.

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