

Review Article

PET studies in epilepsy

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Received May 11, 2015; Accepted June 23, 2015; Epub October 12, 2015; Published October 15, 2015

Abstract: Various PET studies, such as measurements of glucose, serotonin and oxygen metabolism, cerebral blood flow and receptor bindings are available for epilepsy. ¹⁸Fluoro-2-deoxyglucose (¹⁸F-FDG) PET imaging of brain glucose metabolism is a well established and widely available technique. Studies have demonstrated that the sensitivity of interictal FDG-PET is higher than interictal SPECT and similar to ictal SPECT for the lateralization and localization of epileptogenic foci in presurgical patients refractory to medical treatments who have noncontributory EEG and MRI. In addition to localizing epileptogenic focus, FDG-PET provide additional important information on the functional status of the rest of the brain. The main limitation of interictal FDG-PET is that it cannot precisely define the surgical margin as the area of hypometabolism usually extends beyond the epileptogenic zone. Various neurotransmitters (GABA, glutamate, opiates, serotonin, dopamine, acetylcholine, and adenosine) and receptor subtypes are involved in epilepsy. PET receptor imaging studies performed in limited centers help to understand the role of neurotransmitters in epileptogenesis, identify epileptic foci and investigate new treatment approaches. PET receptor imaging studies have demonstrated reduced ¹¹C-flumazenil (GABAA-cBDZ) and ¹⁸F-MPPF (5-HT_{1A} serotonin) and increased ¹¹C-cerfentanil (mu opiate) and ¹¹C-MeNTI (delta opiate) bindings in the area of seizure. ¹¹C-flumazenil has been reported to be more sensitive than FDG-PET for identifying epileptic foci. The area of abnormality on GABAA-cBDZ and opiate receptor images is usually smaller and more circumscribed than the area of hypometabolism on FDG images. Studies have demonstrated that ¹¹C-alpha-methyl-L-tryptophan PET (to study synthesis of serotonin) can detect the epileptic focus within malformations of cortical development and helps in differentiating epileptogenic from non-epileptogenic tubers in patients with tuberous sclerosis complex. ¹⁵O-H₂O PET was reported to have a similar sensitivity to FDG-PET in detecting epileptic foci.

Keywords: PET, Epilepsy, FDG, Neurotransmitter, receptor

Introduction

Epilepsy is an ancient Greek word which means to be taken, seized or attacked. Epilepsy is a central nervous system disorder characterized with recurring seizures caused by disrupted nerve cell activity. Almost 1%-2% of the population is affected by epilepsy. At least two unprovoked seizures are required for an epilepsy diagnosis. The etiologic classification of epilepsy includes idiopathic, symptomatic, and cryptogenic epilepsies. Idiopathic epilepsies are believed to have a genetic basis and generally start in childhood. Symptomatic epilepsies typically follow an identified brain insult such as head injuries, low oxygen during birth, brain tumors, infections, stroke, and abnormal blood levels of substances such as sodium or blood sugar. For cryptogenic epilepsies, the cause of the epilepsy is unknown but many presume

that a cause could be identified with sufficient investigation.

Epileptic seizures are classified as partial and generalized seizures by International League Against Epilepsy (ILAE) [1]. Seizure that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis. Partial seizures (PS) are the most common form of epilepsies (approximately 50% of patients with epilepsy). PS can involve temporal, frontal, parietal and occipital lobes. Temporal lobe epilepsy (TLE) is the most common form of PS. Mesial TLE (mTLE) is the most frequent form of TLE. Mesial temporal sclerosis (MTS) is present in 60-70% of patients with mTLE. Mesial temporal structures include the hippocampus, amygdala, and parahippocampal gyrus. The frontal lobe is the second most com-

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Table 1. PET findings in the area of seizure focus in patients with epilepsy

PET study	Findings
Interictal ^{18}F -FDG	Usually reduced metabolism
Ictal ^{18}F -FDG	Increased and decreased metabolism (complex pattern)*
Post-ictal ^{18}F -FDG metabolism**	Complex pattern, increased or decreased
GABAA-cBZR receptor	Reduced binding
Opioid receptor	Increased mu and delta receptor bindings
Serotonin receptor	Reduced binding
Dopamine receptor	Reduced binding
^{11}C -alpha-methyl-L-tryptophan	Increased uptake
Interictal ^{15}O - H_2O	Usually reduced perfusion
Ictal ^{15}O - H_2O	Increased perfusion

*due to long brain uptake period of FDG, **depending on the time of injection after seizure.

mon origin. Frontal lobe epilepsy (FLE) is featured by short seizures occurring several times a day and often during sleep.

The diagnosis of epilepsy includes a complete physical and neurological examination, extra-cranial or intracranial electroencephalogram (EEG), blood tests, magnetic resonance imaging (MRI), MR spectroscopy, single photon emission computed tomography (SPECT), and positron emission tomography (PET) studies. Treatment with medications usually controls seizures in majority of patients. However, nearly one third of patients with epilepsy become medically intractable and may require surgery. Surgery includes the local resection of the area of seizure. MTS is most often medically refractory, but surgical intervention is relatively effective in majority of the patients. Accurate localization of epileptic focus is important for a successful surgery. Brain perfusion SPECT imaging has been widely used in the detection of epileptic foci. Meta-analytic sensitivities of SPECT in patients with TLE were reported as 44% (interictal), 75% (postictal) and 97% (ictal) [2]. The sensitivities of SPECT in extra-TLE were 66% (ictal), and 40% (interictal) [3, 4]. Ictal image is the most sensitive but not easy to obtain as the seizure lasts for few minutes only and the radiotracer must be readily available at the patient's bedside at the time of seizure onset. PET, particularly PET/computed tomography (PET/CT) provides better quality and higher resolution images as compared to SPECT and allows quantitative measurements. There are various PET tracers to measure glucose, serotonin and oxygen metabolism, cerebral blood flow and receptor bindings in epilepsy. Imaging brain glu-

cose metabolism with ^{18}F Fluoro-2-deoxyglucose (FDG) PET is the most commonly utilized technique in routine clinical practice. The other PET studies require well experienced staff as well as on-site equipment and cyclotron. **Table 1** summarizes the PET findings in the area of seizure focus.

FDG-PET imaging

FDG brain PET, particularly PET/CT, is a well established and widely available imaging technique. ^{18}F -FDG is a radiolabeled glucose analog measuring glucose metabolism. Glucose is the major energy source for brain. Glucose metabolism is tightly connected to neuronal activity. ^{18}F -FDG is transported from the blood into cells by glucose transporters, predominantly GLUT1. Once in the cell, FDG is phosphorylated by hexokinase to form FDG-6-phosphate. Further metabolism of FDG-6-phosphate is limited and it is essentially trapped in the cell.

FDG brain PET/CT imaging protocol is well described in Society of Nuclear Medicine (SNM) and European Association of Nuclear Medicine (EANM) guidelines [5, 6]. Patients should be fasting for 4 to 6 hours prior to the study and avoiding caffeine, alcohol, or drugs that may affect cerebral glucose metabolism. Particularly sedatives, amphetamines, cocaine, narcotics, antipsychotic medications and corticosteroids alter cerebral metabolism. Environment (a quiet, dimly-lit room) should be stable for at least 30 minutes prior to FDG injection and in the subsequent uptake phase (at least 30 minutes). Blood glucose should be checked prior to FDG administration. If it is greater than 150-

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200 mg/dL, the patient is usually rescheduled. When hyperglycemia is present, high circulating insulin levels drive FDG into muscle and results in reduced uptake in the brain. In diabetic patients, best images are achieved in a euglycemic situation during stable therapeutic management. For preoperative evaluation of epilepsy, continuous EEG recording is recommended. Before intravenous injection of FDG, a low dose (10-30 mAs) CT attenuation correction (AC) images are obtained. FDG dose for adults is 185-740 MBq (5-20 mCi). Pediatric dose is 5.18-7.4 MBq (0.14-0.20 mCi). The dose is less for 3D scanners. Images are usually acquired in static technique. Most systems today use 3D acquisition. Static PET acquisition typically begins 30-60 minutes after FDG injection and lasts for 15-30 minutes. On a state of art PET/CT with high dose FDG (740 MBq, 20 mCi), imaging can be completed in 5 minutes. When absolute quantification of regional metabolic rates of glucose is needed dynamic images are acquired. Dynamic acquisition starts at the time of FDG administration and continues for 60-90 minutes (multiple 5-min frames). Filtered backprojection or iterative methods are used for image reconstruction. Measured AC method is used for AC of the images. Visual inspection with or without semiquantitative analysis is the standard method of interpretation.

In normal adult brain, there is high FDG uptake in cerebral and cerebellar cortices and subcortical gray matter with mild FDG uptake in the white matter. FDG uptake in children varies with the patient age. Infants typically show diffusely low metabolic activity [7]. After 4 months of age there is a rapid increase in brain glucose metabolism reaching a peak level by about 4 years of age which is higher than adult brain activity [8, 9]. There is decrease in cerebral metabolic rates with normal aging, primarily in lateral and medial frontal cortex, and anterior cingulate cortex [10-12]. Abnormal regions demonstrate increased, reduced or absent metabolic activity. Semiquantitative analysis helps to detect regional or global mild abnormalities which are not apparent on visual inspection. Semiquantitative analysis involves comparing FDG uptake in regions of interest over selected brain regions. Semiquantitative analysis can be performed manually or via automated software programs [13-15]. FDG-

PET images co-registered to MR images or obtained on an integrated PET/MR scanner provide better structural and functional information. Quantitative analysis (absolute glucose metabolism) requires blood sampling (arterial or arterialized venous blood) with serial measurements. However, in the clinical setting most centers prefer simplified protocols based on static images. PET images are usually obtained in interictal phase. Interictal FDG-PET images usually demonstrate focal hypometabolism. Ictal PET studies are not easy to perform as majority of seizures are unpredictable and short lasting. Another limitation of ictal PET is long brain uptake period of FDG (30-45 minutes) after injection which causes complex pattern of increased and decreased metabolism. Postictal PET can demonstrate complex pattern of increased and decreased metabolism or only increased or decreased metabolism depending on the time of injection after seizure.

Although EEG continues to play a central role in the diagnosis and management of patients with seizure disorders, the sensitivity of EEG is relatively low, ranging between 25-56%. Subclinical seizures in small volumes or deep structures may not be detected with extracranial EEG. Intracranial cortical and particularly depth EEG is invasive and has complications. MRI is highly sensitive and specific for detecting hippocampal sclerosis as well as other structural lesions causing epilepsy but it fails to reveal any apparent abnormality in approximately 20% of the patients with medically refractory epilepsy. MRI may miss mild hippocampal sclerosis and subtle structural lesions. Advanced MRI techniques, such as MR spectroscopy, MR volumetry, diffusion tensor imaging, MR perfusion, and functional MR imaging may provide complementary information but they require high-performance MRI scanners. Magnetoencephalography (MEG), a non-invasive technique for investigating human brain activity, has limited value in identifying epileptic activities in deep-seated areas such as mesial temporal lobe.

Large number of studies have demonstrated that FDG-PET is highly sensitive for presurgical localization of epileptogenic foci in patients with medically refractory partial epilepsy who have noncontributory EEG and MRI. **Figure 1**

PET in epilepsy

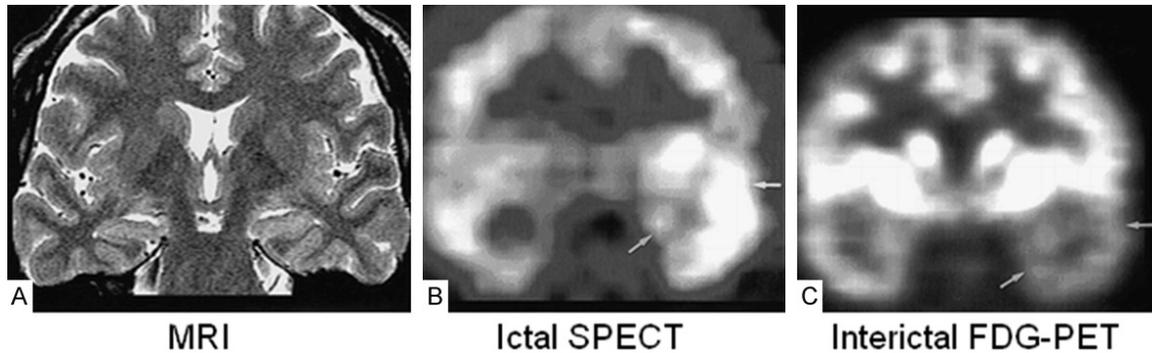


Figure 1. False-negative MR findings in a 30-year-old man with left complex partial seizures. Ictal activity was shown in left temporal area on video/EEG. A. Oblique coronal fast spin-echo T2-weighted MR image (4000/120/4) shows no abnormalities. B. Ictal SPECT scan shows hyperperfusion in left temporal lobe (arrows). Radioactivity ratio between right temporal cortex/left temporal cortex was 1:2.4. C. FDG-PET scan shows hypometabolism in left temporal lobe (arrows). Radioactivity ratio between right temporal cortex/left temporal cortex was 1:0.7. Invasive EEG showed ictal activity in left temporal lobe. After left anterior temporal lobectomy, pathologic diagnosis was hippocampal sclerosis of a mild degree associated with mild cortical dysplasia. Engel's outcome was class II. Reprinted with permission from American Society of Neuroradiology [16].

shows ictal SPECT and interictal FDG-PET images of a man with left complex partial seizures with false negative MRI [16]. The sensitivities of FDG-PET in TLE and extra-TLE were reported as 84% and 33%, respectively, in a meta analytic study in 1994 [3]. In the following years, some of the reported sensitivities of PET for TLE and extra-TLE were 87-90% and 38-55%, respectively [14, 17-19]. In 46 patients with PS and non-contributory EEG, FDG-PET demonstrated unilateral temporal hypometabolism in 26 patients and 18 of 23 were seizure-free after temporal lobectomy [20]. There was also unilateral frontotemporal hypometabolism in 5 patients and frontal hypometabolism in another patient. Interictal PET was able to lateralize the seizure focus in 95% of MRI positive, 69% of MRI equivocal and 84% of MRI negative patients [21]. PET helped in decision making in 53% of pre-surgical patients with normal or discordant MRI [22]. Extra-TLE is higher in children and MRI usually do not show a discrete lesion. In children with frontal lobe epilepsy, the sensitivity and specificity of FDG-PET were 92% and 62.5%, respectively [23].

In majority of FDG-PET studies, the images are obtained in interictal phase. Interictal FDG-PET was reported to be more sensitive than interictal perfusion SPECT [3]. Studies have demonstrated that there is more reduction in regional cerebral glucose metabolic rates than in regional cerebral perfusion in interictal period [24-27]. Interictal PET is a very sensitive technique

for lateralization and general localization of epileptogenic focus, but it cannot precisely define the surgical margin as the area of hypometabolism usually extends beyond the epileptogenic zone. FDG-PET can not always differentiate mesial from lateral TLE as glucose hypometabolism may extend to the lateral aspect of the abnormal temporal lobe.

Studies have compared interictal FDG-PET to ictal SPECT [16, 28-30]. In 117 patients who underwent surgery for intractable neocortical epilepsy, interictal PET and ictal SPECT correctly localized the lesions in 77.7%, and 70.3% of the patients, respectively [30]. In another study, interictal PET and ictal SPECT correctly lateralized the lesion in 85%, and 73% of patients, respectively [16]. Studies have also compared interictal PET with ictal subtraction SPECT (interictal SPECT fused, normalized and subtracted from ictal SPECT) [31, 32]. In one report, interictal PET had 56% sensitivity and ictal subtraction SPECT had 87% in the detection of seizure foci [31]. In children, ictal subtraction SPECT coregistered to MR imaging (SISCOM) localized the epileptic focus in 67% of the patients. This was 57% with FDG-PET [32]. Ictal subtraction SPECT and SISCOM appear to increase the sensitivity of ictal SPECT, but their main limitation is to obtain two SPECT studies, one in interictal and one in ictal period.

Semiquantitative analysis of PET data and coregistration of PET image with MR increase the

sensitivity of PET. Semiquantitative analysis can identify mild abnormalities which are not apparent on visual inspection. Drzezga et al. demonstrated that automated analysis of PET was more sensitive than visual analysis in patients with TLE and extra-TLE [14]. The benefits of PET and MR coregistration in presurgical evaluation of medically refractory epilepsy have also been demonstrated in several studies [33, 34].

Studies have demonstrated that FDG-PET can predict surgical outcome. Greater severity of preoperative hypometabolism in the resected temporal lobe was associated with significantly better postoperative seizure control [35-37]. Severe extratemporal and bilateral hypometabolism was associated with a higher incidence of postoperative seizures [38, 39]. Ipsilateral PET hypometabolism showed a predictive value of 86% for good outcome in meta-analysis of 46 studies [40].

There is limited data on ictal PET imaging [40-45]. Ictal PET studies were performed either in patients with status epilepticus (SE) or induced/provoked seizures [41-43]. SE is an epileptic seizure of greater than thirty minutes or more than one seizure within a thirty minute period without the person returning to normal between them. FDG-PET helped to establish the diagnosis in 8 patients when clinical features, MRI and EEG were incongruent regarding the origin of SE [41]. FDG-PET revealed hypermetabolism in the left orbitofrontal region in a patient suspicious for ongoing nonconvulsive frontal SE [42]. Subsequent FDG-PET following 5 days of oxcarbazepine therapy demonstrated resolution of the hypermetabolic focus in this patient. PET scan obtained in a patient exposed to seizure-eliciting music showed hypometabolism in the right lateral temporal lobe with an area of increased metabolism in the right anteromesial temporal lobe [44].

Postictal PET studies performed at different intervals following most recent seizure showed hyper or hypometabolism depending on the time of injection after seizure [46, 47]. In early postictal phase (seizures within 15 min prior to FDG injection) PET revealed focal hypermetabolism in 3 pediatric patients [46]. The most severe regional hypometabolism occurred more than 48 hours after the seizure and the least severe hypometabolism was at 24-48

hours postictally [47]. The metabolism was intermediate in the first 24 hours. The authors have concluded that it may take longer than 24 hours after a partial seizure to return to its baseline state.

In addition to localizing epileptogenic focus, presurgical PET provides important information on the functional status of rest of the brain. Interictal FDG-PET is considered to be the best imaging technique to assess the functional deficit zone (FDZ). FDZ is defined as the brain area that shows abnormal functioning in the interictal period. Extratemporal hypometabolism is not uncommon in TLE and is associated with a poor seizure outcome after surgery. In forty seven patients with TLE, 18 patients had hypometabolism only in the ipsilateral temporal cortex; the remaining 29 patients had additional cortical hypometabolism confined to the ipsilateral, contralateral or bilateral cerebral cortex [48]. Bilateral temporal lobe hypometabolism (BTH) can be seen in TLE. Seizure-onset zone in patients with BTH may be unilateral or bilateral. BTH in unilateral TLE causes conflict in lateralizing the epileptogenic zone. It was recommended to perform PET scan more than 2 days after the last seizure to avoid this confliction [49]. Chronic epilepsy generally impairs cognition. Depression is common in TLE and after temporal lobectomy and associated with hypometabolism in the frontal lobe.

PET receptor imaging

There are alterations in the neurotransmitters and subreceptors in epilepsy. It is believed that there is abnormally high level of excitatory neurotransmitters increasing neuronal activity or abnormally low level of inhibitory neurotransmitters decreasing neuronal activity in epilepsy. Excitatory glutamatergic neurotransmission is responsible for the initiation and spread of seizure activity, particularly excessive activation of glutamate receptor 5 (mGluR5) [50, 51]. One of the most-studied neurotransmitters that plays a role in epilepsy is γ -aminobutyric acid (GABA). GABA is an inhibitory neurotransmitter. GABA mediated synaptic inhibition is known to be critical in regulating epileptic activity [52]. Endogenous opioid peptides are also involved in epilepsy. Opioid peptides have anticonvulsant action and limit the spread of electrical activity [53]. Increased levels of serotonin have been observed in epileptogenic lesions.

Table 2. PET tracers for receptor imaging in patients with epilepsy

Receptors	PET tracer	Receptor subtypes
GABA	¹¹ C flumazenil (FMZ)*	GABAA-cBZR
Opioid	¹¹ C-carfentanil (CFN)**	mu
	¹¹ C-MeNTI*	delta
	¹¹ C-diprenorphine (DPN)*	mu, delta, kappa
Serotonin	¹⁸ F-cyclofoxy*	mu, kappa
	¹⁸ F-MPPF*	5-HT1A
	¹¹ C-WAY-100635*	5-HT1A
Dopamine	¹⁸ F-FCWAY*	5-HT1A
	¹⁸ F-fallypride*	D2/D3
Acetylcholine	¹⁸ F-FA-85380 (2FA)**	nicotinic-α4β2
	⁷⁶ Br-BDEX*	muscarinic

*: Receptor antagonist; **: Receptor agonist; GABAA-cBZR: γ Aminobutyric acid A-central benzodiazepine receptor; MeNTI: N1'-methylnaltrindole MeNTI; MPPF: 2'-methoxyphenyl-(N-2'-pyridinyl)-p-fluoro-benzamidoethylpiperazine; 5-HT1A: 5-hydroxytryptamine 1A receptor WAY-100635: (3) H-(N-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl) ethyl)-N-(2-pyridyl) cyclohexane-carboxamide; FCWAY: N-[2-[4-(2-methoxyphenyl) piperazino]]-N-(2-pyridinyl) trans-4-fluorocyclohexanecarboxamide; FA-85380: fluoro-A-85380; BDEX: 4-bromodexetimide.

Serotonin exerts antiseizure effects in experimental models mediated by 5-HT1A receptors [54]. Alterations of different dopamine receptor subtypes, particularly D1 and D2, have been associated to different forms of epilepsy [55, 56]. Multiple adenosine receptor subtypes are involved in epilepsy. In particular, adenosine A1 receptor subtype has a role to regulate seizure activity [57]. Histamine 3 receptor subtype, nicotinic and muscarinic acetylcholine receptors (nAChR and mAChR) are also believed to be involved in the pathophysiology of epilepsy.

PET receptor imaging studies have been utilized to understand the role of neurotransmitters in the epileptogenesis and spread of epileptic activity as well as to identify and localize epileptogenic regions and investigate new treatment approaches. There are large number of PET tracers for receptor imaging in human and animal models. **Table 2** summarizes PET receptor imaging tracers used in patients with epilepsy. **Table 3** lists the abbreviations for clinical terms.

¹¹C-flumazenil (FMZ) PET studies targeting GABAA-central benzodiazepine receptor (GABAA-cBZR) complex have demonstrated reduced binding of tracer in epileptic foci in patients

with partial epilepsy [58-63]. FMZ-PET has been found to be more sensitive and accurate than FDG-PET in the detection of cortical regions of seizure onset in patients with TLE and extra-TLE epilepsy [58, 59, 64]. The area of abnormality on FMZ-PET images was smaller and more circumscribed than the area of hypometabolism on FDG-PET images (**Figure 2**) [59, 61, 62, 65]. In patients with mTLE, mesial temporal structures showed reduced FMZ binding and reduction of FMZ binding was restricted to the area of hippocampal sclerosis (HS) with no abnormalities being detected in the temporal neocortex or elsewhere in the neocortex [61, 62]. The reduction in glucose metabolism was more widespread and often involved lateral temporal cortex (LTC) [61]. In one hundred epileptic patients undergoing pre-surgical evaluation, 73% of patients demonstrated FMZ-PET abnormality which was significantly higher in TLE (94%) than in other types of epilepsy (50%) [65]. Increased periventricular FMZ binding was reported to be associated with poor outcome and failure to become seizure free after surgery for TLE with HS [66, 67]. Focal alterations of the BZD receptor density or affinity were not demonstrated in patients with generalized epilepsy [68].

Opioid-receptor PET studies have supported the relationship between opioid peptide receptor availability and seizures. Increased mu and delta receptor bindings in the temporal cortex ipsilateral to the focus were reported in interictal PET studies with ¹¹C-cerfentanil (CFN) and ¹¹C-N1'-methylnaltrindole (MeNTI) [69-71]. Increases in opioid receptor bindings were smaller regionally than were decreases in FDG uptake [70]. Increased mu receptor binding were confined to the middle aspect of the inferior temporal cortex, whereas binding of delta receptors increased in the mid-inferior temporal cortex and anterior aspect of the middle and superior temporal cortex [70]. Various findings were reported with non-specific (mu, delta, and kappa) opioid receptor agonist, ¹¹C-diprenorphine (DPN). Interictal DPN-PET demonstrated no changes in non-specific opiate receptor binding in TLE and idiopathic generalised epilepsy [71, 72]. Reduced interictal DPN binding in medial temporal lobe and LTC was reported in 2 patients with mTLE [73]. Post-operatively, there was a further reduction of

PET in epilepsy

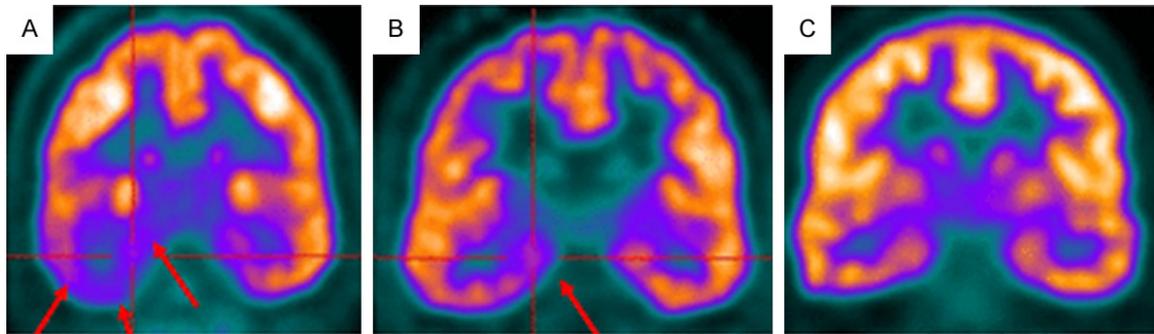


Figure 2. FDG-PET image shows extensive hypometabolism throughout right temporal lobe (arrows) (A). FMZ-PET image shows more restricted localization to mesial temporal region in same patient (arrows) (B). Symmetric FMZ distribution in control subject (C). Reprinted with permission from The Society of Nuclear Medicine and Molecular Imaging [62].

Table 3. Abbreviations for clinical terms

Abbreviation	Definition
FCD	Focal cortical dysplasia
HS	Hippocampal sclerosis
mTLE	Mesial temporal lobe epilepsy
MTS	Mesial temporal sclerosis
LTC	Lateral temporal cortex
PS	Partial seizures
SE	Status epilepticus
TLE	Temporal lobe epilepsy
TSC	Tuberous sclerosis complex
VNS	Vagus nerve stimulation

DPN binding in LTC in these patients. Within hours of spontaneous temporal lobe seizures, postictal binding of DPN was increased in the temporal pole and fusiform gyrus ipsilateral to the seizure focus which gradually returned to baseline [74]. Partial-volume effect (PVE)-corrected DPN-PET images showed post-ictal increases in ipsilateral fusiform gyri and lateral temporal pole which was not evident in uncorrected datasets [75]. After provocation of serial absence seizures, reduced DPN retention in the association cortex has been reported suggesting that endogenous opioids are released in the association cortex at the time of serial absences, lead to increased receptor occupancy, and may have an important role in the pathophysiology of generalised absences [76]. Ictal DPN binding to opioid receptors was reduced in the left parieto-temporo-occipital cortex (Brodmann area 37) in reading-epilepsy [77].

PET studies with various serotonin 5-HT_{1A} receptor antagonists (¹⁸F-FCWAY, ¹¹C-WAY-

100635, and ¹⁸F-MPPF) demonstrated a reduced serotonin 5-HT_{1A} receptor binding in the epileptogenic temporal lobe [78-86]. In addition to reduced binding in the mesial temporal structures, there was also involvement of rest of the temporal regions as well as other cortical and limbic regions. **Figure 3** shows ¹¹C-WAY-100635 PET images of a patient with MRI-negative temporal lobe epilepsy [86]. Depression is the most frequent psychiatric disorder in epilepsy. A relationship between hippocampal ¹⁸F-FCWAY 5HT_{1A} binding and depressive symptoms was reported in patients with TLE and symptoms of depression [87]. To evaluate 5-HT transport and 5-HT_{1A} receptors in TLE and depression, patients were studied with ¹¹C-DASB and ¹⁸F-FCWAY [88]. There was increased ¹¹C-DASB asymmetry in insula and fusiform gyrus and relatively reduced transporter activity in subjects with both TLE and depression, as compared to subjects with TLE alone. PET studies in patients with mTLE have demonstrated that decrease in 5-HT_{1A} receptor binding in temporal regions may play a role in memory impairment [89].

PET studies with various other receptor imaging tracers were also performed in patients and in animal models. PET imaging with a dopamine receptor antagonist, ¹⁸F-fallypride, revealed reduced D₂ and D₃ receptor bindings at the pole and in lateral aspects of the epileptogenic temporal lobe in patients with mTLE and HS [90]. Patients with juvenile myoclonic epilepsy showed a reduction in D₂ and D₃ receptor bindings restricted to the bilateral posterior putamen, suggesting a specific alteration of the dopaminergic system [91]. Glutamate

PET in epilepsy

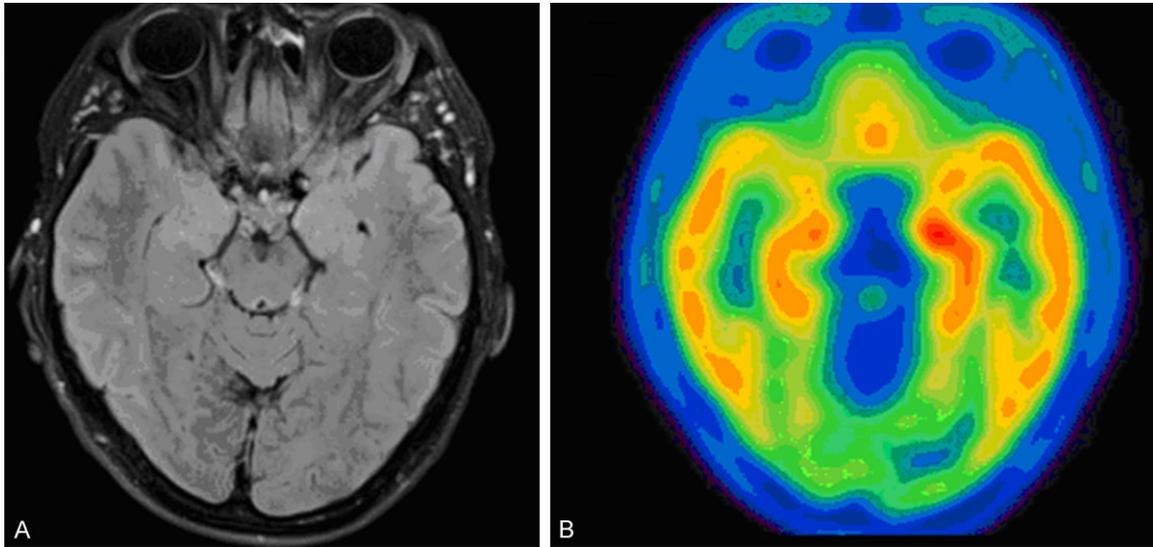


Figure 3. ^{11}C -WAY-100635 PET in a patient with MRI-negative temporal lobe epilepsy and a right temporal EEG focus. A. T1-weighted axial MRI reveals no structural abnormality. B. ^{11}C -WAY-100635 PET imaging shows asymmetric binding with a decrease in both mesial and lateral structures of the right temporal lobe. Reprinted with permission from Elsevier Limited [86].

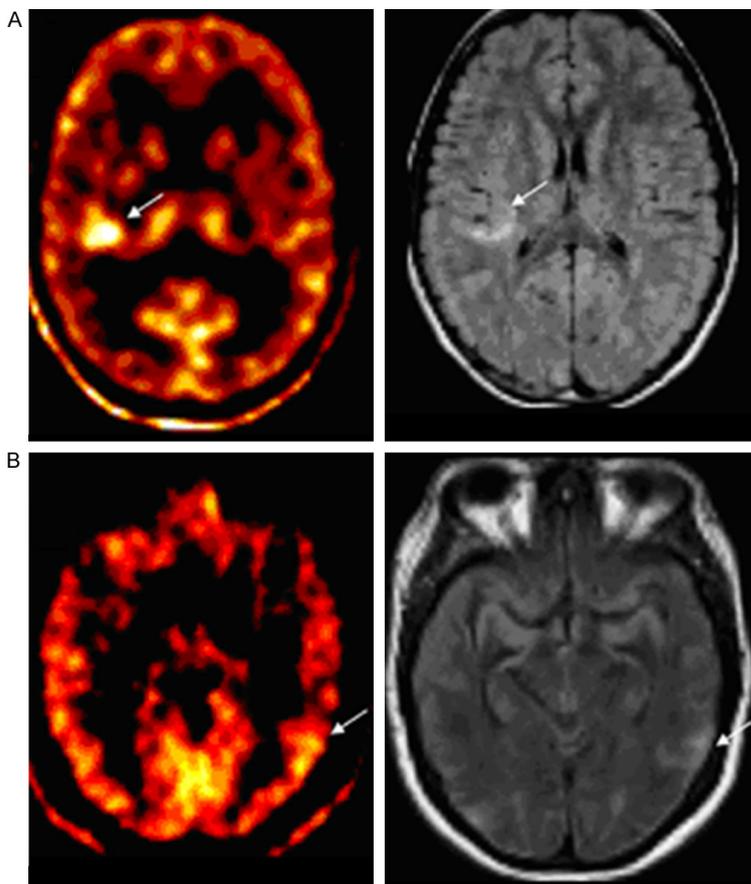


Figure 4. Increased AMT uptake in cortical tubers (arrows). A. Clearly MRI hyperintense right perisylvian tuber in a patient. B. Subtly MRI hyperintense left temporal tuber in another patient. Reprinted with permission from John Wiley and Sons [96].

receptor subtype mGluR5 is an attractive target in epilepsy. Changes of mGluR5 were evaluated using ^{11}C -ABP688 PET during the epileptogenesis in a pilocarpine-induced epilepsy rat model [92]. In chronic epilepsy, ^{11}C -ABP688 binding was reduced in hippocampus and amygdala, whereas in acute period after SE mGluR5 binding was reduced in the whole brain. In subacute period, mGluR5 binding was restored in caudate-putamen, while it was still lower in the rest of the brain. In chronic period, global mGluR5 binding was normalized except in hippocampus and amygdala. PET study with nicotinic AChR agonist, ^{18}F -F-A-85380, demonstrated a regional nAChR density decrease in the prefrontal cortex in patients with autosomal dominant nocturnal frontal lobe epilepsy [93]. Reduced ^{76}Br -BDEX (muscarinic AChR antagonist) concentration was reported in the temporal lobe ipsilateral to the seizure focus in patients with mTLE [94]. To determine

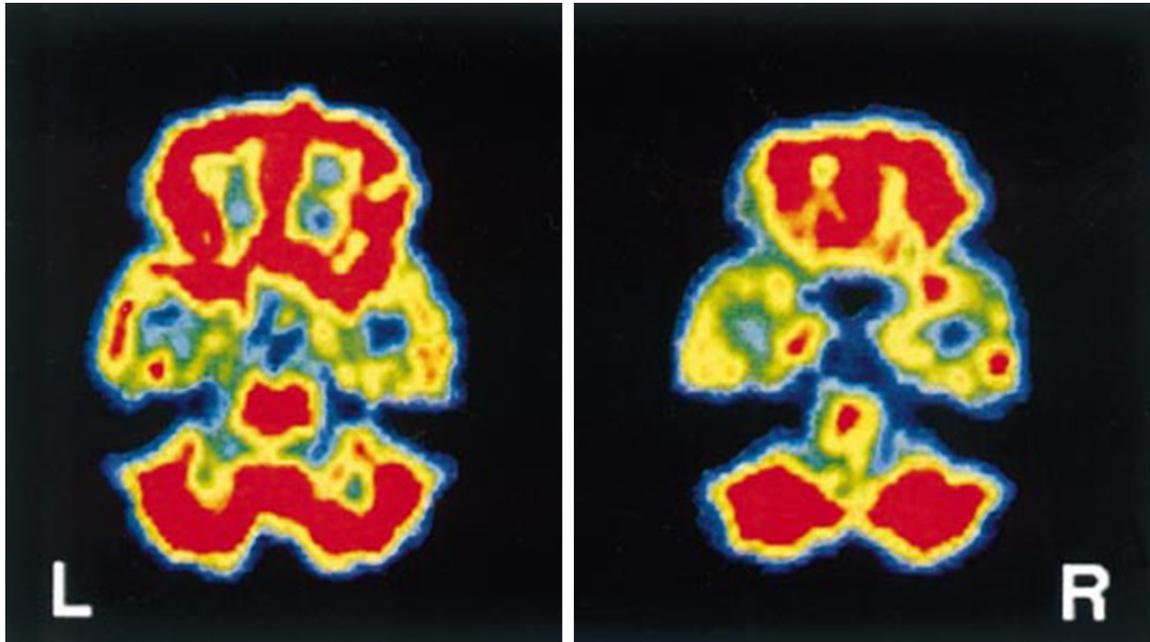


Figure 5. Interictal $^{15}\text{O}\text{-H}_2\text{O}$ PET images in a patient with bilateral temporal lobe epilepsy. Note relative hypoperfusion of temporal lobes compared to the whole brain. Reprinted with permission from John Wiley and Sons [103].

N-methyl-D-aspartate (NMDA) receptor changes, $^{14}\text{C}\text{-}(S)\text{-}[N\text{-methyl}]$ ketamine PET was performed in patients with mTLE [95]. There was 9-34% reduction of tracer radioactivity in the temporal lobes of ictal onset.

Other PET studies

$^{14}\text{C}\text{-}\alpha\text{-methyl-L-tryptophan}$ (AMT) is a radio-labeled tryptophan analogue to study synthesis of serotonin in the brain. Tryptophan is the precursor of serotonin. Interictal PET studies have demonstrated a focal increased uptake of AMT in the epileptogenic area in patients with TLE, cortical dysplasia, cryptogenic partial epilepsy, tuberous sclerosis complex (TSC), and cortical developmental malformations (**Figure 4**) [96-100]. Majority of patients with TSC have seizures. AMT-PET helped in differentiating epileptogenic from non-epileptogenic tubers in patients with TSC [100]. PET localization was mostly seen in patients with frequent interictal abnormalities on the EEG [97]. Studies of brain tissue subsequent to epilepsy surgery in patients with TSC implicated the kynurenine pathway of tryptophan metabolism as a primary mechanism of increased brain tissue retention of AMT in epileptogenic brain regions, rather than alterations in serotonin synthesis [101]. AMT-PET can detect the epileptic focus within

malformations of cortical development. Focal increase of cortical AMT uptake in children was less sensitive but more specific for the lobe of seizure onset than corresponding FDG-PET hypometabolism, and it was often associated with epileptogenic cortical developmental malformations [102]. In children with intractable, neocortical epilepsy with and without malformations of cortical development, the specificity of AMT-PET for detecting seizure onset lobe was equally high in lesional (97%) and nonlesional groups (100%), whereas sensitivity was higher in the lesional than the nonlesional group (47% versus 29%) [99].

Oxygen-15 water ($^{15}\text{O}\text{-H}_2\text{O}$) is an inert, diffusible flow tracer. It allows quantitative measurement of rCBF. The physical half-life of ^{15}O is approximately 2 minutes and its production requires an on-site cyclotron. $^{15}\text{O}\text{-H}_2\text{O}$ PET was performed for both identification of the language dominant hemisphere and in the lateralization of the epileptic focus in preoperative patients with complex partial seizures (CPS) [103]. Intracarotid amytal procedure was discordant with PET language mapping in 1 out of 24 cases. For epileptic focus lateralization, $^{15}\text{O}\text{-H}_2\text{O}$ PET was highly sensitive (87%) and specific (100%). **Figure 5** demonstrates $^{15}\text{O}\text{-H}_2\text{O}$ PET images of a patient with bilateral temporal lobe

epilepsy [103]. In the analysis of 35 patients who had an anterior temporal lobectomy for medically intractable seizures FDG and $^{15}\text{O}\text{-H}_2\text{O}$ were highly correlated in demonstrating the epileptic focus [104]. FDG and $^{15}\text{O}\text{-H}_2\text{O}$ PET showed significant asymmetries in 83% and 77% of cases, respectively. Using $^{15}\text{O}\text{-H}_2\text{O}$ PET, Henry et al. evaluated acute blood flow changes and efficacy of vagus nerve stimulation (VNS) in partial epilepsy [105]. Seizure-frequency changes ranged from 71% decrease to 12% increase during VNS. Only the right and left thalami showed significant associations of rCBF change with seizure-frequency change. Increased right and left thalamic CBF correlated with decreased seizures. PET with ^{15}O steady state or bolus inhalation technique was used to provide quantitative values of regional CBF, oxygen consumption (CMRO2) and oxygen extraction ratio (OER) in patients with CPS during the interictal state and in patients during SE [106, 107]. Interictal scans showed zone(s) of hypoperfusion without significant variation of the OER in approximately 80% of patients [106]. In all cases, ictal scans revealed a focal or multifocal increase in CBF and CMRO2. Significant interictal changes in rCMRO and rCBF were demonstrated in patients with CPS [107]. While the hemisphere containing the abnormal focus showed the more marked changes, particularly with respect to rCMRO2 the contralateral hemisphere was also abnormal with respect to normal aged matched controls.

In some TLE patients with amygdala enlargement, an increased ^{14}C -methionine (MET) uptake (a radiolabeled amino acid measuring protein synthesis) was observed in the enlarged amygdala [108]. Focal cortical dysplasia (FCD), a neuronal migration disorder, has been recognized as a cause of intractable epilepsy. MET-PET was useful for identifying FCD as a high uptake area [109].

Conclusion

Interictal FDG-PET is more sensitive than interictal SPECT and has similar sensitivity to ictal SPECT for presurgical localization of epileptic foci in patients with noncontributory EEG and normal MR or MR findings discordant with the EEG findings. In addition to localizing epileptic focus, FDG-PET provides additional important information on the functional status of the rest of the brain. The main limitation of interictal

FDG-PET is that it cannot precisely define the surgical margin as the area of hypometabolism usually extends beyond the epileptogenic zone. FDG-PET can not always differentiate mesial from lateral TLE as glucose hypometabolism may extend to the lateral aspect of the abnormal temporal lobe.

PET studies have demonstrated reduced binding of specific tracers to GABAA-cBDZ and 5-HT1A serotonin receptors as well as increased binding to mu and delta opiate receptors in the area of seizure. FMZ-PET (GABAA-cBDZ receptor binding) has been reported to be more sensitive than FDG-PET for identifying epileptic foci. The area of abnormality on GABAA-cBDZ and opiate receptor binding images is usually smaller and more circumscribed than the area of hypometabolism on FDG images which is important for precise definition of surgical margin. 5-HT1A serotonin receptor binding can be reduced not only in mesial temporal structures but also in the rest of the temporal regions as well as other cortical and limbic regions. Depression is common in patients with epilepsy. 5-HT1A PET serotonin receptor imaging studies can help to understand the association between epilepsy and depression. Studies have demonstrated that AMT-PET (to study synthesis of serotonin) can detect the epileptic focus within malformations of cortical development and helps in differentiating epileptogenic from non-epileptogenic tubers in patients with TSC. A focus of increased AMT uptake is highly specific for epileptic focus. $^{15}\text{O}\text{-H}_2\text{O}$ PET perfusion imaging has high sensitivity in demonstrating the epileptic focus. Despite their many advantages, majority of non-FDG brain PET studies are not widely available and performed in limited centers only as they require well experienced staff with on-site radiochemistry equipment and cyclotron.

Disclosure of conflict of interest

None.

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