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Epilepsy

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Positron emission tomography (PET) has a key role in the management of patients with focal epilepsy as a well-established, functional imaging modality. Especially among various PET agents to evaluate brain function, ^{18}F-fluorodeoxyglucose (FDG) has been widely used because it reflects neuronal activity and allows quantification of cerebral glucose metabolism using tracer kinetic modeling. In the management of patients with medically intractable epilepsy, FDG PET became a routine process to localize epileptogenic foci, particularly in cases of patients presenting with normal anatomic structures on magnetic resonance imaging (MRI). Recently, this pivotal role of FDG PET in presurgical evaluation had been challenged by high-quality MRI [1].

Despite this trend, the role of PET as a functional imaging modality in the management of patients with epilepsy seems secure in terms of both demonstrating the epileptogenic zones and better understanding of the neurobiology of epilepsy. FDG PET could provide useful information to localize the epileptogenic focus even in patients with medically intractable focal epilepsy who have unremarkable MRI scans [1]. To investigate neurochemistry, which is considered crucial in epileptogenesis and spread of epileptic activities, several PET tracers have been introduced and actively explored its feasibility in clinical practice [2]. Moreover, the introduction of an epoch-making experimental tool, a dedicated small animal PET scanner and animal model for epilepsy, has accelerated investigations to unveil secrets of epilepsy.

FDG PET

Surgical interventions would be an accepted treatment option to effectively alleviate seizures in approximately 20–30% of the patients with focal epilepsy who became resistant to antiepileptic drugs [3, 4]. Although the success rates of surgical interventions in patients with temporal lobe epilepsies reach almost 85% [5–8], those rates decrease 50% to 60% in patients with cortical origin epilepsies [9, 10]. In this regard, careful selection of eligible patients and precise localization of the epileptogenic zones are imperative to achieve

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E.E. Kim et al. (eds.), *Clinical PET and PET/CT: Principles and Applications*,
DOI 10.1007/978-1-4419-0802-5_12, © Springer Science+Business Media New York 2013

Table 12.1 Correct localization of MRI, 18F-FDG PET, and ictal SPECT

	Pathology (%)	Surgical outcome (%)
MRI	72	77
^{18}F-FDG PET	85	86
Ictal SPECT	73	78

(Modified from reference 12.15)

a seizure-free outcome and minimize side effects related with unsuccessful surgery, and thus meticulous presurgical evaluations including scalp electroencephalography (EEG) and various imaging studies are required.

FDG PET, as a noninvasive evaluation tool, has been reported to have high sensitivities with 60–90% in lateralizing temporal lobe epilepsy (TLE) [11]. On interictal FDG PET, the epileptogenic focus is usually seen as a hypometabolic area, which is considered to be seizure-related changes in the brain. The pathophysiologic basis of the hypometabolism remains elusive, but it has been suggested that the hypometabolism in the hippocampus may reflect the hippocampal neuronal loss, a histopathologic hallmark of medial temporal sclerosis [12].

In regard to the diagnostic performance of various imaging methods to localize the epileptogenic foci, sensitivities were varied between medial temporal lobe epilepsy and neocortical epilepsies [13]. The diagnostic performance for extratemporal neocortical epilepsy is not particularly high. Recently, the introduction of nuclear imaging analysis methods such as statistical parametric mapping (SPM) helped the localization of the epileptogenic foci with improved sensitivities [13]. In a previous study using SPM, we investigated the diagnostic performance of FDG PET in pediatric patients with TLE, and the introduction of SPM was found to be helpful for the localization of the epileptogenic zones [14].

The sensitivity of FDG PET was compared in a head-to-head fashion with MRI or ictal single-photon emission computed tomography (SPECT) using ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) or ethylene cysteinate dimer [15] (Table 12.1). Among 118 patients who were operated on for medial temporal and neocortical epilepsies and were followed up for more than one year, the sensitivity of FDG PET was 85%.

Diagnostic Performance of FDG PET in Medial Temporal Lobe Epilepsy

Medial temporal lobe epilepsy is well known for its pathologic diagnostic criteria of hippocampal sclerosis and/or atrophy. These hippocampal changes are easily found by the recent generation MRI machines. Both the quantitative and the qualitative MRI interpretation give similar diagnostic effectiveness for TLE with the MRI machines. In cases of hipppocampal changes clearly identified on MRI, FDG PET reveals equally well the epileptogenic zones in medial temporal lobe epilepsy (Fig. 12.1a).

The advanced equipment and acquisition methods such as 3-T MRI have increased the sensitivity of localization of epileptogenic zones. However, despite these advancements, MRI reveals no significant anatomic structures in the 20–25% of the patients with medically intractable epilepsy [16]. For those patients, FDG PET could provide useful data for lateralizing the lesion as well as the desirable location for an invasive scalp EEG recording. The use of FDG PET is reported to be cost effective, especially in patients with unremarkable MRI scans [11].

In brief, FDG PET is helpful mainly for three types of medial TLE. The first type is represented by patients with ambiguous sclerosis (Fig. 12.1b). In a few patients with medial TLE, hippocampal sclerosis is not prominent even on MRI with the most recent techniques. The 3-T MRI with fluid-attenuated inversion recovery (FLAIR) and multiple channel coils could identify relevant abnormalities only in 20% of patients with previously unremarkable MRI scans [1]. The second type is of bilateral sclerosis and/or atrophy (Fig. 12.1c). Quite a few confusing cases have been filed among 600 fully investigated epilepsy patients at our institution. The third type is represented by those patients with inherently normal MRI findings (Fig. 12.1d). FDG PET and ictal SPECT were found to be similarly effective at localizing epileptogenic zones in nonlesional (MRI-negative) medial temporal lobe epilepsy [17].

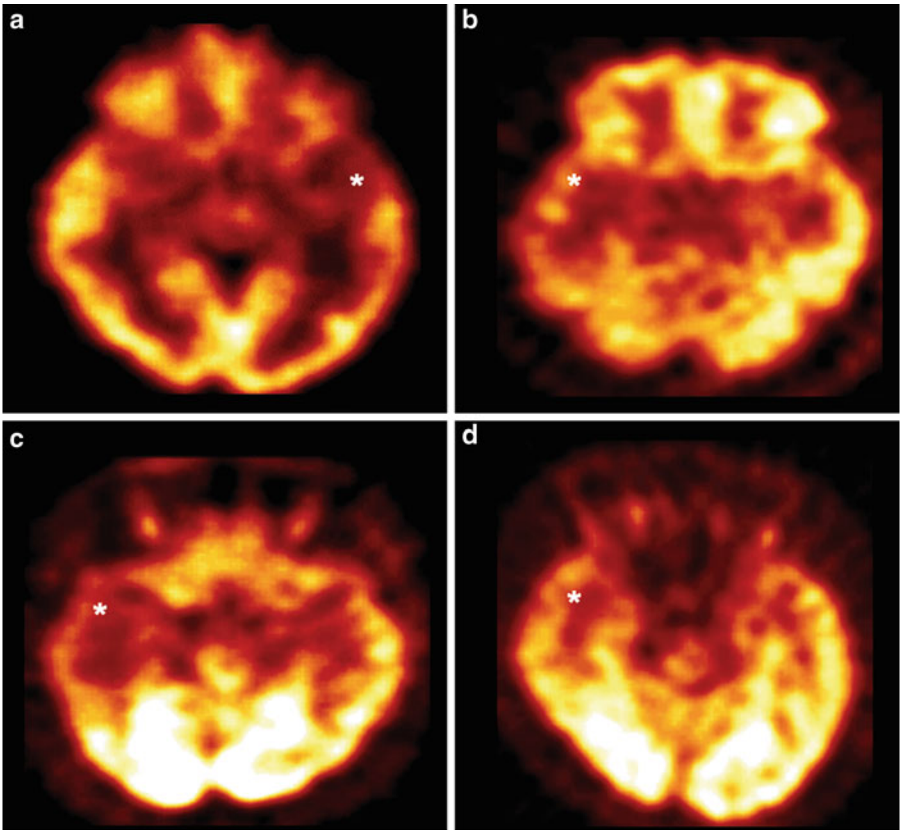

Fig. 12.1 Selected axial FDG PET images of lower brain for medial temporal lobe epilepsy. (**a**) A typical matching case with hippocampal atrophy and hypometabolism with decreased uptake of ^{18}F-FDG (*) in the left temporal lobe. (**b**) A case with ambiguous ictal EEG but with definite hypometabolism with decreased activity (*) in the right temporal lobe. (**c**) An example of bilateral hippocampal atrophy on MRI but unilateral hypometabolism (*) in the right temporal lobe. (**d**) A nonlesional cryptogenic case on MRI but with mild hypometabolism (*) in the right temporal lobe. All four patients underwent surgery with outcomes of Engel class 1

Diagnostic Performance of FDG PET in Neocortical Epilepsy

About one third to one half of medically intractable patients have neocortical epilepsy [18–20]. Neocortical epilepsy consists of lateral temporal, frontal, occipital, and parietal lobe epilepsy, in decreasing order of prevalence [19]. Neocortical epilepsy poses two types of problems in localization of epileptogenic zones. The first is that if MRI shows multiple candidate foci of the epileptogenic zones, it cannot be verified which is the culprit lesion for the seizure generation. The second is that if MRI does not show any structural lesion, that is to say, when the lesion is 'cryptogenic', it is difficult to determine where to apply subdural grids and strips to find the seizure focus during subdural EEG studies. In such cases, FDG PET is helpful in providing useful information on the virtual location of subdural electrodes to find the epileptogenic zone. FDG PET can at least lateralize cryptogenic lesions, although it cannot localize a lesion.

According to our previous study [21], positive predictive value of FDG PET in cryptogenic epilepsy is over 70%. Localization rates are different for various epileptogenic lobes. Lateral temporal lobe or frontal lobe epilepsies are relatively easy to diagnose among complex partial seizure patients. In frontal lobe epilepsy, the sensitivity of FDG PET was 36% in patients without structural lesions on MRI and 73% in patients with

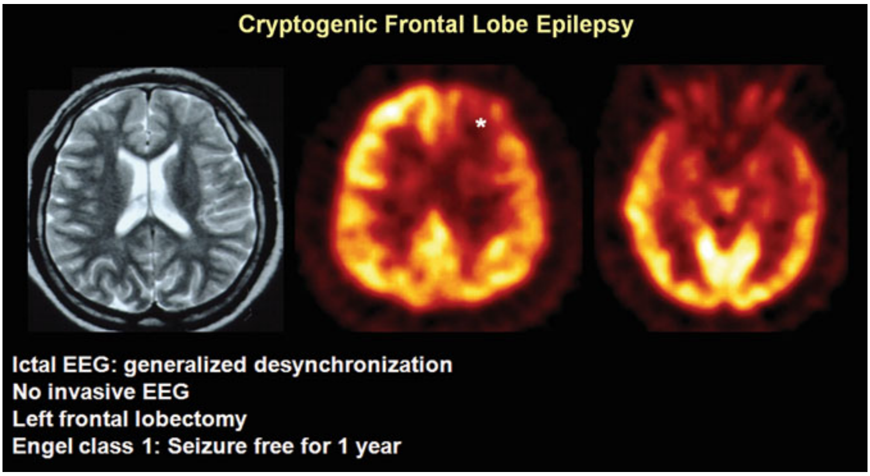

Fig. 12.2 A case with cryptogenic frontal lobe epilepsy. Selected axial T2-weighted, MR image of the brain was normal, and ictal EEG also was nonlocalizing. Selected axial FDG PET showed images of the head, definitive hypometabolism with decreased uptake of ^{18}F-FDG (*) in left frontal lobe. After successful frontal lobectomy, the patient became seizure-free

structural lesions in frontal lobe epilepsy [22]. In nonlesional cryptogenic cases, epileptogenic zones yield similar decreased metabolism to the lesions in explicit cases with subdural lesions (Fig. 12.2).

On the contrary, it is not easy to localize epileptogenic zones in occipital lobe epilepsy [23]. Areas showing the most severe hypometabolism are limited to the occipital lobes in some patients (Fig. 12.3), however, they are not limited in others. In those other cases, the areas of highest perfusion were also not limited to occipital lobes on ictal SPECT. The hypometabolism was localized even to the ipsilateral temporal lobes in a few patients (Fig. 12.4). Epileptogenic zones could have been misdiagnosed for temporal lobes in those patients. As for the occipital lobe epilepsy, the localization rate was found to be 47% by MRI and 60% by PET [23]. In such confusing cases of occipital lobe epilepsy, the examination of visual symptoms and visual field is mandatory [23].

Comparison of Interictal FDG PET with Interictal Perfusion SPECT

The diagnostic performance of interictal SPECT for localization of epileptogenic zones is somewhat disappointingly low as compared with that of interictal PET. The sensitivity of interictal perfusion SPECT was 44% on average by a meta-analysis [5], and 34% in our cohort study including both temporal and neocortical epilepsy cases. The sensitivities of interictal PET have been reported to be improved over those of interictal SPECT (73–97%) [24–26].

Considering the dogma of metabolism and perfusion coupling in the brain, it is important to figure out the significance of, or the reason for, this discrepancy in the sensitivities of the two functional imaging modalities representing metabolism and perfusion. The reason why interictal FDG PET is excellent but interictal SPECT is poor for the localization of epileptogenic zones could be explained as follows.

Among greater than 300 patients, we identified 14 patients with increased perfusion in the zones that was determined to be epileptogenic by surgical outcome or invasive studies [27]. Four of those were patients in whom interictal SPECT was performed on the second day after ictal episode. The other four patients, seemingly hyperperfused, were studied on the third to fifth day after ictus (Fig. 12.5a, b). This means that the interictal SPECT was in fact not performed at the interictal phase. Subclinical seizure activity just

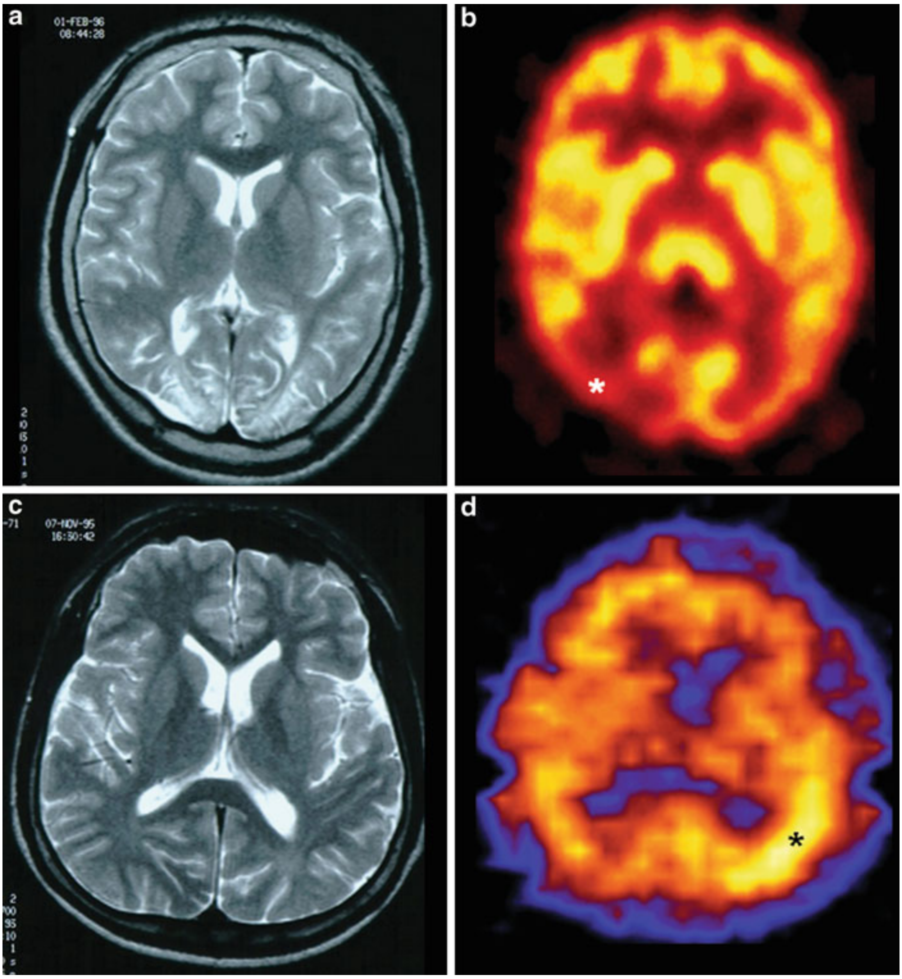

Fig. 12.3 Cases of occipital lobe epilepsy. Selected T2-weighted axial MR image of the brain (**a**) was normal, but metabolism with ^{18}F-FDG was decreased in the right occipital lobe epilepsy (*) on the axial image of the head (**b**). In another case, the MR image (**c**) was normal, but perfusion with ^{99m}Tc HMPAO was increased in the left occipital lobe (*) on ictal SPECT of the head (**d**). Both patients became seizure-free after neocortical resection

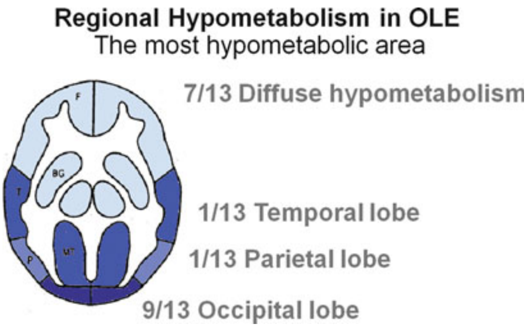

Fig. 12.4 Regional prevalence if interictal hypometabolism on ^{18}F-FDG PET in occipital lobe epilepsy. Occipital lobe is the most common site of hypometabolism

prior to or during interictal studies might have resulted in this increased perfusion at the epileptogenic zones.

On the other hand, 'delayed postictal perfusion abnormalities', even long after the previous ictus, could have resulted in the increased perfusion [28]. During the delayed postictal period at 6 h after ictal SPECT, we found remnant hyperperfusion in one half of patients (Fig. 12.5c–e). In one patient, severe hypoperfusion was found on delayed postictal SPECT, but showed recovery on interictal SPECT. Based on these findings, we suggest that even with EEG monitoring to

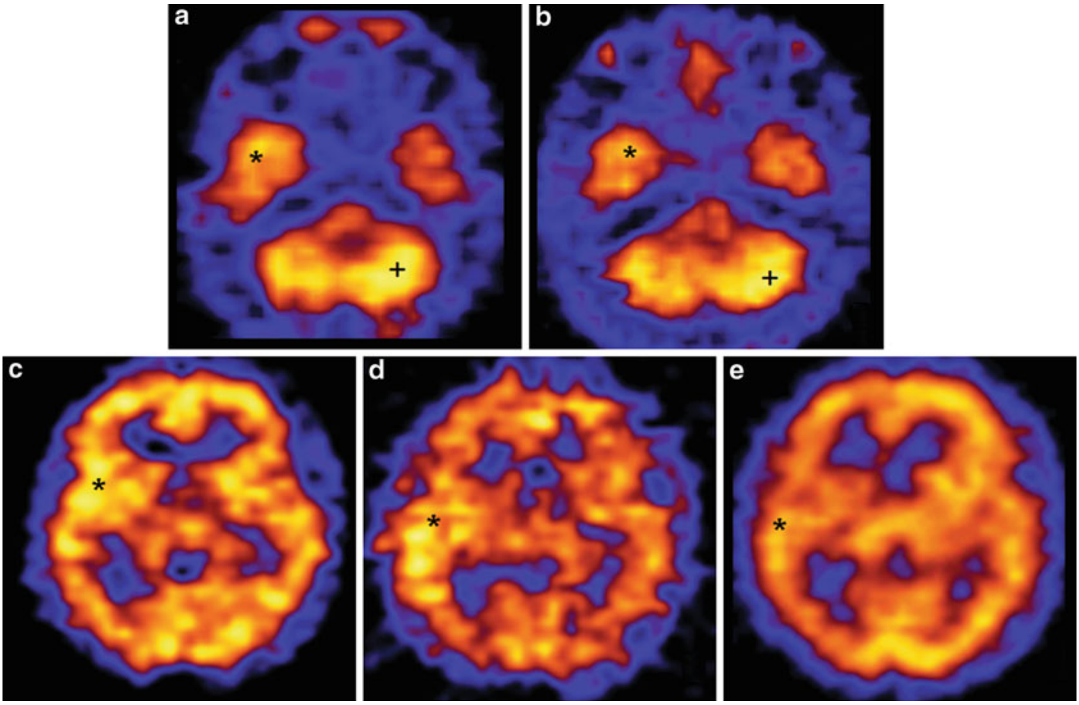

Fig. 12.5 Hyperperfusion on interictal SPECT using ^{99m}Tc HMPAO and delayed postictal hyperperfusion after ictus. In a patient with surgically confirmed right temporal lobe epilepsy, on the fourth day after ictal study (**a**), axial images of the head taken on interictal SPECT (**b**) showed similar increased perfusion in the right temporal lobe (*) and crossed cerebellar hyperperfusion (+). In the other patient with right temporal lobe epilepsy, perfusion was increased in the right temporal lobe (*) on ictal SPECT (**c**) and also on 6-h delayed SPECT (**d**). On interictal SPECT (**e**), perfusion was relatively decreased in this temporal lobe (*)

prove that there is no ictal discharge during interictal SPECT, it cannot be verified that the 'true' interictal SPECT has been obtained.

Voxel-Based Analysis of FDG PET

SPM is a voxel-based approach for determining the significantly different area from normal controls (Fig. 12.6). After spatially transforming and smoothing the individual PET data using the general linear model, the voxel count of the individual patient is compared with those of the normal controls. This analysis method is a very robust analytic tool to compare statistically abnormal cerebral perfusion with normal controls [22, 29, 30].

Interestingly, SPM analysis of ^{15}O-water PET, FDG PET, and ^{99m}Tc-HMPAO interictal SPECT revealed that in the same patients the areas of hypoperfusion were mostly concordant with but smaller than the areas of hypometabolism (Fig. 12.7) [31]. This apparent uncoupling of perfusion and metabolism in epileptogenic zones is another reason why interictal perfusion SPECT is inferior to interictal FDG PET in localizing epileptogenic zones.

On SPM analysis in frontal lobe epilepsy, using an uncorrected probability value of 0.005 as the threshold, the sensitivity of SPM analysis reached that of visual assessment. Sensitivity is decreasing as stricter thresholds are chosen to find abnormal area of decreased perfusion (Fig. 12.8).

Quantification Using Automatic Volume of Interest on Population-Based Atlas

This method is structured on population-based standard anatomy, which was developed by the Montreal Neurological Institute and named SPAM (Fig. 12.9). SPAM, an acronym for "statistical

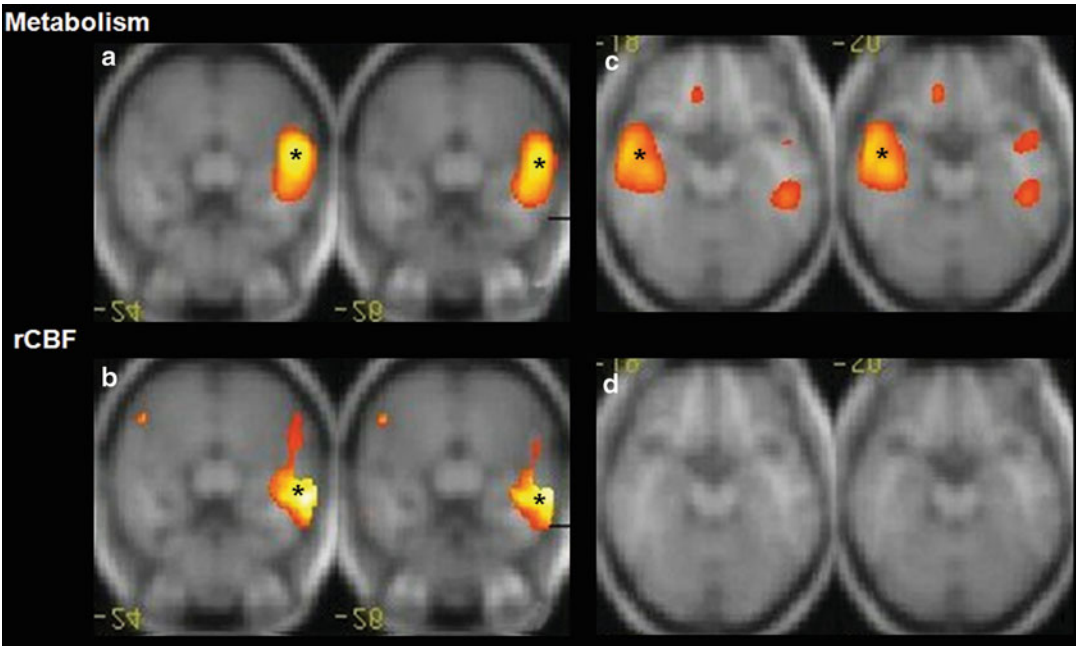

Fig. 12.6 SPM analysis results of ^{18}F-FDG PET and ^{15}O-water PET superimposed on MRI. Activities are the voxels that differ from the normal controls. In a coupled case, the left temporal lobe (*) was found to have hypometabolic voxels on axial FDG PET images (**a**) and hypoperfused voxels on water PET (**b**). In an uncoupled case, the right temporal lobe (*) was found to have hypometabolic voxels on FDG PET axial images (**c**), however, there was no area of hypoperfusion on water PET (**d**)

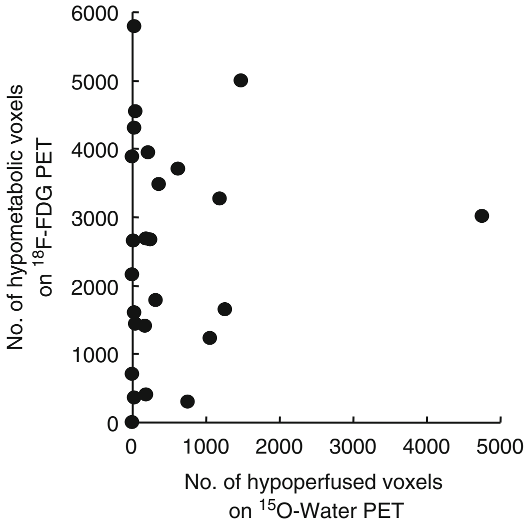

Fig. 12.7 Number of hypoperfused voxels and hypometabolic voxels on ^{15}O-water PET and ^{18}F-FDG PET in the epileptogenic temporal lobes. Each data point represents voxel number per epileptogenic whole temporal lobe per patient. Numbers of hypometabolic voxels tended to be much greater than those of hypoperfused voxels

probabilistic anatomic map," differs from SPM. SPM is a voxel-based approach, whereas SPAM is an area-based approach. SPAM is an objective and operator-independent method of volume of interest (VOI) drawing. We have a population-averaged anatomic definition of gyri and lobes in MRI template format. To construct SPAM, the Montreal group collected, parceled, and segmented normal MR images from 152 young subjects. Original PET images are transformed to an MRI template and the voxel counts are multiplied by the probabilities obtained from the SPAM template. For example, if the right hippocampus is chosen, the resulting image shows the probabilities of each voxel belonging to the right hippocampus. This method was first used to objectively quantify the asymmetric index, and these asymmetric indices could be used to localize epileptogenic zones on FDG PET [31].

The methods to use SPAM for evaluation of extent and severity of hypometabolism on FDG

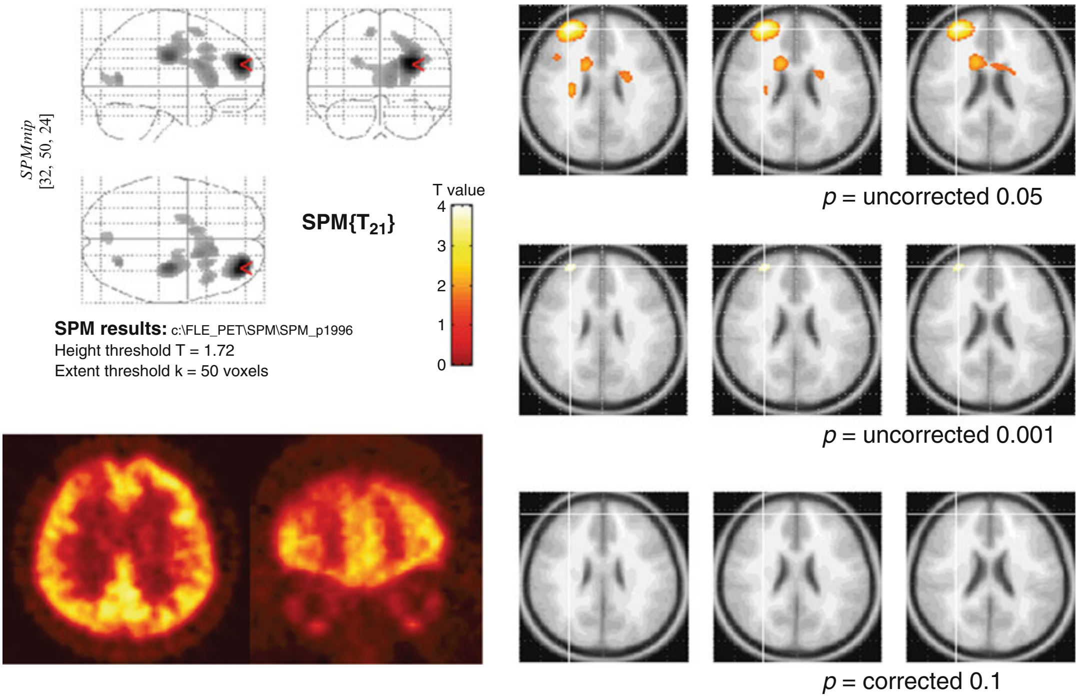

Fig. 12.8 Example of SPM analysis with varying threshold. According to cutoff value of voxel height, SPM analysis became less sensitive when stricter criterion was applied. Sensitivity decreases according to the decrease in probability value

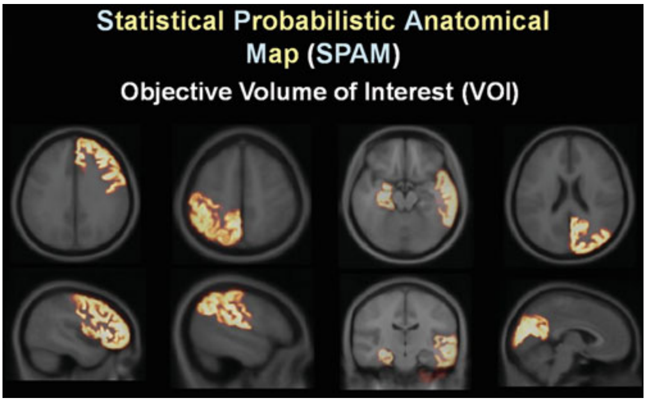

Fig. 12.9 SPAM)as an objective VOI) in PET image processing. Frontal and parietal (*left*) as well as temporal and occipital (*right*) lobes were displayed on the MRI template. These SPAM masks can be used as a VOI on the MRI template

PET in the epileptogenic zones are depicted in Fig. 12.10. The relation of hypometabolism and surgical prognosis of medial temporal lobe epilepsy could be evaluated. By successful application of SPAM to six gyri of temporal lobes, this analysis revealed that focal severity and extent were not related to the surgical outcome in medial temporal lobe epilepsy [32].

Prognostic Values of FDG PET in Surgical Interventions

The prognostic values of FDG PET in presurgical evaluations have been investigated both in TLE and neocortical epilepsies. The focal hypometabolism on presurgical FDG PET are known to have a significant correlation with postoperative

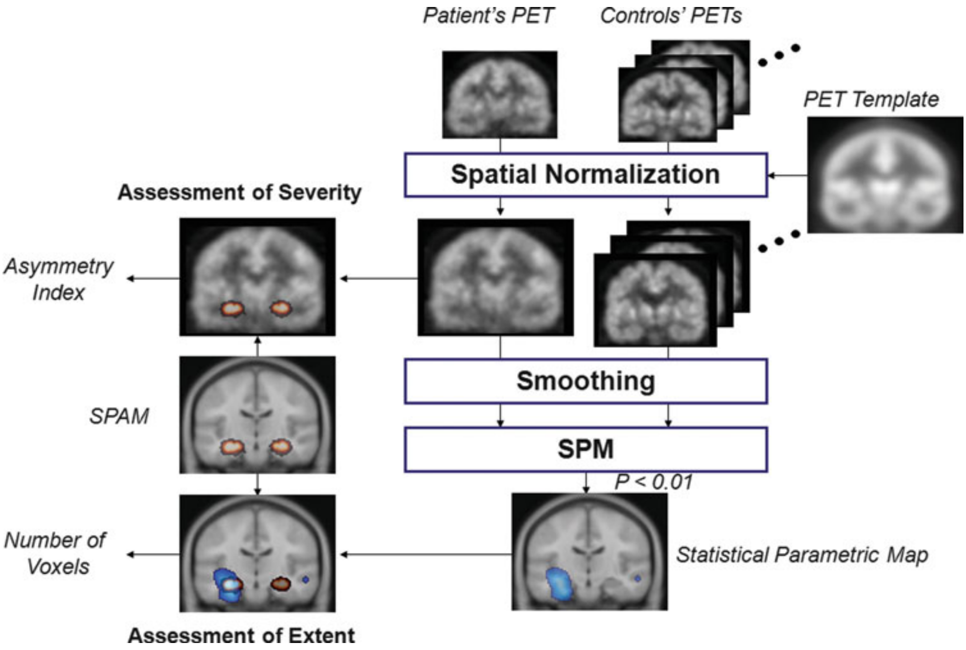

Fig. 12.10 Assessment of severity and extent of hypometabolism. Asymmetric indexes were calculated on six pairs of VOIs to represent the temporal lobe significant regional hypometabolism was estimated by comparing the PET images with those of controls by using SPM. The extent of hypometabolic area for each VOI was determined by counting the number of voxels with significantly decreased hypometabolism in each VOI segmented

seizure-free outcomes [33, 34]. By a meta-analysis dealing with predictive diagnostic values of FDG PET in TLE patients, unilateral temporal lobe hypometabolism could predict a good surgical outcome in 86% of patients, and in 80% of patients with normal MRI [35]. Although MRI itself is strongly predictive of surgical outcome in TLE [33], FDG PET seems to have a comparably high predictive value and even to achieve clinical benefit in the patients with suspected TLE and normal MRI. In addition, presurgical FDG PET is sure to be cost effective for localization of epileptogenic zones, especially if its use is restricted to the evaluation of patients in whom MRI and scalp EEG do not provide a definitive answer [11].

In neocortical epilepsies, surgical outcomes as well as localization rates of epileptogenic zones were lower than those of TLE. However, according to our previous study, the localizing values of FDG PET and interictal EEG were well correlated with a seizure-free outcome, and the positive predictive value of FDG PET was 63% in patients with cryptogenic neocortical epilepsy [36].

Beyond FDG PET in Epilepsy

In vivo neurochemistry, considered to be responsible for neuronal modulation, has had much attention in the past decades with the hope of revealing the pathophysiology of epilepsy. In particular, γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter that plays a major role in regulating neuronal excitability throughout the central nervous system, is supposed to play the key role in epilepsy [37]. Besides the GABAergic system, other neurotransmitters such as serotoninergic, dopaminergic systems have also been suggested to have a significant pathophysiologic role in the epileptic brain. In this regard, PET agents for GABAergic, serotoninergic, dopaminergic systems, etc. have been actively investigated to evaluate the involvement of theses neurotransmitters in vivo.

PET with ^{11}C-flumazenil (FMZ), which binds to GABA$_A$ receptor, has been widely used to investigate the status of GABAergic system in TLE patients. On FMZ PET, epileptogenic zones

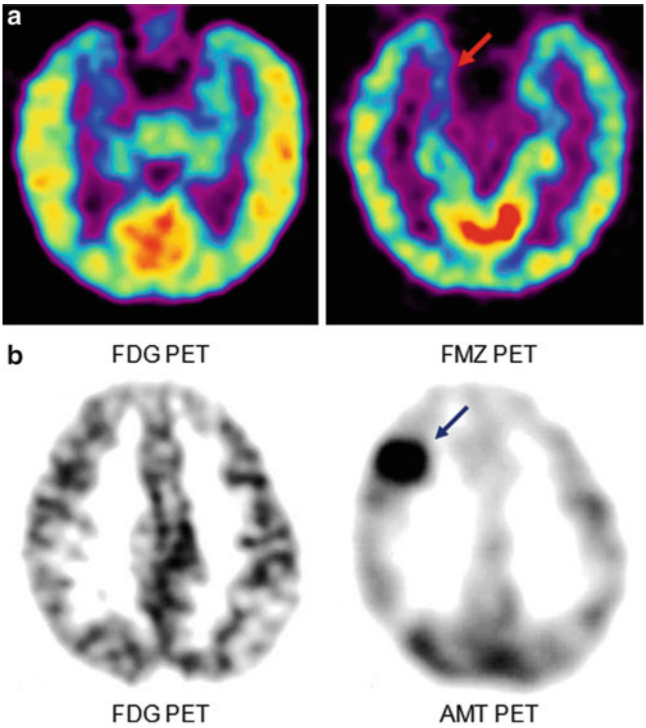

Fig. 12.11 PET scans using radiotracers other than FDG in patients with focal epilepcies. Epileptogenic focus in the right temporal lobe showed relatively decreased glucose metabolism and reduced FMZ uptake (**a**: Modified from Ref. [38]). Epileptogenic focus, proved to be cortical dysplasia later on histology, showed no abnormal glucose metabolism, but increased AMT uptake in the right frontal cortex (**b**: Modified from Ref. [45])

show decreased FMZ uptake as compared with the contralateral homotopic reference region and the remaining neocortex (Fig. 12.11a) [38]. However, careful interpretation is needed for the abnormalities on FMZ PET because decreased FMZ uptake could be seen not only in the epileptogenic zone but also in the remote area. Several hypostheses including a secondary epileptogenesis model, multifocal cortical dysplasia, and underlying pathology associated with increased susceptibility to seizures have been suggested to explain the presence of the multiple decreased FMZ sites remote from the epileptogenic zones [39]. Recently, a novel ^{18}F-labeled PET agent (^{18}F-flurorflumazenil) binding to GABA $_A$ receptor was reported and expected to facilitate the use of FMZ PET in clinical practice [40].

To evaluate the serotonergic system, PET agents for serotonin metabolism or serotonin receptor have been developed. ^{11}C-alpha-methyl tryptophan (AMT), an analog of tryptophan, reflects serotonin synthesis in vivo or induction of the kynurenine pathway [41, 42]. AMT PET has been suggested to be useful to localize epileptogenic zones in cortical malformations (Fig. 12.11b) [43–45]. Increased cortical AMT uptake was most sensitive in children with tuberous sclerosis [43]. For the evaluation of the serotonin receptor status, ^{18}F-MPPF, an antagonist of the 5HT$_{1A}$ receptor, has been investigated in patients with focal epilepsies. A recent study reported that MPPF PET could lateralize an epileptogenic lobe with a sensitivity of 90%, and proved its usefulness in the presurgical evaluation of TLE patients [46].

The pathophysiologic role of the dopaminergic system in the epileptic brain is not yet clearly understood. Recently, the striatal dopaminergic system became an important target for both basic and clinical research because it was reported to play a key role in modulation of seizure activity in animal studies [47]. To characterize the striatal dopaminergic system in vivo, ^{18}F-fallypride, a high-affinity dopamine D$_2$/D$_3$-receptor antagonist, has been actively used in animal studies as well as in the clinical setting. With the introduction of dedicated PET scanner for small animals, new PET agents for in vivo neurochemistry are expected to make advances in the understanding of the pathophysiology of epilepsy.

Conclusion

FDG PET is helpful in localizing epileptogenic zones, especially in patients with nonlesional epilepsy on MRI. Quantitative methods such as SPM and SPAM are believed to have the ability to enhance the objectivity of the analysis to find epileptogenic zones by revealing hypometabolic areas. In the near future, various PET agents other than FDG could be utilized to unveil the nature of the epilepsy.

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