

PET in seizure disorders

Andrew B. Newberg, MD^{*}, Abass Alavi, MD

*Division of Nuclear Medicine, Hospital of the University of Pennsylvania, 3400 Spruce Street,
110 Donner Building, Philadelphia, PA 19104, USA*

Epilepsy affects 0.5% to 1% of the population and can cause focal, partial, generalized, and absence seizures and several unusual types. Seizure disorders often begin in childhood and are treated with a variety of pharmacologic or surgical interventions for those refractory to medical therapy. Functional imaging, with both PET and single-photon emission CT (SPECT), has been highly useful in the diagnosis, management, and follow-up of patients with seizure disorders (Fig. 1). The ability of functional imaging to provide important information about seizures derives from the fact that epileptic conditions result in significant physiologic alterations in the brain. These physiologic changes occur both during seizures and in the interictal state. Because generalized seizures affect a large part of the brain, it is typically more difficult to isolate the originating focus from other areas that are secondarily affected on functional imaging studies. For partial seizures and other types of seizures that originate from a specific focus, however, functional imaging can be useful for localizing the primary site. Functional imaging also helps in the understanding of the pathophysiology of seizure disorders.

PET imaging in particular has been used in the management of patients with seizure disorders over the past two decades. In general, during an epileptic seizure, cerebral metabolism and cerebral blood flow are markedly increased. During the interictal period, both cerebral metabolism and cerebral blood flow are decreased [1]. In patients with generalized seizures, interictal fluorine-18–fluorodeoxyglucose (^{18}F)-

FDG) PET studies have revealed no focal areas of hypometabolism [2]. The focus of partial seizures (with or without secondary generalized seizures) can be identified using FDG-PET, however, because the seizure foci have increased metabolic activity during the seizure and decreased metabolic activity between seizures [3–8]. It has been shown that single hypometabolic regions can be identified in 55% to 80% of patients with focal surface electroencephalography (EEG) abnormalities [4,9–11]. These areas of decreased metabolism often appear more extensive in size than do anatomic abnormalities observed on MR imaging [1,12]. Interictal PET is also a useful technique in patients with an unlocalized surface ictal EEG seizure focus, and it can be used to reduce the number of invasive EEG studies [13,14].

Interictal PET imaging

Interictal PET scanning has been used in a variety of seizure disorders for diagnostic and research purposes. The most commonly studied disorders include temporal lobe epilepsy and frontal lobe seizures. For example, an interictal PET study [15] in patients with complex partial seizures compared cerebral glucose metabolism and blood flow with various clinical variables, such as duration of seizure disorder, age at seizure onset, frequency of complex partial seizures, history of secondary generalization, history of febrile seizures, and MR imaging evidence for mesial temporal sclerosis. In this study, only the duration of the seizure disorder correlated with the degree of interhemispheric asymmetry in glucose metabolism and blood flow. The degree of asymmetry was significantly greater for glucose uptake

^{*} Corresponding author.

E-mail address: newberg@rad.upenn.edu (A.B. Newberg).

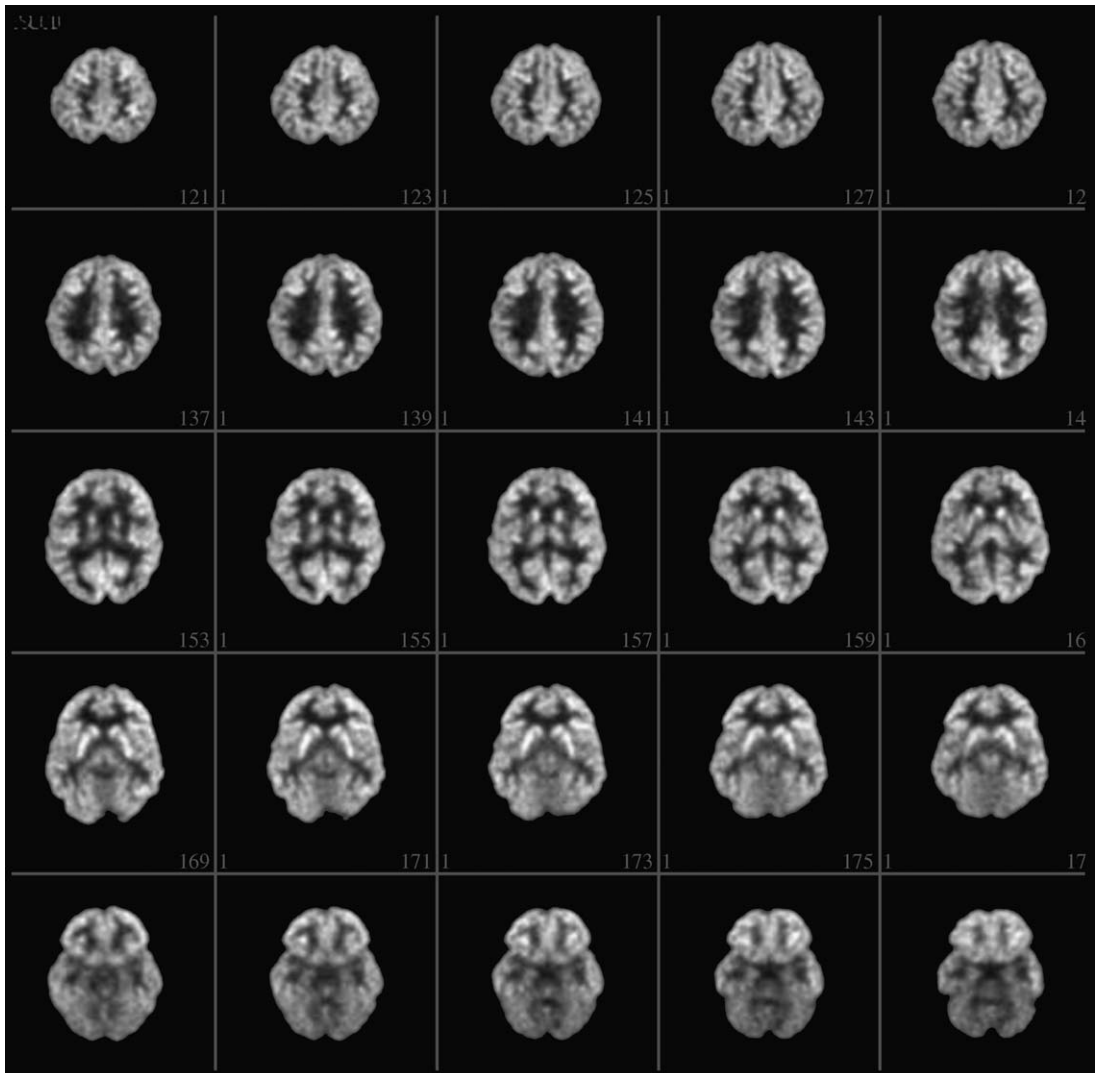


Fig. 1. Normal FDG-PET scan using a high-resolution bismuth germanate–dedicated head scanner. There is symmetric activity throughout the cortical gyri and subcortical structures.

than for blood flow suggesting that there is a relative uncoupling of metabolism and blood flow that is a progressive process. This uncoupling may result from the differential response of glucose metabolism and blood flow to chronic seizure activity. Another study of a single patient with bifrontal seizures demonstrated improvement in metabolic abnormalities after medical control of the seizures [16]. A study in contrast to the two reports described previously, however, did not find any association between complex partial seizure frequency and lifetime number of secondarily caused generalized seizures and hippocampal volume or metabolism [17]. These authors

concluded that the progression of metabolic or pathologic abnormalities may not be altered by adequate seizure control. Simply the presence of an epileptic focus might be associated with progressive neuronal injury even if the patient may be well-controlled medically.

A number of confounding clinical issues that may affect global or regional cerebral metabolism, such as the type of seizures, time since the most recent seizure, neuropsychiatric conditions such as depression (Fig. 2), and use of anticonvulsants (Fig. 3), require consideration in the evaluation of PET scans. Because it is not clear which factors play a role in the

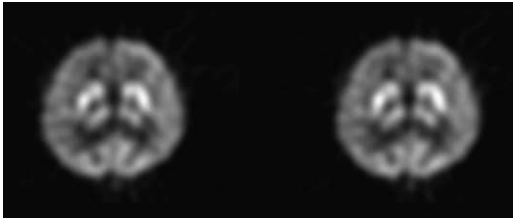


Fig. 2. FDG-PET study using a dedicated head PET of a subject with seizures demonstrating severely decreased metabolism throughout the entire cortex with relative preservation of the subcortical structures. This does not localize a seizure focus and is more consistent with depression or selected psychopharmacologic agents.

metabolic landscape of patients with complex partial seizures, Savic et al [18] investigated whether the metabolic pattern of interictal PET may be related to the EEG and clinical features of the seizure that preceded the scan. For this study, patients were classified into four groups: (1) focal limbic (characterized by auras or staring spells); (2) widespread limbic (including automatisms); (3) complex partial seizures with posturing; and (4) secondarily generalized seizures. The findings from this study showed that hypometabolism was limited to the epileptogenic zone if the preceding seizure was focal limbic, whereas patients with widespread limbic seizures had hypometabolism that included one or several additional areas of the limbic cortex. Patients with posturing were found to have hypometabolism in the extralimbic frontal lobe. Patients with secondarily generalized seizures were found to have significant cerebellar and parietal hypometabolism. The results of this study suggested that the mechanisms involved in the generation of a seizure that precedes a PET scan influences the interictal hypometabolic pattern and that it is important to consider the type of nonhabitual seizure that precedes a PET scan when interpreting images. A study by Barrington et al [19] addressed the application of simultaneous scalp EEG

during FDG administration to determine the exact ictal or interictal state of the patient with intractable seizures. This study demonstrated that seizures occur infrequently during FDG administration and that concurrent scalp EEG may not be necessary unless there is a significant problem with interpretation of the PET scan. Another study compared interictal regional slow activity as measured by scalp EEG with FDG-PET imaging and showed that the presence of such EEG activity had a high correlation with temporal lobe hypometabolism [20]. Interictal regional slow activity was not specifically related to mesial temporal sclerosis or any other pathology. The authors indicated that the findings from this study suggest that the hypometabolism observed on PET may delineate a field of reduced neuronal inhibition, which can receive interictal and ictal propagation.

Most patients with epilepsy respond to medical therapy. A certain number of patients, however, are found to be refractory to such treatments. One FDG-PET study in adolescents showed that detection of hypometabolism in the area of the seizure focus is associated with a poorer response to drug treatment compared with those without such findings [21].

One of the most effective treatments for partial epilepsy in patients refractory to medical interventions is surgical removal of the involved area, both in the pediatric and adult populations. Using high-resolution PET imaging, accurate localization of seizure foci can be achieved to help select appropriate candidates for surgical intervention [3–5,8,22]. Studies have also found that after surgical excision of the seizure foci, there is usually significant improvement in the function of the rest of the brain [23]. One study by Juhasz et al [24], however, suggested that it is the border zones of hypometabolic areas that may represent epileptogenic areas. Although somewhat contradictory to other studies, this finding helps to explain why some areas of hypometabolism miss seizure foci and still provides support for the notion that hypometabolic areas are related to seizure foci

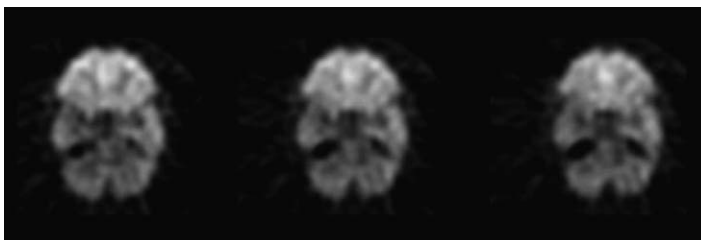


Fig. 3. Interictal FDG-PET study using a dedicated head PET of a subject with seizures. A specific seizure focus could not be identified, but there is bilaterally decreased metabolism in the cerebellum. This is a frequent finding in patients on antiseizure medications, such as phenytoin.

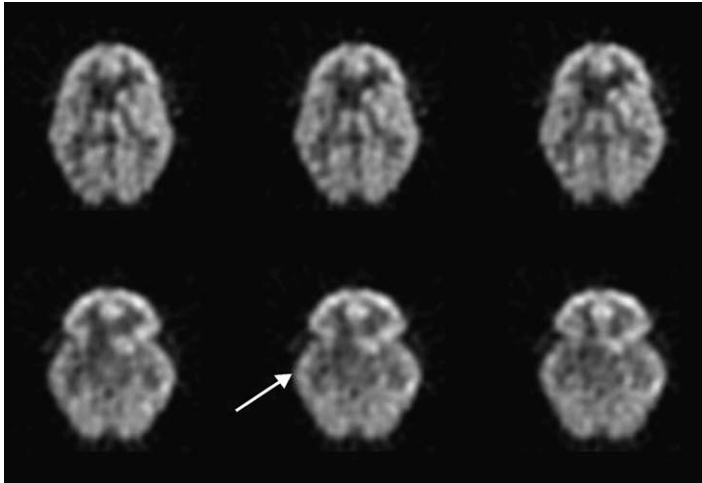


Fig. 4. Interictal PET images from a dedicated head PET of a subject with right temporal lobe seizure shown as decreased glucose metabolism in the right temporal lobe (*arrow*).

even though it may be the border zones that truly represent areas of seizure onset. Future studies are necessary to confirm these initial findings.

In terms of specific brain structures, the temporal lobe is the most common focus of partial epilepsy (Figs. 4 and 5). Initial studies showed that the sensitivity of PET in detecting temporal lobe epilepsy seizure focus is over 70% [25–37]. A later study by Sperling et al [38], however, has shown a positive finding on PET in only 44% of patients with temporal lobe epilepsy who had normal CT scans. Another study has shown that false lateralization can occur, reflected as hypometabolism of the temporal lobe

contralateral to the site of seizure focus as determined by EEG or MR imaging [39]. This is not a common phenomenon, however, as reflected in the sensitivity and specificity of PET for detecting seizure foci. PET imaging is also useful in detecting metabolic abnormalities in pediatric patients suggesting that focal functional deficits appear early in patients, especially those with medically refractory temporal lobe epilepsy [40]. PET imaging may help in the early identification of these patients.

Newer methods for analyzing PET images have also been explored, such as statistical parametric mapping in which each pixel represents a z-score

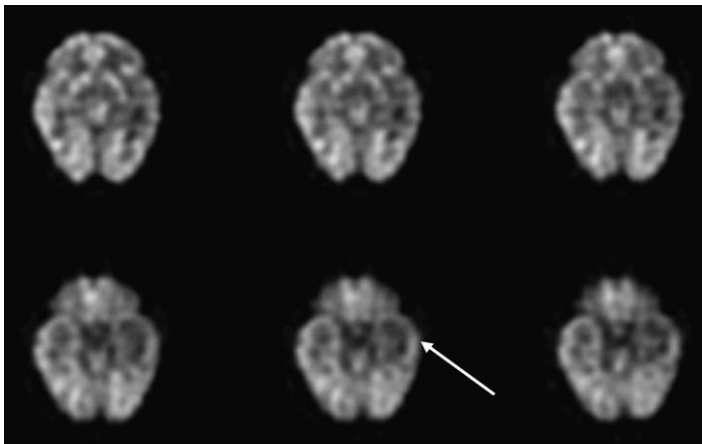


Fig. 5. Interictal PET images from a dedicated head PET of a subject with left temporal lobe seizure shown as decreased glucose metabolism in the left temporal lobe (*arrow*).

value determined by using the mean and standard deviation of count distribution in each individual patient. A study using statistical parametric mapping compared hemispheric asymmetry on FDG-PET images in patients with mesial temporal lobe epilepsy with controls [41]. When the statistical parametric mapping program was used to detect temporal interhemispheric asymmetry, hypometabolism was identified on the side chosen for resection in most cases (sensitivity, 71%; specificity, 100%) and was predictive of favorable postsurgical outcome in 90% of the patients. After a correction for multiple comparisons, statistical parametric mapping also identified temporal lobe hypermetabolic areas and extratemporal cortical and subcortical hypometabolic areas on the side of resection, but also on the contralateral side. An analysis of interictal FDG-PET scans in 17 patients with surgically treated temporal lobe epilepsy showed that the mean z-scores were significantly more negative in anterolateral and mesial regions on the operated side than on the nonoperated side in those patients who were seizure free, but not in those with ongoing seizures postoperatively [42]. Statistical parametric imaging correctly lateralized 16 of 17 patients, but only the anterolateral region was significant in predicting surgical outcome.

PET studies have also shown changes in areas distant from the seizure focus in patients with temporal lobe epilepsy. One FDG-PET study showed ipsilateral hypometabolism of the seizure focus in the temporal pole, but relatively increased metabolism in the ipsilateral mesiobasal region [43]. Contralateral to the seizure focus, metabolism was increased in the lateral temporal cortex and mesiobasal regions. A study of patients with bilateral temporal lobe epilepsy demonstrated that approximately 10% of the PET scans from seizure patients had bilateral temporal lobe hypometabolism [44]. When compared with patients with unilateral temporal lobe hypometabolism, patients with bilateral temporal lobe hypometabolism had a higher percentage of generalized seizures; were more likely to have bilateral, diffuse, or extratemporal seizure onsets; and had bilateral or diffuse MR imaging findings. Medical treatment was less successful in patients with bilateral temporal lobe hypometabolism and these patients also had worse social and cognitive functioning. Finally, patients with bilateral temporal lobe hypometabolism had a worse prognosis for seizure remission after surgery. A more recent study showed that patients with bilateral temporal lobe hypometabolism had more frequent nonlateralized ictal EEG pattern, anterior temporal white matter changes, and less frequent aura and

unilateral dystonic posturing [45]. This study showed no substantial difference in postoperative outcomes, however, between patients with bilateral or unilateral temporal lobe involvement on PET.

Another important aspect of seizure studies is how to distinguish those patients who will do well postoperatively from those who will be less likely to benefit from temporal lobectomy. In this regard, PET studies have yielded controversial results. One PET study did not find any correlation between the severity of abnormal temporal lobe blood flow and the frequency of postoperative seizures [46]. This study, however, had a limited number of patients and may not have been able to detect statistical differences. Other studies have shown that in those patients with hypometabolism only in the affected temporal lobe, there is a higher likelihood of a successful outcome [47–49]. It has also been shown that patients with a greater degree of hypometabolism in the temporal lobe (ie, a more distinct asymmetry) tended to have a better outcome than those with a lesser degree of asymmetry [48,50,51]. It may be that those patients without significant hypometabolism of the affected temporal lobe (ie, minimal asymmetry between the temporal lobes) might have extratemporal or bitemporal seizure foci. These patients may be less amenable to surgical resection. This is corroborated by other studies that have shown that patients with hypometabolism in the contralateral hemisphere to the epileptic focus on EEG may be more likely to have postoperative seizures [52,53] and those patients with extratemporal hypometabolism tend to have a higher likelihood of postoperative seizures (Fig. 6) [47,54].

Several studies have indicated that those patients with mesial temporal hypometabolism on PET imaging have a higher probability of being seizure free postoperatively than those patients with hypometabolism in other parts of the temporal lobe [51]. Other studies, however, have suggested that lateral temporal lobe hypometabolism is a good predictor of a seizure-free postoperative outcome [13,50]. Despite the findings regarding the association of temporal lobe hypometabolism with postoperative seizure outcome, several studies have not shown such a relationship [55,56]. Other investigators have explored the use of different statistical methods to show that using a discriminant and multivariate analysis, temporal lobe hypometabolism was a good predictor of postoperative seizure outcome [57]. Furthermore, a study comparing MR imaging with PET found that patients with white matter changes on MR imaging in the temporal lobes had greater reductions in glucose metabolism in the same regions [58]. These patients

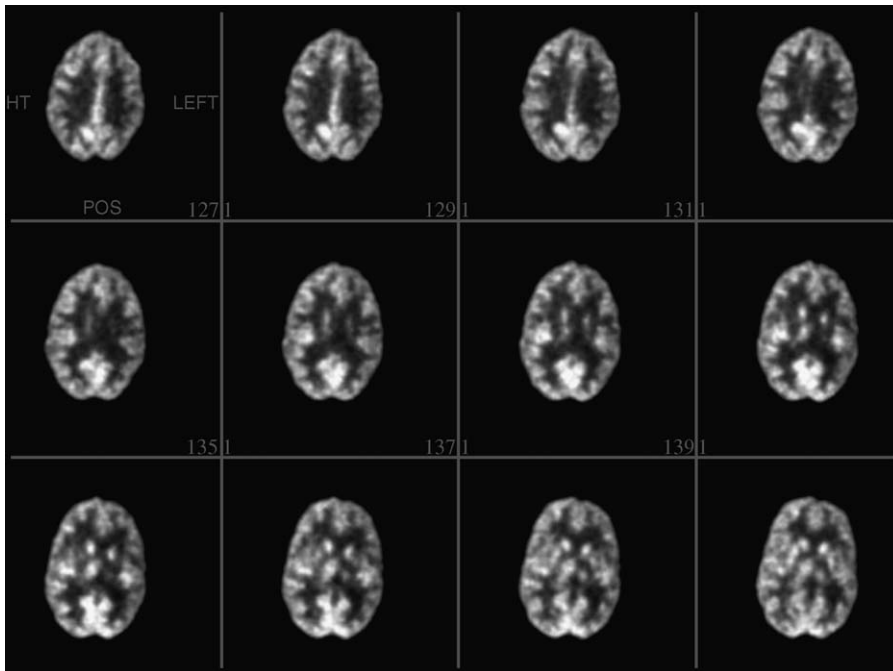


Fig. 6. Interictal FDG-PET study using a dedicated head PET of a subject demonstrating hypometabolism in the entire left hemisphere including the thalamus and basal ganglia. A specific seizure focus could not be identified.

also had better postsurgical outcomes suggesting that MR imaging and PET findings can be used in a complementary manner.

The thalamus may be an important structure to evaluate in patients with temporal lobe epilepsy with regard to postoperative seizure outcome. The findings from one study suggested that metabolic dysfunction of the thalamus ipsilateral to the seizure focus becomes more severe with long-standing temporal or frontal lobe epilepsy, and also with secondary generalization of seizures [59]. One research paper showed that of 64 patients who were seizure free postoperatively, all had either no thalamic metabolic asymmetry or asymmetry in the same direction as that of the temporal lobe removed (ie, the thalamus ipsilateral to the hypometabolic temporal lobe appeared to have reduced metabolism) [60]. No patients who were seizure free had thalamic asymmetry in the reverse direction as that of the temporal lobe removed (ie, the thalamus contralateral to the hypometabolic temporal lobe appeared to have reduced metabolism). In contrast, 5 (31%) of 16 patients with postoperative seizures of any degree had thalamic asymmetry in the reverse direction as that of the temporal lobe removed. Furthermore, all five patients with this reverse thalamic asymmetry were found to have some degree of postoperative seizures. Even patients with

ipsilateral thalamic hypometabolism had a slightly higher risk for having postoperative seizures in comparison with those patients with no asymmetry. Another study also demonstrated ipsilateral thalamic hypometabolism in patients with mesial temporal lobe epilepsy; however, the outcome associated with this finding was not described [61]. Contralateral thalamic hypometabolism as a predictor of poor postoperative seizure outcome may be taken to reflect a widespread pattern of seizure activity. Despite persistent seizures in patients with reverse thalamic asymmetry, however, there was still some degree of seizure activity improvement. Although the finding of reverse thalamic asymmetry may provide important prognostic information, surgery can still be an effective intervention in patients with medically refractory temporal lobe seizures.

PET imaging has also been used after surgical interventions to determine the metabolic landscape postsurgery. A study of eight patients undergoing temporal lobectomy had follow-up PET scans at least 6 months after surgery [62]. Half of the patients showed improved glucose metabolism in the formerly hypometabolic areas that were remote to the surgical site and ipsilateral to the epileptogenic foci. Patients who showed bilateral temporal hypometabolism preoperatively had contralateral temporal hypome-

tabolism after surgery. Several areas, particularly the frontal lobes, actually showed increased glucose metabolism after surgery. The authors concluded that hypometabolism in remote areas ipsilateral to the seizure focus may demonstrate reversibility after surgery and may be caused by inhibition by the intercortical pathways. Contralateral temporal hypometabolic areas that persist after surgery may be caused by a different mechanism, and neither specifically indicates the presence of seizure foci nor affects the seizure outcome. PET imaging in a patient after entorhinoamygdalohippocampectomy performed with the newer surgical technique of gamma knife and low marginal doses showed relative improvement in metabolism in the lateral temporal lobe with persistently decreased metabolism in the mesial temporal lobe [63].

The other major site of the seizure focus in partial epilepsy is the frontal lobe (Fig. 7). Because many of these seizures begin in the medial or inferior aspects of the frontal lobe, scalp EEG readings do not provide adequate localization of foci [64–67]. Franck et al [68] used interictal FDG-PET to study 13 patients with presumed frontal lobe epilepsy and found PET to be the best modality for localizing seizure foci in this location. Further, the authors suggested that PET might help in determining the site of surgical excision or suggest a contraindication to surgical intervention in patients with multiple or bilateral foci. A study of 180 surgical specimens from patients with frontal lobe epilepsy found a high correlation between hypometabolic regions on interictal PET images and structural, histopathologic changes in the surgical specimens [69]. This study is supported by an earlier study in which FDG-PET images revealed decreased frontal lobe metabolism in 64% of patients with frontal lobe seizures as determined by electroclinical ictal localization [70]. A study of pediatric patients demonstrated a similar sensitivity of FDG-PET in detecting frontal lobe seizure foci [71]. PET scans, however, demonstrated hypometabolism restricted to

the frontal lobes in approximately 62%. The remaining patients demonstrated hypometabolism that exceeded the epileptogenic region indicated by ictal EEG. What this extrafrontal hypometabolism may actually represent is not clear, but may be caused by either additional epileptogenic areas, effects of diaschisis, seizure propagation sites, or secondary epileptogenic foci. Regardless, the findings from the studies on frontal lobe epilepsy suggest that FDG-PET scanning is a sensitive and specific technique for investigating patients with seizures of probable frontal lobe origins.

Seizure foci in other areas have also been detected using FDG-PET. A patient with seizures originating in the parietal lobe demonstrated hypermetabolism in the affected parietal lobe during an interictal PET scan [72]. The authors suggested that this hypermetabolism might have been related to the clustering of seizures in this patient so that the scan may have actually represented an ictal state. A more recent evaluation of parietal lobe seizures demonstrated that the sensitivity for detecting the seizure focus was comparable for MR imaging, PET, and SPECT, although MR imaging was the highest at approximately 64%, whereas PET had a sensitivity of only 50% [73]. The results indicate that parietal lobe seizures are much more difficult to localize than either temporal or frontal lobe seizures.

Ictal PET imaging

Performing ictal PET studies is more logistically impractical primarily because of the relatively short half-life of positron-emitting isotopes, such as [^{18}F] [74]. Several ictal PET studies have been reported, however, which have been successful in the determination of seizure foci in patients with partial seizures. In these studies, the seizure focus appears as a hypermetabolic area. In earlier studies, Chugani et al [75] have devised a classification system to describe

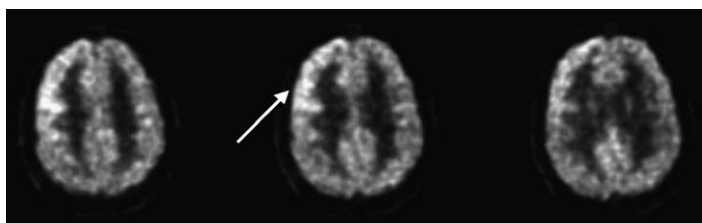


Fig. 7. Ictal FDG-PET study using a high-resolution GSO-dedicated head scanner of a subject demonstrating hypermetabolism in the right frontal lobe (arrow) compared with the rest of the cortical areas. This indicates a seizure focus in the right frontal lobe.

the metabolic patterns observed in children with partial complex seizures. Specifically, three major metabolic patterns were observed and were based on the degree and type of subcortical involvement. The type I pattern was defined as asymmetric glucose metabolism of the striatum and thalamus. Patients with this pattern often showed unilateral cortical and crossed cerebellar hypermetabolism. The type II pattern included symmetric hypermetabolism in the striatum and thalamus, which was associated with hypermetabolism of the hippocampal or insular cortex. Interestingly, the type II pattern also included diffuse neocortical hypometabolism and the absence of any cerebellar abnormalities. The type III pattern showed hypermetabolism that was restricted to the cerebral cortex with normal metabolism in the striatum and thalamus. Despite defining these three patterns of FDG-PET findings, this study could not correlate the PET findings with EEG or clinical features of the seizure disorders in these patients.

Another ictal PET study using oxygen-15–water ($[^{15}\text{O}]\text{-H}_2\text{O}$) showed that complex partial seizures are associated with bilaterally increased cerebral blood flow in a number of cortical areas, particularly the temporal and frontal lobes [76]. In addition, these patients also had increased blood flow to the subcortical areas, which are activated during ictus.

Surgical planning with PET

Several studies have used PET imaging for the purpose of planning surgical interventions. Duncan et al [77] used $[^{15}\text{O}]\text{-H}_2\text{O}$ PET in conjunction with anatomic images from MR imaging, which helped to determine the brain regions involved with motor activity, visual perception, articulation, and receptive language tasks in pediatric patients before temporal, and even extratemporal, surgery. At follow-up, the patients who underwent both temporal lobectomy and extratemporal resection for a neoplastic or nonneoplastic seizure focus were seizure-free with minimal postoperative morbidity. The authors note that no child sustained a postoperative speech or language deficit. Interestingly, when patients had prenatal cortical injury, PET demonstrated reorganization of language areas to new adjacent areas or even to the contralateral hemisphere. One study used ictal PET overlaid onto the corresponding MR imaging to determine successfully the seizure focus and to help with neurosurgical planning [78]. Cognitive activation paradigms using PET imaging have been suggested as an alternative approach to the evaluation of functional and epileptogenic zones for presurgical

evaluation in patients with epilepsy [79]. More work is needed to determine the most clinically efficacious paradigms for different seizure types. The authors suggest that the strength of activation PET studies lies in the ability to study shifts in cognitive circuitry that accompany a fixed neuropathologic entity for both groups of similar subjects and individuals. These techniques may enhance the understanding of the fundamentals of brain plasticity and may be used in the future to predict precise surgical risks.

By combining PET and MR imaging data, these studies demonstrated an enhancement in surgical safety, definition of optimal surgical approach, delineation of the seizure focus, and facilitation of maximum resection and optimization of the timing of surgery. Noninvasive presurgical brain mapping with PET can reduce the risk and improve neurologic outcome in seizure patients undergoing surgical resection.

Receptor PET imaging

PET imaging to measure various neurotransmitter systems has been used to study patients with seizures. Initial studies of benzodiazepine receptor activity in temporal lobe epilepsy showed decreased benzodiazepine receptor activity in the medial temporal lobe [80]. This reduction in benzodiazepine receptor activity may correlate with the frequency of seizures [81]. A more recent study compared the results obtained from FDG with carbon-11–flumazenil ($[^{11}\text{C}]\text{-FMZ}$) [82]. FDG-PET images showed a large area of hypometabolism in the epileptogenic temporal lobe (as determined by other diagnostic studies including scalp EEG and MR imaging). Both FDG-PET and $[^{11}\text{C}]\text{-FMZ}$ PET reliably revealed the epileptogenic temporal lobe and neither agent proved superior to the other. This study did not find any correlation between the degree of hypoactivity in either $[^{18}\text{F}]\text{-FDG}$ or $[^{11}\text{C}]\text{-FMZ}$ PET and the grading of mesial temporal sclerosis according to the Wyler criteria observed with MR imaging. Furthermore, this study compared the PET results with those obtained with interictal iodine-123–iomazenil ($[^{123}\text{I}]\text{-IMZ}$) SPECT and found that the later was highly inaccurate in localizing the affected temporal lobe. It has been suggested that in the pediatric population, $[^{11}\text{C}]\text{-FMZ}$ PET may have a useful clinical role in patients with partial epilepsy who have normal or subtle changes on FDG-PET, in patients with bilateral FDG findings but unifocal seizure activity on EEG, and in patients after surgical resection who continue to have seizures [83]. This latter group often demonstrates large areas

of hypometabolism on FDG-PET in the area of the resection that may also include remaining epileptogenic foci.

Another study compared changes in benzodiazepine receptors in the thalami of patients with temporal lobe epilepsy [84]. The dorsal medial nuclei showed significantly lower glucose metabolism and [^{11}C]-FMZ binding on the side of the epileptic focus. Interestingly, the lateral thalami showed bilateral hypermetabolism and increased [^{11}C]-FMZ binding. A significant correlation was found between the [^{11}C]-FMZ binding in the dorsal medial nuclei and that in the amygdala. These PET abnormalities were associated with a significant volume loss in the ipsilateral thalamus as determined by anatomic MR imaging. Decreased benzodiazepine receptor binding in the dorsal medial nucleus may be caused by neuronal loss, as suggested by volume loss on MR imaging, but this decrease also may indicate impaired γ -aminobutyric acid transmission in the dorsal medial nucleus, which has strong reciprocal connections with other parts of the limbic system. The increased glucose metabolism and [^{11}C]-FMZ binding in the lateral thalamus was hypothesized to represent an up-regulation of γ -aminobutyric acid-mediated inhibitory circuits. Frontal lobe epilepsy is associated with significantly reduced benzodiazepine receptor density in the anterior cerebellum contralateral to the seizure focus [85].

A study using the receptor ligand [^{11}C]-FMZ to evaluate six patients with frontal lobe seizures [86] reported that the seizure focus was correctly identified by [^{11}C]-FMZ PET as an area of decreased benzodiazepine receptor density in all patients studied. Furthermore, the area with reduced benzodiazepine receptor density was better delineated than the corresponding hypometabolic region observed with FDG-PET images. Several other studies of benzodiazepine receptors showed that the areas of abnormal benzodiazepine receptor binding were more extensive than anatomic abnormalities observed on MR imaging or even than the hypometabolic areas observed on interictal FDG-PET [87,88].

There are several studies that have demonstrated the involvement of the opioid neurotransmitter systems in seizure physiology. Several PET studies using the δ -receptor selective antagonist [^{11}C]-methylaltrindole and [^{11}C]-carfentanil, which measures μ -receptor binding in patients with temporal lobe epilepsy, have shown increased receptor activity in the affected temporal lobe [89–91]. When compared with interictal FDG-PET, the binding of opiate receptors was increased and [^{18}F]-FDG uptake decreased in the temporal cortex ipsilateral to the

seizure focus [91]. Furthermore, decreases in [^{18}F]-FDG uptake were more widespread than were the increases in opioid receptors. There were also different regional binding patterns for the δ - and μ -receptors. Increases in μ -receptor binding were localized to the middle aspect of the inferior temporal lobe and binding of δ receptors increased in the middle and superior temporal lobe. The fact that there are differences in the regional binding of the μ - and δ -opiate receptors suggests that they may play different roles in seizure physiology.

Other seizure disorders

There are many other types of seizure disorders that have been investigated using PET imaging. Absence seizures are a common form of epilepsy associated with brief spells of loss of consciousness and is associated with 3-Hz generalized spike-wave activity on EEG. The actual site of the seizure origin, however, has been difficult to detect and localize. An [^{15}O]- H_2O PET cerebral blood flow study was performed on eight patients with idiopathic generalized epilepsy in whom typical absence seizures were induced by voluntary hyperventilation [92]. This study showed that there was a global increase in blood flow during the typical absence seizures. There was also a focal increase in mean thalamic blood flow. This study, however, although indicating an important role of the thalamus in the pathogenesis of absence seizures, was unable to show that the thalamus was the origin of the seizure activity. An earlier ictal FDG-PET study of patients in absence status showed decreased metabolic rates throughout both cortical and subcortical structures compared with interictal scans [2]. A comparison with single absence attacks suggested that there is a pathophysiologic difference between the two states. A recent case study reported localizing absence seizures in one patient to the right frontal lobe using ictal PET [93]. No evidence was found for a change in [^{11}C]-FMZ binding with absence seizures. This result, together with those of a study showing no abnormality of [^{11}C]-FMZ binding interictally in patients with childhood and juvenile absence epilepsy, does not support a primary role for the benzodiazepine binding site of the γ -aminobutyric acid-A receptor in the pathogenesis of absence seizures [94].

Another unusual epileptic disorder consists of focal inhibitory motor seizures that result in ictal paralysis. A study of this type of seizure disorder showed that these patients had a centroparietal epileptogenic focus on SPECT that was also sug-

gested by other neuroimaging studies [95]. In particular, MR imaging showed centroparietal structural lesions in most of the patients. In one patient with a normal MR imaging scan, there was right centroparietal hypometabolism on PET imaging. Given these findings, the authors suggest that it is important to distinguish such seizures from transient ischemic attacks and migraine, which may not have the same imaging findings.

There have been a few reports of imaging studies in patients with cortical heterotopia. A report of FDG-PET imaging in patients with diffuse band heterotopia revealed similar and even higher deoxyglucose uptake in the layer of cortical heterotopia compared with the normal cortex [96]. The authors suggested that the findings might represent persistent synaptic activity in the heterotopic neurons, which is unaffected by age or by the time-course of epilepsy. A hexamethylpropyleneamine oxime SPECT image has also been reported in an epileptic patient with a rare form of diffuse subcortical laminar heterotopia detected on MR imaging [97]. The interictal SPECT scan of this patient revealed identical or increased perfusion of the laminar heterotopia as compared with that of the overlying cortical mantle. The SPECT scan also showed decreased perfusion in the left temporal lobe that agreed with the type of complex partial seizures and the EEG finding of frequent generalized spike-wave complexes with a slight left-sided dominance.

Infantile spasms may occur either because of an underlying, identifiable cause (symptomatic group) or may be idiopathic (cryptogenic group). PET studies have found that cryptogenic spasms have focal cortical regions of hypometabolism in the interictal period [98,99]. Further, the focal areas found on PET correspond to areas of EEG abnormalities. A recent study suggested that there are multifocal areas of hypometabolism in such patients and that the structures involved are associated with specific disease characteristics [100]. For example, frontal hypometabolism correlated with the degree of mental retardation, hypotonia, and ataxia. Temporomesial hypometabolism correlated with the occurrence of obtunded states, and parietal changes were associated with the occurrence of myoclonic seizures and spike-wave discharges. Because of the poor prognosis of infants with infantile spasm, surgical removal of the abnormal foci identified by PET has been attempted. The results indicated that 75% of the patients remain seizure free, whereas others improved markedly after surgery [101].

Lennox-Gastaut syndrome, the triad of 1- to 2.5-Hz spike-wave pattern on EEG, intellectual im-

pairment, and multiple seizure types, has been investigated with PET and four patterns have been described [102]. The four metabolic subtypes are (1) unilateral focal, (2) unilateral diffuse hypometabolism, (3) bilateral diffuse hypometabolism, and (4) normal metabolism [103,104]. Because this disorder is often refractory to anticonvulsant therapy, surgical intervention has been attempted with subsequent control of seizure activity [105]. PET imaging may provide useful information regarding the type of surgical intervention necessary in these patients. A more recent study of Lennox-Gastaut syndrome, in relation to other epileptic encephalopathies, demonstrated that PET scans were normal in all children with typical de novo Lennox-Gastaut syndrome but showed cortical metabolic abnormalities in three of four with atypical de novo Lennox-Gastaut syndrome, five of six with Lennox-Gastaut syndrome following infantile spasms, six of eight with severe myoclonic epilepsy in infancy, and four of six with an unclassified epileptic encephalopathy [106]. The findings from this study suggest that some children with epileptic encephalopathies previously thought to have primary generalized or multifocal seizures may have a unifocal origin for their seizures. If a focal origin is observed, then surgical intervention may be useful as a treatment modality in these cases.

Patients with Sturge-Weber syndrome, characterized by facial capillary nevus (port-wine stain) and ipsilateral leptomeningeal angiomas, often develop epileptic seizures because of the intracranial, extracerebral vascular malformation. Like infantile spasms and Lennox-Gastaut syndrome, Sturge-Weber syndrome is usually refractory to medications and requires surgical intervention. In conjunction with CT and MR imaging, PET has been useful in helping to determine the surgical technique (usually a hemispherectomy) necessary in these patients [107]. PET imaging usually shows widespread unilateral hypometabolism ipsilateral to the facial nevus [108]. Not unlike other seizure disorders, hypermetabolism is noted ipsilateral to the facial nevus during the ictal period.

Summary

PET imaging has been widely used in the evaluation and management of patients with seizure disorders. The ability of PET to measure cerebral function is ideal for studying the neurophysiologic correlates of seizure activity during both ictal and interictal states. PET imaging is also valuable for

evaluating patients before surgical interventions to determine the best surgical method and maximize outcomes. PET will continue to play a major role, not only in the clinical arena, but also in investigating the pathogenesis and treatment of various seizure disorders.

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