CHAPTER 15

Positron-emission Tomography in Epilepsy

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POSITRON-EMISSION TOMOGRAPHY OF BRAIN GLUCOSE METABOLISM

Basic Technique and Principles

Positron-emission tomography (PET) is a noninvasive functional imaging method of measuring local chemical functions in various body organs. In the brain, PET has been applied in the study of local glucose and oxygen utilization, blood flow, protein and DNA synthesis, as well as neurotransmitter synthesis, uptake and receptor binding. Unlike structural cerebral imaging studies, PET images are functional representations of various aspects of brain activity. PET can be used to measure baseline functional activity as well as physiologic or pathologic changes and responses (e.g. elicited by behavioral or pharmacologic manipulations) in cerebral activity.

The PET technique employs a camera consisting of multiple pairs of oppositely situated detectors, which are used to record the paired high energy (511 keV) photons traveling in opposite (≈180°) directions as a result of positron decay (1, 2). The size and cross-sectional geometry of the detectors largely determine the spatial accuracy of the localization of the positron-emitting source. Tracer kinetic models that mathematically describe physiologic or biochemical reaction sequences of compounds labeled with positron-emitting isotopes permit a characterization of the kinetics and the mathematical expression for calculating actual rates of the biologic process being studied (3). The amount of activity measured in an organ depends on the kinetics of the metabolic process, the transport properties between the blood and the cellular site of the process, and the amount and time course of delivery of the activity to the organ by the blood (1).

The most widely available PET tracer is 2-deoxy-2[^{18}F] fluoro-D-glucose (FDG) to measure glucose metabolism of various organs. FDG is also the most commonly used tracer for epilepsy studies, although several other tracers have been used or proposed to image the epileptic brain (Table 15.1). FDG is similar to 2-[^{14}C]deoxyglucose, an analog of glucose and a tracer used in autoradiography studies of various animals used in laboratory experiments. In FDG, hydrogen on the number 2 carbon is substituted with the positron emitter ^{18}F (half-life: 110 min).

FDG is transported in tissue and phosphorylated to FDG-6-phosphate in the same manner as glucose. However, FDG-6-phosphate is not a substrate for the next reaction step of glycolysis, and also not a significant substrate for glycogen synthesis or for the pentose shunt. Thus, since it cannot immediately leave the cell, phosphorylated FDG gets trapped without significant further metabolism, and its location and amount can be measured by PET as the ^{18}F decays. FDG is similar to glucose in its plasma to tissue transport and phosphorylation; thus, under steady-state conditions, FDG uptake reflects the utilization rate of exogenous glucose. In the brain, this rate is highly related to the synaptic density and functional activity of the brain tissue.

In order to quantify the measured process, e.g. to determine absolute glucose metabolic rates in various brain regions using FDG PET, it is necessary to perform independent measurements of the activity as a function of time in the arterial blood. Unlike for PET measurements of many other functions, accurate estimation of local cerebral metabolic rates can be achieved by obtaining a single set of PET images, provided that the arterial input function (from either timed arterial blood samples or dynamic PET scanning of the left ventricular blood pool) has been acquired. When analyzing pediatric PET scans, however, one has to keep in

TABLE 15.1. *PET Tracers and Their Clinical Use in Epilepsy*

Isotope	Half-life	Tracer	Target Function	Change in Epileptic Focus	Clinical Use
^{18}F	109 min	2-deoxy-2[^{18}F]fluoro-D-glucose (FDG)	Glucose metabolism	Interictal decrease* Ictal increase	TLE (nonlesional) ETLE Childhood epilepsy
		^{18}F-cyclofoxy	Mu and kappa opiate receptors	Increase	n.e.
^{11}C	20 min	[^{11}C]-flumazenil	$GABA_A$ receptors	Decrease	TLE/dual pathology ETLE
		α[^{11}C]-methyl-L-tryptophan	Tryptophan metabolism to serotonin or quinolinic acid	Increase	Tuberous sclerosis ETLE
		[^{11}C]FCWAY	$5\text{-}HT_{1A}$ receptors	Decrease	n.e.
		(S)-[*N*-methyl-[^{11}C]ketamine	NMDA receptors	Decrease	n.e.
		[^{11}C]doxepin	Histamine H_1 receptors	Increase	n.e.
		[^{11}C]carfentanil	Mu opiate receptors	Increase	n.e.
		[^{11}C]methyl-naltrindole	Delta opiate receptors	Increase	n.e.

* Except if cortex is actively spiking during uptake period.
ETLE, extra-temporal-lobe epilepsy; n.e., not established in clinical practice; TLE, temporal lobe epilepsy.

mind that absolute metabolic rates undergo major physiologic changes during brain development, with a temporary increase of brain metabolism above normal adult levels followed by a gradual decline to reach adult levels by the end of adolescence (4, 5). Furthermore, in patients with epilepsy, absolute glucose metabolic rates can be affected (usually decreased) by antiepileptic drugs (such as barbiturates, phenytoin, carbamazepine, benzodiazepines, or valproate) (6–8). These effects can be diminished by calculating metabolic rates normalized to the whole brain metabolism.

In clinical practice, however, absolute quantification is not always necessary. Since the regional *pattern* of cerebral glucose metabolic is largely fixed after 1 year of age (5), focal decreases or increases in FDG uptake can be reliably identified using activity images without calculating absolute glucose metabolic rates. In patients with unilateral seizure foci (that are potential candidates for epilepsy surgery if the seizures are medically intractable), use of asymmetry indices created from activity measured in various portions of the presumed epileptic hemisphere and from the contralateral homologous brain regions is a simple and sensitive method of detecting focal functional abnormalities of cortical and subcortical structures of the epileptic brain.

Clinical Use of FDG Positron-emission Tomography Studies in Epilepsy

Temporal Lobe Epilepsy

Initial FDG PET studies were performed more than two decades ago in patients with intractable complex partial seizures of temporal lobe origin, and showed localized glucose metabolic changes (interictal hypometabolism) that apparently coincided with the general location of the electroencephalography (EEG)-defined epileptic focus (Fig. 15.1) (9–11). The sensitivity of PET to identify the epileptogenic temporal lobe has significantly improved, and is estimated to be around 85–90% or even beyond (12–15), largely as a result of the application of high-resolution scanners and advanced analytic methods. FDG PET can show relative temporal hypometabolism in more than 50% of patients with nonlateralized surface ictal EEG findings (16). Thus, application of PET in the evaluation of patients with intractable epilepsy has had a significant impact on management (16–18). In many cases, use of FDG PET could replace invasive EEG monitoring (depth electrodes) that, before the widespread application of advanced MRI techniques, was often otherwise inevitable.

Recent advances in analysis techniques of MRI (including application of fluid attenuation recovery techniques, hippocampal volumetry, and proton magnetic resonance spectroscopy) have led to very reliable noninvasive detection of hippocampal sclerosis by MRI, eliminating the need for functional imaging or invasive EEG monitoring in the majority of patients with temporal lobe epilepsy (TLE). In fact, FDG PET rarely provides additional clinical information when hippocampal atrophy is obvious on MRI (13). Therefore, PET is now generally reserved for those cases in which MRI fails to provide the necessary lateralization information. A recent study has lent support to this by showing that FDG PET is indeed able to lateralize the epileptic focus in TLE patients with subtle or absent quantitative MRI abnormalities (19). This study also demonstrated that glucose metabolism in medial temporal structures is often reduced over and above the severity of histopathologic changes, although the pathomechanism of hypometabolism remains to be determined.

A recent study on children with new-onset seizures found lower incidence of focal hypometabolism than expected from previous data obtained from patients with long-term, intractable epilepsy (20), suggesting that at least some of the hypometabolic areas may be the consequence of repeated seizures rather than simply indicating an area that is the

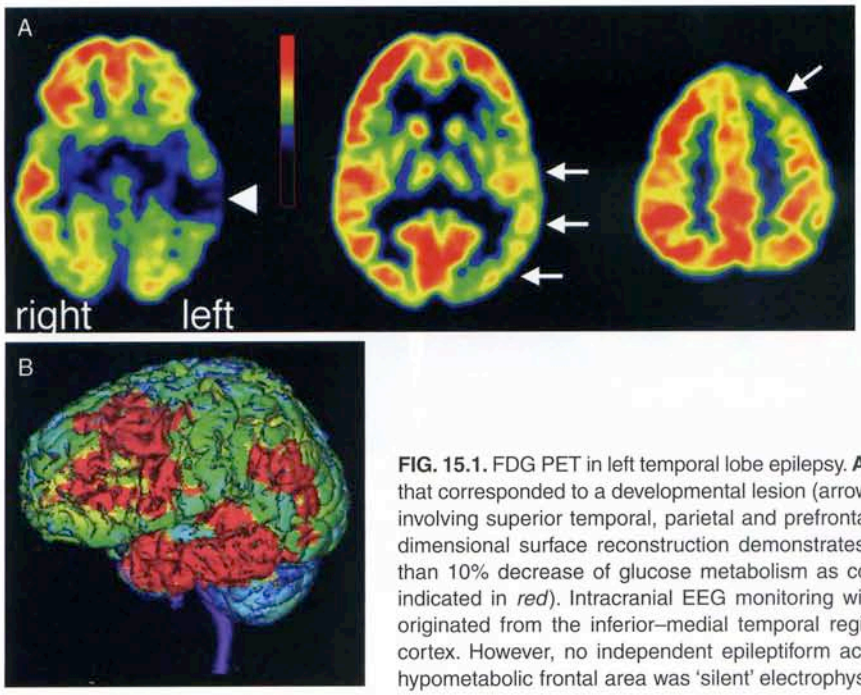

FIG. 15.1. FDG PET in left temporal lobe epilepsy. **A.** Severe hypometabolism in the left temporal region that corresponded to a developmental lesion (arrowhead) in a 10-year-old girl. Milder hypometabolism involving superior temporal, parietal and prefrontal cortex can be also seen (arrows). **B.** The three-dimensional surface reconstruction demonstrates the extent of hypometabolism (areas with more than 10% decrease of glucose metabolism as compared to contralateral homologous regions are indicated in *red*). Intracranial EEG monitoring with subdural grids demonstrated that the seizures originated from the inferior–medial temporal region, with occasional spread to the inferior frontal cortex. However, no independent epileptiform activity occurred in the frontal cortex and the large hypometabolic frontal area was 'silent' electrophysiologically.

primary site of seizures. Postoperative recovery of hypometabolism in remote areas in the frontal lobe after successful resection of the temporal focus (21, 22), also suggests that some of the hypometabolic areas are largely functional and potentially reversible if the primary epileptogenic region is excised.

It has been extensively demonstrated that interictal hypometabolic regions are not strictly confined to the presumed temporal epileptogenic zone or to the brain tissue showing pathologic changes, but commonly extend beyond temporal structures (12, 13, 23–25). Additional brain regions most commonly demonstrating interictal hypometabolism in TLE include ipsilateral parietal and frontal cortex as well as thalamus (Fig. 15.1B); these remote cortical regions, however, rarely show epileptiform activity on EEG and their resection is usually not necessary to alleviate seizures. Nevertheless, intracranial EEG studies should address extratemporal cortex with hypometabolism in cases where scalp ictal EEG abnormalities are not strictly confined to the temporal lobe but show a wider field potentially involving these extratemporal regions.

In addition to commonly extending beyond epileptogenic brain regions, the actual degree of glucose metabolic changes depends on the physiologic state of the tissue. For example, seizures during the tracer uptake and even frequent interictal spikes can significantly increase local glucose metabolism and can potentially mask or falsely lateralize hypometabolic epileptic foci (26–29). Therefore, continuous EEG monitoring during the FDG uptake period is essential to avoid false interpretation of focal abnormalities of glucose metabolism (30). Ictal FDG PET studies are often difficult to interpret also because they often reveal complex patterns of increased and decreased glucose metabolism (reflecting a mixture of ictal and postictal metabolism). In these cases, FDG PET may have to be repeated in the interictal state or use of another PET tracer may become necessary.

Extratemporal Lobe Epilepsy

Early FDG PET studies in extratemporal epilepsy found focal, regional, or hemispheric hypometabolism in approximately two-thirds of adult patients with frontal lobe foci, and these abnormalities correlated well with electroclinical ictal localization (31). Using high-resolution PET scanning, da Silva et al. (32) reported unilateral frontal lobe hypometabolism in 85% of epileptic children with a frontal lobe focus and normal CT and MRI scan. The location of frontal lobe PET abnormality corresponded to the area of seizure onset in four-fifths of the patients. Recent studies have demonstrated consistently that computerized analysis of FDG PET scans may assist accurate and objective identification of extratemporal lobe epileptic foci (33–35).

When onset of frontal lobe seizures is in the neonatal period or in infancy, an underlying structural lesion is often present even when the MRI is normal (Fig. 15.2). Under these circumstances, FDG PET can be useful in defining an area of hypometabolism that both correlates with the extent of microdysgenesis (36) and delineates the general area of epileptogenicity. However, the extent of abnormal neocortical metabolism often exceeds the electrophysiologically defined epileptogenic region. Correlation studies between

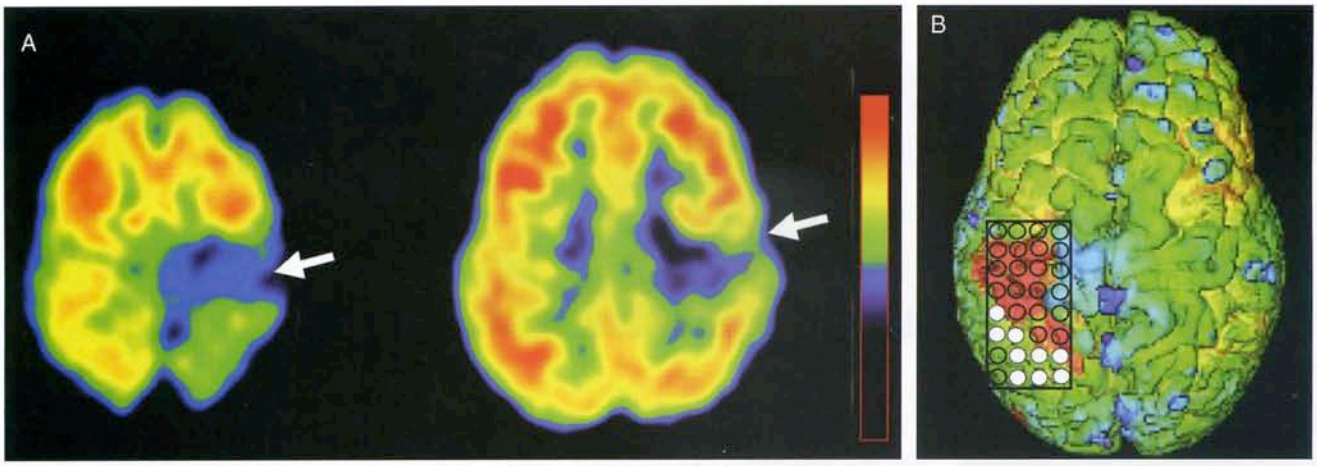

FIG. 15.2. A. FDG PET showing a well-defined area of hypometabolism in the superior parietal cortex of a 7.5-year-old girl with intractable seizures that started at 2 years of age. MRI was unremarkable but the abrupt decrease of cortical metabolism on PET suggested a lesion. **B.** Three-dimensional surface reconstruction from volumetric MRI (top view), superimposed with the FDG PET abnormality (>10% decrease of glucose metabolism; *red area*) as well as the subdural electrode array. The seizures originated from electrodes located behind the PET abnormality (white circles), while the hypometabolic cortex was 'silent' (these electrodes are represented by black open circles). Histology from the resected parietal tissue showed cortical dysplasia with balloon cells.

neocortical FDG PET abnormalities and ictal and interictal intracranial EEG data have demonstrated that, although FDG PET can detect abnormal cortical areas in patients with normal structural neuroimaging, and can correctly identify the general region of the epileptogenic cortex, it has limited specificity for the precise area of seizure onset (37, 38). Consistent with this, the extent of glucose hypometabolism ipsilateral to the seizure focus did not correlate with the epileptogenic tissue to be resected as determined by intracranial EEG (39). Nevertheless, findings from FDG PET can be useful to guide the placement of subdural electrodes, which otherwise must solely rely on seizure semiology and scalp electrode findings. Use of more specific tracers or application of other functional imaging modalities (e.g. ictal SPECT) can also help further, more precise, delineation of the epileptogenic tissue; this becomes particularly important when the epileptic focus potentially involves eloquent brain regions (primary motor, speech or visual areas).

Positron-emission Tomography Scanning of Epilepsy Syndromes in Childhood

Application of FDG PET has improved our understanding of the possible pathomechanism of epilepsy in various pediatric epilepsy syndromes and also has had an impact on their clinical management. For example, based on their electroclinical features, infantile spasms have been considered to be generalized seizures resulting from complex cortico-subcortical interactions. However, on PET scanning, most infants diagnosed with 'cryptogenic' spasms have focal or multifocal cortical regions of abnormal glucose utilization (Fig. 15.3). Histologic analysis of such regions (when a surgical resection is undertaken) often reveals areas of cortical dysplasia that are commonly missed by MRI (40, 41).

When a single region of abnormal glucose utilization is apparent on PET, corresponding to the EEG focus, and the spasms are intractable, surgical removal of the focus with abnormal metabolism results not only in seizure control but also in reversal of the associated developmental delay.

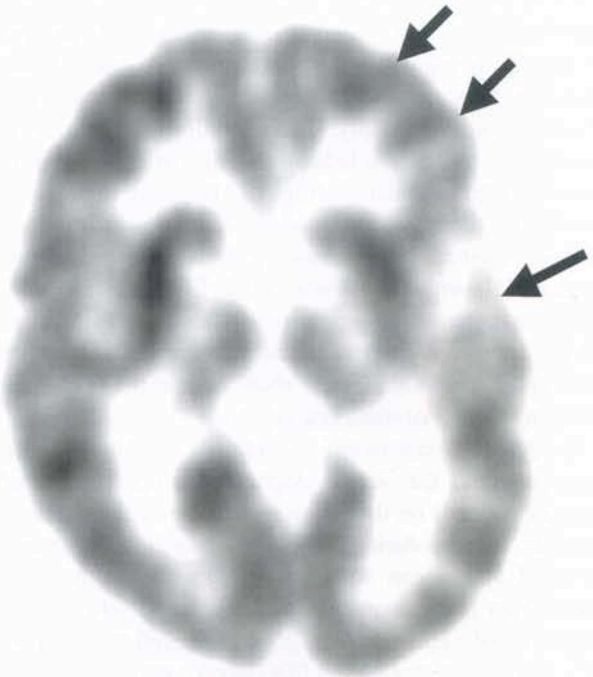

FIG. 15.3. Left frontal and temporal hypometabolism (arrows) in a 13-month-old boy with cryptogenic infantile spasms.

Most patients with bilateral multifocal areas of hypometabolism are not surgical candidates; however, if all seizures arise from one area, resective surgery may ameliorate the epilepsy but not improve cognitive status to the same extent as in those infants with a unifocal PET abnormality. When the pattern of glucose hypometabolism is generalized and symmetric, a lesional etiology is not likely and neurometabolic or neurogenetic disorders should be considered in further evaluating the child.

In children with *Lennox–Gastaut syndrome* (triad of multiple seizure types, developmental delay, and 1–2.5 Hz generalized 'slow' spike and wave EEG pattern), PET has provided a new classification based on metabolic anatomy. Four metabolic subtypes have been identified: unilateral focal, unilateral diffuse and bilateral diffuse hypometabolism, as well as normal patterns (42, 43). Patients with unilateral focal and unilateral diffuse patterns may be occasionally considered for cortical resection provided that there is concordance between PET and ictal EEG findings.

In patients at the advanced stage of *Sturge–Weber syndrome*, FDG PET typically reveals widespread unilateral hemispheric hypometabolism ipsilateral to the facial port wine stain in a distribution that commonly extends beyond the structural abnormalities depicted on CT or MRI scans (44, 45) (Fig. 15.4). The seizures often arise from the mildly hypometabolic cortex outside the region of the visible angioma or cortical atrophy.

The advantage of using PET in Sturge–Weber syndrome is to delineate the extent of functional involvement of cortical areas outside the region of the angioma, and MRI-detected atrophy, thus assisting in the assessment of candidacy for early hemispherectomy or focal cortical resection. FDG PET scans in these patients may also assess the rapidity of hemispheric demise and, indeed, those patients whose affected hemisphere becomes severely hypometabolic rapidly may not require surgical intervention because, in a sense, they are undergoing 'autohemispherectomy' and forcing the contralateral hemisphere to undergo reorganization changes early and optimally. This is in contrast to those patients whose affected hemisphere shows mild hypometabolism associated with persistent seizures and cognitive delay; these are the subjects who require surgical intervention to enhance effective reorganization in the contralateral hemisphere while brain plasticity is at a maximum during development (45).

Hemimegalencephaly is a developmental brain malformation characterized by congenital hypertrophy of one cerebral hemisphere with ipsilateral ventriculomegaly. When the epilepsy is medically uncontrolled, cerebral hemispherectomy is recommended. Glucose metabolism PET studies suggest that children with hemimegalencephaly often show additional less pronounced abnormalities in the opposite hemisphere, thus accounting for the suboptimal cognitive outcome even with complete seizure control (46). FDG PET is, therefore, a useful diagnostic tool in such children to assess the functional integrity of the contralateral hemisphere prior to hemispherectomy and helps predict cognitive outcome, which, in children with hemimegalencephaly, is generally worse than in children who have undergone hemispherectomy for other conditions, such as congenital hemiplegic cerebral palsy, Sturge–Weber syndrome or Rasmussen's encephalitis.

Rasmussen's syndrome is an example where FDG PET can facilitate early diagnosis and management. In the early stage of this disease, CT and MRI are often unremarkable for several months after the clinical manifestation of the disease. In this stage of the disease, however, FDG PET scanning already shows areas of abnormal metabolism restricted mostly to the frontal and temporal regions, whereas the posterior cortex is usually preserved (47) (Fig. 15.5). Pathologic changes seen in the resected cortex are more pronounced in cortical areas of abnormal glucose metabolism than in

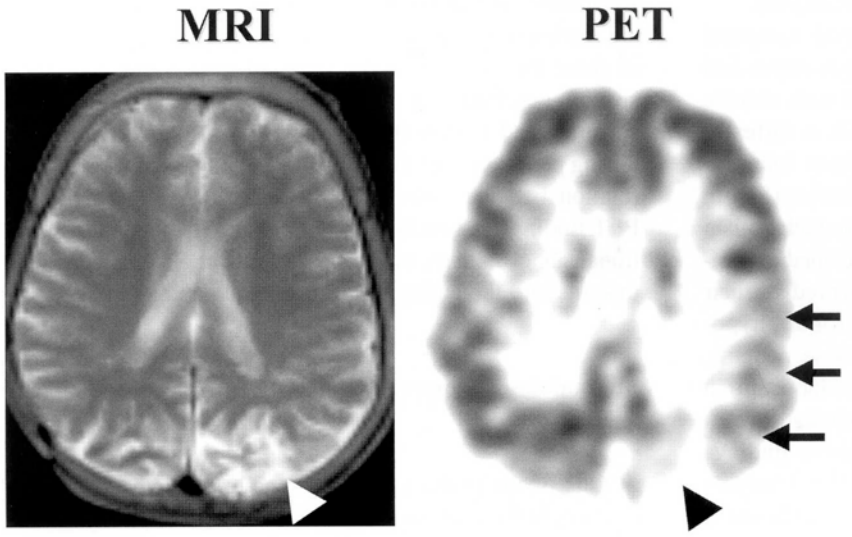

FIG. 15.4. MRI and FDG PET in Sturge–Weber syndrome. The child had a left occipital angioma with an underlying atrophy visualized on the MRI (arrowhead). This area showed minimal metabolism on PET, but a less severe hypometabolism extended far beyond the structural abnormality into the left parietal cortex (arrows). Seizures associated with Sturge–Weber syndrome often originate from moderately hypometabolic cortex.

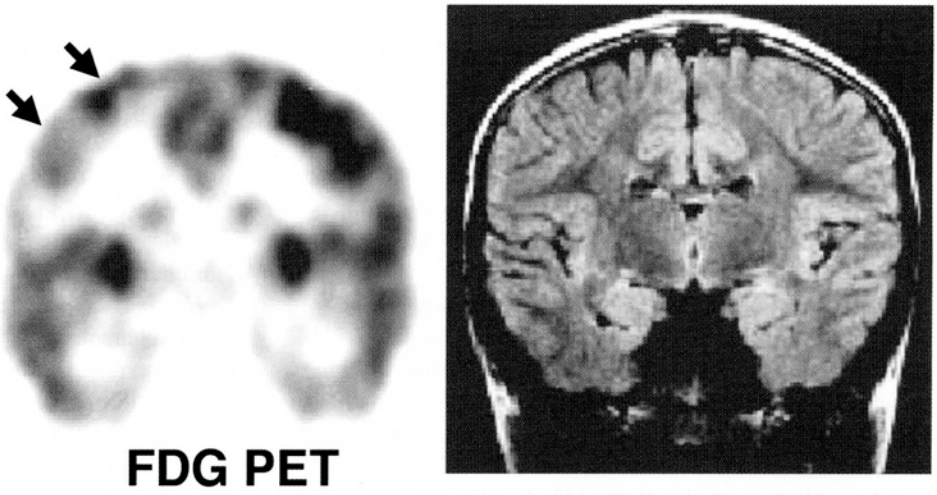

FIG. 15.5. Marked right frontal hypometabolism (arrows) in a child with Rasmussen's syndrome, 8 months after the onset of first seizure. MRI (including T2 and FLAIR sequences) was still unremarkable.

regions showing normal metabolism. Thus, FDG PET performed early during the course of Rasmussen's syndrome can facilitate the correct diagnosis and may also guide the site of brain biopsy when indicated.

Metabolic Correlates of Cognitive and Behavioral Abnormalities in Epilepsy

As discussed above, focal or regional glucose metabolic abnormalities on PET commonly extend beyond the presumed epileptogenic zone. These nonepileptogenic dysfunctional areas are of clinical interest because they often are associated with neuropsychological correlates. For example, in patients with unilateral TLE, presence of bitemporal glucose hypometabolism is associated with poor memory performance (48). In addition, TLE patients who perform poorly in tests of frontal lobe function often exhibit hypometabolism of the frontal lobe in addition to the temporal lobe epileptogenic zone, and impairment of verbal and performance intelligence measures in patients with TLE is associated with prefrontal involvement on the PET scan (49).

In infants with epileptic spasms, bilateral temporal hypometabolism (typically affecting both hippocampus and superior temporal gyri) is strongly associated with autistic features or pervasive developmental delay (50). A different pattern of bitemporal hypometabolism has been found in children with TLE and interictal aggressive behavior (51). In this latter group of patients, bitemporal hypometabolism was present in the temporal neocortex but the medial temporal (limbic) structures were relatively preserved in their glucose metabolism. Bilateral medial prefrontal hypometabolism was also a common finding in these patients, and the severity of temporal cortical hypometabolism in relation to the preserved medial temporal metabolism correlated well with the severity of aggression. These findings suggest that disinhibition of medial temporal lobe structures by temporal neocortex (and perhaps medial prefrontal cortex) may be important in producing a phenotype of aggression. On the other hand, if the medial temporal lobe structures are also hypometabolic, an autistic phenotype is seen, as in monkeys that have been subjected to bilateral medial temporal lesions (52).

NEURO-RECEPTOR AND LIGAND POSITRON-EMISSION TOMOGRAPHY STUDIES

Positron-emission tomograph scanning of various neurotransmitter systems has been a rapidly evolving field of functional neuroimaging in neurology and psychiatry during the past decade. In epilepsy, the main emphasis of this effort is to find new PET tracers that are able to detect focal neurotransmitter and/or receptor abnormalities of the epileptic brain, thus providing a better, more specific noninvasive delineation of epileptic foci. Indeed, development of novel PET tracers targeting neurotransmitter systems has proved to be feasible, and a handful of these tracers are increasingly becoming clinically utilized in several epilepsy centers worldwide. In this section, we summarize the most important methodologic aspects and emerging clinical applications of these PET tracers in the study of human epilepsy, with special emphasis on patients with medically intractable seizures, and review the current role of these PET tracers during presurgical evaluation. We also demonstrate how correlation between structural MRI and ligand/neuroreceptor PET findings can facilitate more accurate detection of functional abnormalities in the epileptic brain, to provide new insights into the pathophysiology of human epilepsy.

Methodologic Aspects of Ligand/Neuroreceptor PET Scanning

One of the major targets of functional neuroimaging in epilepsy is the gamma-aminobutyric acid (GABA) system in

the brain. GABA is the major inhibitory neurotransmitter in the human brain, and GABAergic mechanisms play a key role in regulating central nervous system excitability and susceptibility to seizures (53). The action of GABA is mediated in part by the $GABA_A$ receptor complex, the site of action of numerous therapeutic pharmacologic agents (such as benzodiazepines) and several drugs of abuse. Flumazenil is a benzodiazepine antagonist that binds to the alpha subunit of the $GABA_A$ receptor. The PET tracer [^{11}C]flumazenil (FMZ) can be used to obtain quantitative images of $GABA_A$ receptor binding.

Patients undergoing FMZ PET should not take drugs (such as benzodiazepines) that directly interact with the $GABA_A$ receptors. In clinical studies with FMZ PET, patients taking benzodiazepine drugs have generally been excluded, but the effects of drugs that result in allosteric interactions with $GABA_A$ receptors have not been well studied. Chronic vigabatrin treatment was associated with decreased regional $GABA_A$ receptor binding in young children with partial seizures or infantile spasms (106), but no similar effects were reported in adults (54). Age-related changes in FMZ binding have been reported in humans (55) and, in normal adult volunteers, baseline FMZ binding values are 25–50% lower (depending on the brain region) than those in children around 2 years of age (measured in the nonepileptic hemisphere of children with epilepsy).

During FMZ PET scanning in children, sedation is often unavoidable. Among commonly used sedatives, pentobarbital was reported to have no significant effect on in-vitro FMZ binding (56). Chloral hydrate (1000 mg taken orally) was found to cause a negligible increase of in-vivo FMZ binding of the whole brain in a small group of adults with partial epilepsy (55).

Quantification of FMZ PET images can be performed using a three-compartmental model (57) or a simpler two-compartmental model (58). This latter model yields parametric images of the volume of distribution (V_D) of the tracer in tissue and the ligand influx rate constant (K_1). V_D is a macroparameter incorporating both receptor density (B_{max}) and receptor affinity (K_D), and represents B_{max}/K_D. These two components can only be separated by applying more than one injection with different FMZ concentrations, i.e. to obtain multiple PET scans and produce a Scatchard plot. Such studies are feasible and may be useful to estimate receptor density and affinity in vivo (59) but are not practical. For example, even two PET studies in the same patient would allow for a suboptimal Scatchard analysis with only two points. On the other hand, V_D images allow visualization of a quantitative measure of $GABA_A$ receptor binding and are much easier to obtain.

Direct comparisons of in-vivo FMZ binding using PET with ex-vivo binding measured in resected epileptic tissues using [^{3}H]FMZ autoradiography showed that, after correction for partial volume effects, the degree of in-vivo FMZ binding correlated well with ex-vivo measurements of $GABA_A$ receptor binding in the epileptogenic hippocampi of patients with medial TLE (60). However, laminar analysis of resected spiking cortex from patients with TLE suggests that decreased in-vivo FMZ binding is not necessarily due to decreased $GABA_A$ receptor density but may be due to complex changes that include both B_{max} and K_D in different cortical layers. In fact, [^{3}H]FMZ autoradiography studies showed increased B_{max} in cortical layers V–VI of spiking cortex but decreased receptor affinity that outweighed the increased binding such that the net effect was a decrease in V_D shown as an area of decreased FMZ uptake on the PET images (61).

The cortical-layer-specific increase of receptor number may be a compensatory mechanism for decreased GABAergic input. Limited spatial resolution of PET precludes laminar analysis of cortical FMZ binding in vivo, but the findings demonstrate that decreased FMZ binding on PET may be the result of spatial summation of multiple changes in $GABA_A$ receptor function. This may explain why, in some patients with focal epilepsy, no focal abnormalities of in-vivo FMZ binding can be detected in the EEG-determined epileptic focus, while others show focal increases of FMZ binding on PET.

A drawback of absolute quantification yielding FMZ V_D images is the requirement of arterial blood sampling to provide blood input function. Elimination of arterial blood sampling can facilitate more widespread clinical application of FMZ PET scanning and is particularly desirable in the pediatric patient population. In fact, visual as well as objective detection of focal cortical and subcortical abnormalities for clinical purposes can be reliably achieved using FMZ 'activity' images that do not require arterial blood sampling. Comparison of focal FMZ abnormalities in patients with neocortical epileptic foci showed that summed FMZ 'activity' images obtained between 10 and 20 minutes after tracer injection represented the best overall agreement between FMZ activity and V_D images, as compared to activity images obtained from an earlier (5–10 min) or later (15–30 min) time frame (62). Slight differences between the V_D and FMZ activity images can be caused by the tracer influx parameter K_1.

Another neurotransmitter system that has proved to be important in the functional neuroimaging of epilepsy is the serotonergic system and tryptophan metabolism. In-vitro observations showing increased serotonin (5-HT) content and immunoreactivity in human epileptic tissue (63, 64) have led to the application of the PET tracer α[^{11}C]methyl-L-tryptophan (AMT) in the study of epilepsy. AMT is an analog of tryptophan (the precursor of 5-HT), and is converted in the brain to α[^{11}C]methyl-serotonin, which is not a substrate for the degradative enzyme monoamine oxidase, and therefore accumulates in serotonergic terminals. This has been demonstrated in rats, where labeled AMT accumulated in high concentration in serotonergic cell bodies in the raphe nuclei (65). α[^{3}H]methyl-serotonin present in nerve terminals was released by K^+-induced depolarization, suggesting that this tracer is stored with the releasable pool of serotonin (66). Further, AMT, unlike tryptophan, is not incorporated into proteins in significant amounts (65, 67) and is therefore a suitable tracer for the measurement of serotonin synthesis

in vivo in humans with PET, although it does not measure the absolute rate of serotonin synthesis.

Studies in animals (65, 68) and humans (69, 70) have suggested that the kinetic behavior of AMT can be described by a three-compartmental model using first-order rate constants. After transport of AMT across the blood–brain barrier, free AMT in the cytoplasm is either metabolized (to α[^{11}C]methyl-serotonin or via the kynurenine pathway; see below), or is irreversibly trapped, presumably in a serotonin synthesis precursor pool. The unidirectional uptake rate constant (K-complex) represents the combined unidirectional uptake into all three pools. The K-complex was found to be stable within an individual, and the rank order of regional brain values for this parameter is consistent with the rank order for serotonin content in the human brain (71).

An alternative route of tryptophan metabolism in the brain is via the enzymes 2,3-dioxygenase and indoleamine 2,3-dioxygenase, which are part of the kynurenine pathway. Under normal circumstances, levels of the metabolites of these pathways are 100–1000-fold lower than the concentration of tryptophan in the brain (72) and thus metabolites of the kynurenine pathway do not contribute significantly to the accumulation of AMT. Under pathologic conditions, however, induction of indoleamine 2,3-dioxygenase (e.g. by infections, viruses, or interferons) can lead to significant metabolism of tryptophan along the alternative kynurenine pathway. Among numerous metabolites of this pathway, quinolinic acid is neurotoxic, and a strong convulsant through its agonist action at the excitatory *N*-methyl-D-aspartate (NMDA) receptors. In fact, preliminary data from surgically resected brain tissue from children with tuberous sclerosis complex and intractable epilepsy have indicated that accumulation of quinolinic acid may contribute to the high in-vivo uptake of AMT in epileptogenic cortex (73).

In addition to using AMT for evaluating serotonin synthesis and tryptophan metabolism via the kynurenine pathway, an emerging approach is to image 5-HT_{1A} receptors by PET. Using [^{11}C]-WAY, 5-HT_{1A} receptor binding can be reliably measured in vivo (74). Preliminary PET studies in TLE showed decreased [^{18}F]FCWAY binding in the temporal lobe ipsilateral to the seizure focus as defined by EEG data (75).

Further PET tracers for in-vivo investigation of other neurotransmitter systems, such as [^{11}C]carfentanil (76), ^{11}C-diprenorphine (77), or 18F-cyclofoxy (78) for opiate receptors, [^{11}C]doxepin for histamine H_1 receptors (79), and (*S*)-[*N*-methyl-^{11}C]ketamine for NMDA-receptors (80) have not been adequately tested in epileptic patients but preliminary studies suggest that they may also be potentially useful in detecting epileptic cortex (see also Clinical applications, below).

Data Analysis

Qualitative visual analysis of ligand and neuroreceptor PET studies can be satisfactory for clinical purposes, with certain limitations. For example, since FMZ binding is relatively high in the medial temporal structures, unilateral decrease of FMZ binding in the hippocampus can be reliably identified, while bilateral symmetric decreases might be hard to interpret visually. Visual interpretation is also reliable to detect unilateral focal cortical decreases of FMZ binding but, again, is less reliable in detection of bilateral FMZ PET abnormalities and is not accurate in defining the extent of cortical areas with abnormal receptor binding.

Anatomical accuracy of ligand and neuroreceptor PET abnormalities can be enhanced by co-registering PET images with high-resolution MRI. This approach is especially useful when functional activity in very small brain structures, such as hippocampus, amygdala, or thalamic nuclei, is to be measured. High-resolution MRI-based partial volume correction enhances detection of FMZ binding in these structures (24, 81) and provides higher sensitivity to alterations than visual evaluation in patients with TLE, where focal decrease of FMZ binding in the medial temporal structures as well as in the thalamus ipsilateral to the seizure focus is common. One such study using PET/MRI co-registration found that the reduction in hippocampal FMZ binding is over and above what would be expected from loss of hippocampal volume, thus indicating that atrophy is not the sole determinant of $GABA_A$ receptor binding decrease in medial TLE and that other factors also contribute to decreased hippocampal FMZ binding (81).

Objective interpretation of PET images can be also performed using voxel-by-voxel analysis with statistical parametric mapping (SPM) (82). SPM is a robust, objective method of comparing patient groups with normal control groups, can detect common abnormalities of FMZ binding (83, 84), and is also applied to other types of PET measurement. This approach often reveals subtle abnormalities that are difficult to appreciate by visual or region-of-interest (ROI)-based image analysis. For example, using SPM and FMZ PET, involvement of the insular cortex was reported in 60% of patients with medial TLE (84). The presence or absence of such abnormalities did not predict surgical outcome but their regional distribution (anterior vs posterior insula) was related to ictal symptoms (emotional vs somesthetic symptoms, respectively).

The SPM analytic approach has been also useful to delineate focal abnormalities of cortical FMZ binding in patients with neocortical epileptic foci, including those with normal MRI and those with structural lesion (85, 86). Unlike previous ROI-based studies, these SPM studies consistently showed not only focal decreases but also increases of FMZ binding (85, 87), although the exact nature of these abnormalities is not entirely clear. Some of the areas showing increased FMZ binding coincide with focal cortical developmental malformations (88). Since no detailed EEG comparisons have been performed, the causative relationship between these focal abnormalities and epileptogenicity is not established.

In a recent study of 10 patients with malformations of cortical development, correction for partial volume effects for the area of MRI-defined malformation as well as for

adjacent and overlying regions was applied (108). This study found decreased FMZ binding in some of the malformations but increased binding in some adjacent volumes of interest. Altogether, these studies demonstrate that objective analytic approaches are capable of identifying otherwise unappreciated abnormalities of abnormal FMZ binding that often extend beyond the structurally abnormal cortex representing functional abnormalities of $GABA_A$ receptors.

The SPM technique also allows objective analysis of FMZ binding in the white matter (which normally shows very low FMZ binding) by applying explicit white matter masking (90). These studies showed *increased* FMZ binding in the normal appearing temporal lobe white matter ipsilateral to the epileptic focus in patients with TLE and normal MRI. These white matter abnormalities were associated with microdysgenesis demonstrated by histopathology. In this case, FMZ V_D provided an in-vivo neuronal marker indicating increased number of white matter ectopic neurons in the epileptogenic temporal lobe. This is a potentially important finding, considering that ectopic neurons can contribute to epileptogenesis by providing an aberrant circuitry (91).

A drawback of voxel-based analytic approaches is that warping of native images to a predefined template requires smoothing, and results in a reduction of the original image resolution. An alternative objective method of delineating cortical PET abnormalities is based on analysis of asymmetries of small homologous cortical regions (33). The procedure uses native (unwarped) PET images and allows identification of abnormal cortical tracer content based on asymmetry indices derived from small bilateral homotopic cortical areas according to a predefined cutoff threshold (typically between 8% and 15%, depending on the PET tracer used), determined from PET scans of normal control subjects. The only major assumption made is that one of the hemispheres (contralateral to the presumed epileptic focus) is for the most part normal, and can serve as an internal control for the other hemisphere containing the epileptic focus. This, of course, is not always a valid assumption and is one of the pitfalls of the method.

The program marks all cortical segments in which the asymmetry of activity concentration exceeds the cutoff threshold. These marked PET images are then co-registered with the volumetric MRI image of the patient, and the PET abnormalities are surface-rendered, i.e. they are directly displayed on the cortical surface reconstructed from the patient's high-resolution MRI (Fig. 15.6). For patients undergoing subdural EEG recording, the locations of intracranial electrodes can be accurately identified and visualized on the three-dimensionally rendered brain surface by using digital X-ray images with fiducial markers (92, 93) or digital intraoperative photographs showing locations of electrode contacts on the cortex (94). These techniques allow direct comparison of objectively defined functional imaging abnormalities with ictal and interictal intracranial EEG datasets. Such comparisons provide a powerful way of exploring the functional relationship between ligand/neuroreceptor and electrophysiologic abnormalities of the epileptic cortex.

In patients with epilepsy and structural brain lesion(s), multimodal imaging of co-registered structural (MRI) and functional (PET or SPECT) abnormalities allows analysis of functional abnormalities in the lesions themselves as well as in the perilesional cortex (38, 95, 96). The benefit of simultaneous analysis of PET and MRI images has been well demonstrated in children with the tuberous sclerosis complex and intractable epilepsy (95). In these patients, MRI and FDG PET typically show multiple, typically bilateral lesions, but the seizures often originate from one of the lesions, as suggested by seizure semiology and ictal EEG.

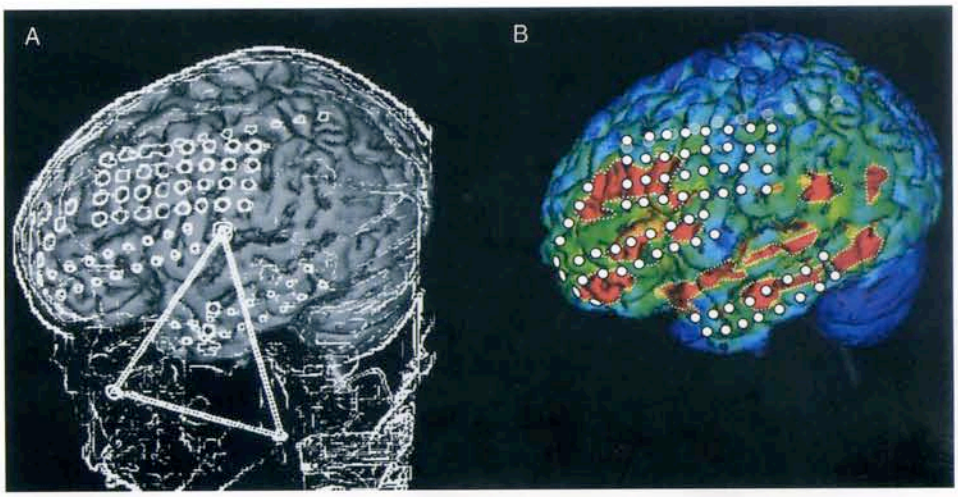

FIG. 15.6. X-ray-based identification of subdural grid electrodes for PET co-registration on the three-dimensional brain surface, reconstructed from volumetric MRI. **A.** The X-ray and MRI image datasets are co-registered using fiducial markers (two on the left and one on the right side), which form a triangle in the image space. **B.** Locations of the grid electrodes derived from the co-registered X-ray, superimposed to the brain surface, showing the objectively defined PET abnormalities in the left frontal and temporal cortex. A 1×10 electrode grid is located in the medial frontal–temporal area and cannot be directly visualized on the lateral surface.

However, neither MRI nor FDG PET can identify the epileptogenic lesion. In contrast, AMT PET often shows relatively increased uptake in the epileptogenic lesions and decreased uptake in the remaining ones (see Clinical applications, below). Thus, measurement of relative AMT uptake in the MRI-identified lesions can help differentiate epileptogenic from nonepileptogenic tubers.

Clinical Applications

Flumazenil Positron-emission Tomography Scanning of $GABA_A$ Receptors

Among various neuroreceptor PET tracers used in epilepsy, FMZ is the one that has been most widely applied clinically. Initial studies using PET with FMZ showed significantly reduced binding in the epileptic focus of patients with partial epilepsy (97). Since then, several PET studies have demonstrated that areas of decreased FMZ binding commonly occur in patients with intractable partial epilepsy of both temporal and extratemporal origin, and that these abnormal regions tend to be spatially more restricted than corresponding regions of cortical glucose hypometabolism (15, 23, 59, 98).

Temporal Lobe Epilepsy

Flumazenil PET is highly sensitive in TLE and shows decreased FMZ binding in the sclerotic hippocampus in patients with medial TLE (23, 83). This high sensitivity of FMZ PET can be particularly useful in patients with a potentially epileptogenic cortical lesion when presence of dual pathology (co-existence of neocortical lesion and hippocampal sclerosis) is suspected (99) (Fig. 15.7). Undiagnosed dual pathology can be a source of surgical failure, since resection of both the cortical lesion and the affected hippocampus is necessary to optimize the surgical results. In some cases FMZ PET can detect multiple areas of decreased binding, including both the hippocampus and neocortical areas that do not show any obvious lesion on MRI. In such cases, intracranial EEG recordings are necessary to determine whether both the hippocampal and neocortical area is epileptogenic or, alternatively, one of them is the primary focus and the other may represent remote abnormality of $GABA_A$ receptors; such areas are often targeted by rapid seizure spread (see also Extratemporal epilepsy, below).

Since decreased FMZ binding in pure medial TLE is largely (although not completely) confined to the affected temporal lobe, FMZ PET can be also helpful in patients where medial TLE is suspected (based on seizure semiology and/or ictal EEG recordings) but FDG PET shows additional extratemporal hypometabolism. Such regions of hypometabolism (most commonly in parietal or prefrontal cortex) may be seen with chronic epilepsy and do not necessarily indicate epileptogenicity, but may be associated with cognitive dysfunction. One comparative analysis of such cases suggested that decreased FMZ binding represents localized neuronal loss and/or receptor changes in the epileptogenic zone, whereas the more extensive glucose hypometabolism on FDG PET may reflect diaschisis (23). On the other hand, extratemporal cortical involvement on FMZ PET of patients with suspected TLE warrants caution, and may require consideration of intracranial EEG monitoring of the affected extratemporal areas, especially if the electroclinical findings cannot definitively exclude the extension of epileptogenic areas beyond the temporal lobe. Nevertheless, with clinical application of advanced MRI techniques, the overwhelming majority of patients with intractable TLE and hippocampal sclerosis do not require FMZ (or other types of) PET studies during their presurgical evaluation, and the use of FMZ PET is the subject of individual consideration.

The clinical significance of FMZ PET abnormalities in TLE and normal hippocampal volumes is less established.

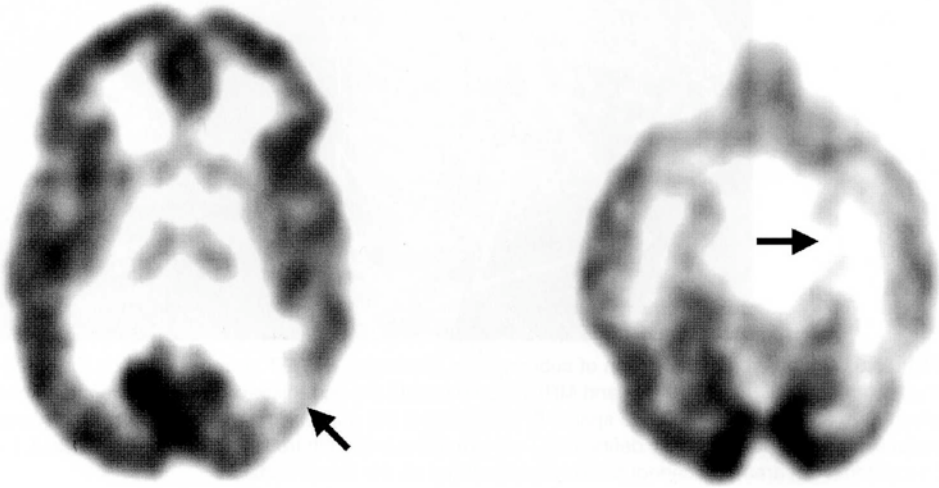

FIG. 15.7. [^{11}C]Flumazenil PET detecting dual pathology (arrows) consisting of a dysplastic area in the left posterior temporal region and decreased FMZ binding in the ipsilateral hippocampus indicating hippocampal sclerosis.

Transient and falsely lateralizing FMZ PET asymmetries have been reported in three patients with normal hippocampal MRI by Ryvlin et al. (100). In contrast, Lamusuo et al. (101) found decreased temporal FMZ binding ipsilateral to the EEG-defined seizure focus in 46% of medial TLE patients with normal hippocampal volumes. Histologic examination verified the presence of hippocampal damage in these cases, suggesting that FMZ PET can be useful to lateralize the epileptic temporal lobe in some TLE patients with normal volumetric MRI.

Using a more complex analytic method (by combining SPM and an MRI-based volume-of-interest approach with partial volume correction) in a similar group of MRI-negative TLE patients, Koepp et al. (102) found focal decreases and/or increases of FMZ binding ipsilateral to the presumed epileptic focus in 80% of the cases. However, these abnormalities did not consistently localize the epileptic focus. Altogether, these studies demonstrate a relatively high prevalence of focal FMZ binding abnormalities in TLE patients with normal MRI, but it remains unclear how these changes contribute to the presurgical evaluation of these patients and how they affect outcome after surgery.

Extratemporal Epilepsy

Since current surgical results remain suboptimal in extratemporal (neocortical) epilepsies, especially in the pediatric population, there has been a great deal of interest in applying neuroreceptor PET tracers in the presurgical evaluation of such patients, with special emphasis on those with normal MRI or cortical developmental malformations. Studies to date indicate that FMZ PET is a promising imaging modality, which often shows decreased binding in the presumed epileptic focus shown on EEG even when the MRI appears normal (Fig. 15.8). Comparisons with intracranial ictal EEG findings have shown 57–100% sensitivity of FMZ PET in detecting neocortical epileptic foci, depending on the patient population and the applied analytic approach (15, 37, 103, 104). In a detailed comparison of objectively defined, surface-rendered FDG and FMZ PET abnormalities (using an asymmetry-based approach; see Analysis) and intracranial EEG data, Muzik et al. (37) found areas of decreased FMZ binding to be significantly more sensitive for detecting zones of seizure onset and frequent interictal spiking than areas of glucose hypometabolism. A close spatial relationship between seizure onset zone and the area showing reduced FMZ binding also has been reported in patients with cortical dysplasia (105).

Collectively, these findings suggest that FMZ PET is a useful clinical tool to further delineate potentially epileptogenic neocortex and to guide and enhance subdural electrode coverage for intracranial EEG monitoring. One of the few studies that have analyzed surgical outcome data in young patients who underwent cortical resection following FMZ PET scanning, found that complete resection of cortex with preoperative FMZ PET abnormalities was associated with excellent surgical outcome even in the absence of a structural lesion on MRI (39).

A subgroup of patients with neocortical epileptic foci shows area(s) of decreased FMZ binding remote from the seizure focus (Fig. 15.9). The exact nature of these abnormalities is not known. Comparisons with outcome data indicate that resection of such remote FMZ abnormalities is not

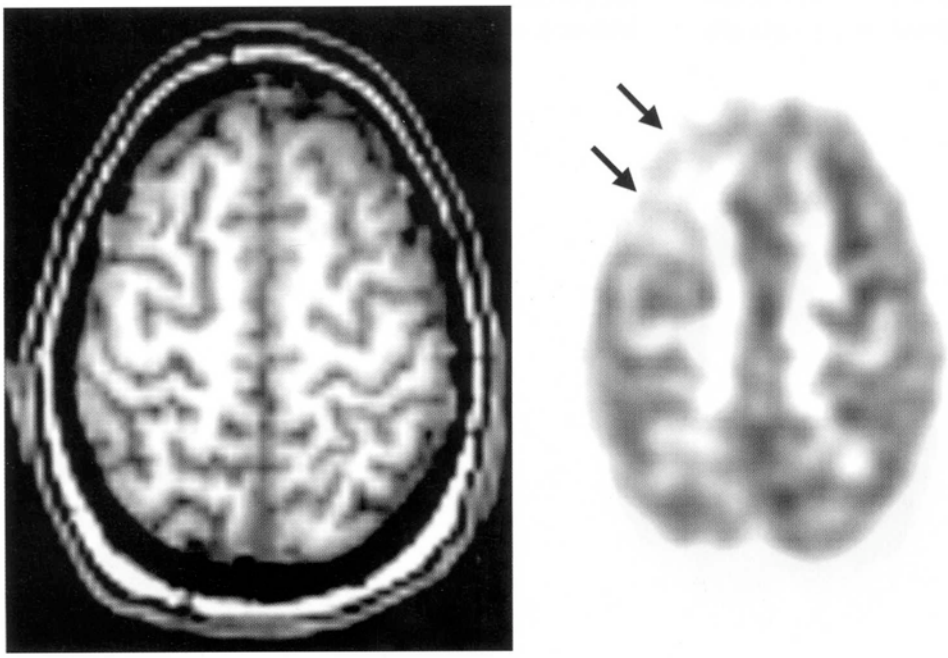

FIG. 15.8. Decreased [^{11}C]flumazenil binding in the right frontal cortex (arrows) in a patient with right frontal lobe epilepsy and normal MRI. The location of the seizure focus was verified by intracranial EEG monitoring.

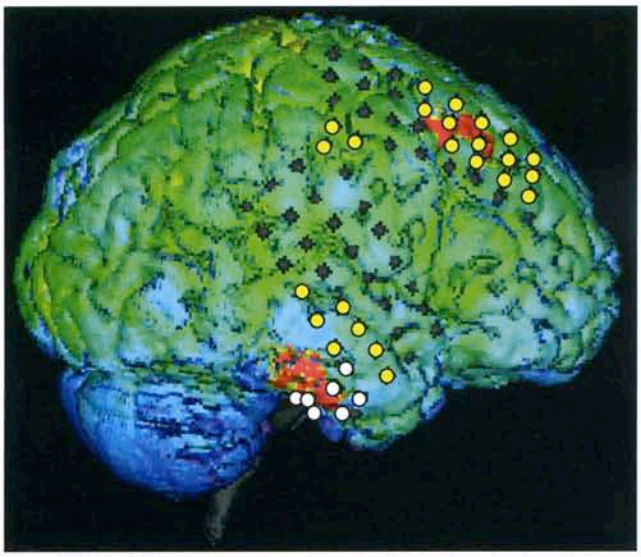

FIG. 15.9. Flumazenil (FMZ) PET abnormalities (red areas indicating areas with >10% decreases of FMZ binding on the three-dimensionally reconstructed surface) detecting the seizure focus (white electrodes in the right inferior temporal region) as well as a remote frontal cortical area that has shown frequent interictal spiking (yellow electrodes) on intracranial EEG.

always necessary to achieve long-term seizure freedom (provided that the seizure focus has been removed), although many of these remote areas appear to be targeted by rapid seizure spread as shown by intracranial ictal EEG recordings (104, 39). In fact, Savic et al. (107) reported postoperative recovery of such remote FMZ binding abnormalities (located in the primary projection areas of the seizure focus) in four patients with medial TLE following successful surgical resection of the primary epileptic focus. Furthermore, in patients with lesional epilepsy, remote cortical areas with decreased FMZ binding were located in ipsilateral synaptically connected regions, and were associated with seizure onset early in life and chronic intractable epilepsy (104).

Altogether, these data suggest that cortical areas with decreased FMZ binding, particularly if located in projection areas targeted by seizure propagation, may be related to repeated seizures over a relatively long period, and might represent potential areas of secondary epileptogenesis. This hypothesis, however, must be tested through further studies.

Occasionally, FMZ PET does not show any obvious focal abnormalities in patients with nonlesional extratemporal epilepsy. This is not common, but represents a limitation of FMZ PET. Further studies comparing FMZ with other PET tracers that have the capability of delineating epileptic brain regions will be useful. In fact, preliminary studies suggest that AMT PET may be helpful in some of these FMZ-negative cases (see below).

In patients with neocortical epilepsy and brain lesion, FMZ PET reliably detects most lesions, and the magnitude of decreased FMZ binding varies according to the type of lesion (98, 96, 99). Decreased FMZ binding, however, commonly extends to the perilesional cortex (Fig. 15.10), and the size of this perilesional abnormality is usually smaller than the corresponding perilesional hypometabolism shown with FDG PET (104, 96, 105). Perilesional FMZ PET abnormalities are often not concentric but eccentric, and show a good correspondence with epileptiform activity on intracranial EEG. Recently, Hammers et al (108). used a quantitative approach and found not only decreases but also increases of FMZ binding in cortex overlying or adjacent to focal cortical dysplasia. These studies support the notion that abnormal $GABA_A$ receptor binding is not confined to the cortical malformations visible on MRI, but extend beyond the structural lesion.

Objective, quantitative analysis of the FMZ PET images and their correlation with structural imaging and electrophysiologic findings are essential for optimal detection and interpretation of focal abnormalities. Further comparisons with new, emerging functional imaging modalities such as

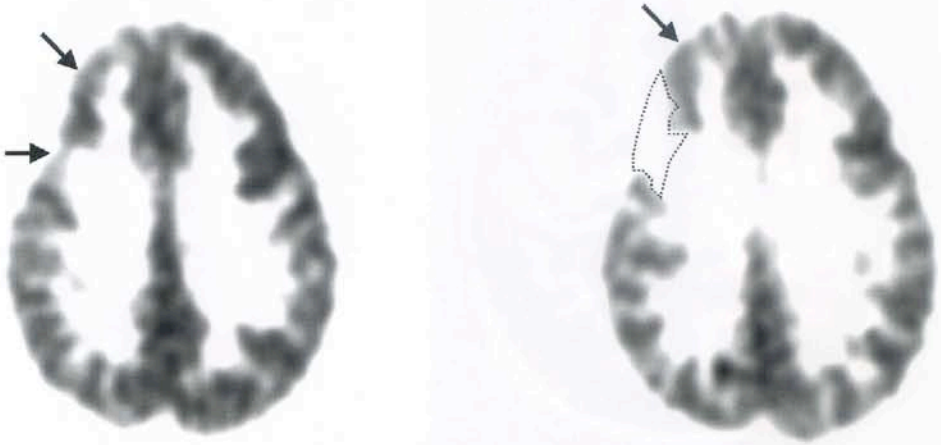

FIG. 15.10. [^{11}C]Flumazenil (FMZ) PET in a patient with a right frontal lesion (cyst) and intractable frontal lobe epilepsy. The lesion itself (delineated by dotted line) showed no FMZ binding, while the perilesional cortex showed decreased FMZ binding (arrows). The seizures originated from the right prefrontal cortex.

functional MRI, magnetic resonance spectroscopy, or magnetic source imaging may help further understand the significance of in-vivo $GABA_A$ receptor abnormalities in the pathogenesis of human partial epilepsy.

Idiopathic Generalized Epilepsy

Flumazenil PET studies in idiopathic generalized epilepsies have provided somewhat controversial findings. Savic et al. (109) first reported normal FMZ binding in cerebral cortex and decreased receptor density in the thalamus of adult patients with idiopathic generalized epilepsy. Prevett et al. (110, 111) found no differences in regional FMZ V_D values between at rest scans and images obtained during absence seizures, and also when compared to normal controls. In contrast, Koepp et al. (112) reported a significant global increase of FMZ V_D in the cortex, thalamus, and cerebellum in patients with idiopathic generalized epilepsy, with no effect from subsequent treatment with valproate. These findings are consistent with those from electrophysiologic studies in idiopathic generalized epilepsies and provide some support for the role of the thalamus in the pathogenesis of absence seizures. However, none of the studies have shown conclusively the initiation site of the seizures, and the role of ligand/receptor PET in the diagnosis of idiopathic generalized epilepsies remains limited.

Imaging Tryptophan Metabolism by Positron-emission Tomography

Although AMT PET is currently available in only a handful of epilepsy centers, it appears to have strong clinical applications in selected cases of epilepsy. The first successful clinical application of AMT PET in intractable epilepsy was demonstrated in children with the tuberous sclerosis complex who were being considered for resective epilepsy surgery (113). (Fig. 15.11). In fact, AMT PET was the first PET tracer capable of differentiating between epileptogenic and nonepileptogenic lesions in the interictal state in children with tuberous sclerosis. Subsequently, it was found to be useful also in patients with other types of neocortical epilepsy, by showing increased uptake of AMT in the epileptogenic regions.

While the specificity of focally increased AMT uptake for the epileptic focus appears to be very high, its sensitivity is suboptimal and seems to depend on the underlying etiology as well as the analytic approach applied. For example, in a cohort of 63 consecutive patients with tuberous sclerosis and intractable epilepsy, visual assessment identified increased AMT uptake in only 28 cases (44.4%) but when MRI-based quantitative assessment of the AMT images was applied, the sensitivity increased to 79% (114). This apparent discrepancy is due to the fact that nonepileptogenic tubers typically show decreased AMT uptake and that some epileptogenic tubers showing relatively increased AMT uptake cannot be easily differentiated from adjacent normal cortex without quantitative analysis following coregistration with MRI (95).

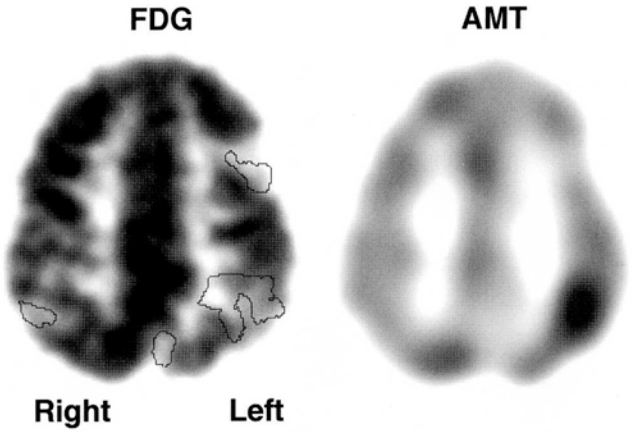

FIG. 15.11. FDG and α[^{11}C]methyl-L-tryptophan (AMT) PET scans in a patient with tuberous sclerosis and intractable seizures. FDG PET shows the typical finding of multiple areas with hypometabolism, consistent with multiple tubers. The outlined regions on the FDG PET represent individual tubers delineated on co-registered MRI images. AMT PET shows very high uptake (dark area) in the left parietal region, from where the seizures originated. The remaining tubers showed normal or decreased uptake.

Recent studies in nontuberous sclerosis patients have shown that AMT PET can occasionally detect epileptic cortex in patients with normal MRI (115) and that histologically verified (macroscopic or microscopic) cortical dysplasia is associated with a higher occurrence of increased AMT uptake as compared to cases with nonspecific gliosis in the surgical specimen (116). This finding is consistent with previous human epileptic tissue studies showing serotonergic hyperinnervation in dysplastic tissues but not in cortex from patients with cryptogenic epilepsy (64). Comparisons with FDG PET also showed that the area of increased AMT uptake, if present, is significantly more restricted than the extent of corresponding glucose hypometabolism. Furthermore, in some instances, AMT PET can identify epileptogenic cortex even if FDG and/or FMZ PET do not show any obvious focal abnormality (Fig. 15.12).

Although clinical experience with AMT PET is limited in medial TLE, this method does not appear to be particularly useful in localizing medial temporal foci associated with hippocampal sclerosis. However, a recent study demonstrated that AMT PET can be useful to identify the epileptic focus in patients with TLE and normal hippocampal volumes (117). In addition, AMT PET scanning in patients with previously failed neocortical resection may disclose nonresected cortex with increased AMT uptake, especially if the histology had shown cortical developmental malformation. In these cases, AMT PET has the advantage of showing increased uptake in potentially epileptogenic areas and,

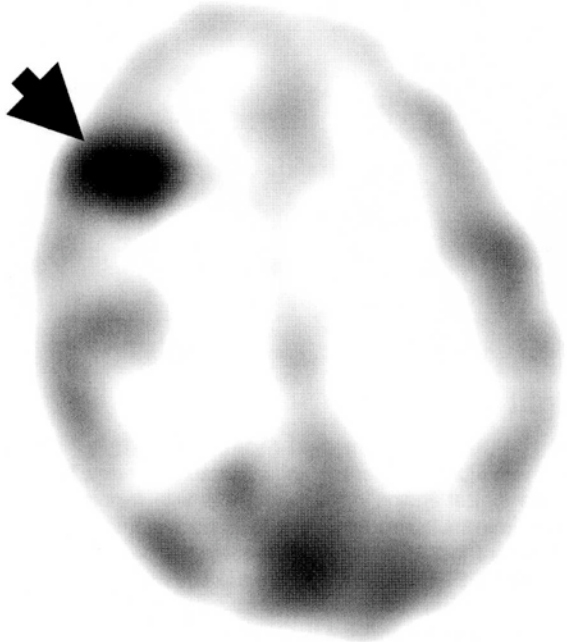

FIG. 15.12. α[^{11}C]Methyl-L-tryptophan (AMT) PET scan detecting epileptogenic cortex in a patient in whom neither FDG nor [^{11}C]flumazenil PET were localizing. Increased AMT uptake was seen in the epileptogenic right frontal lobe (arrow). The focus was verified by intracranial EEG. Histology showed cortical dysplasia in the surgical specimen following right frontal resection, which resulted in seizure freedom.

unlike MRI or interictal FDG or FMZ PET, can differentiate epileptogenic cortex from nonepileptic tissue damage caused by the initial surgery.

Opiate and Other Receptor Positron-emission Tomography Studies in Epilepsy

Clinical experience with opiate, histamine, and NMDA neuroreceptor PET tracers is limited, and their current role in presurgical evaluation is not well established. Endogenous opioid peptides modulate neural transmission in the hippocampus, and recurrent seizures induce changes in the expression of opioid peptides and receptors (118). Animal studies suggest that endogenous opioid release may play a role in termination of seizures (119). Consistent with this, serial absence seizures were found to be associated with an acute (15–41%) reduction of [^{11}C]diprenorphine (a nonspecific opiate receptor ligand) binding to association areas of neocortex (120), suggesting that occupation of opiate receptors by an endogenous opioid substance may contribute to seizure termination. Similarly, Koepp et al. (121) reported decreased [^{11}C]diprenorphine binding in the left parieto-temporo-occipital cortex of patients with reading induced epilepsy, scanned in the activated state. In addition, increased interictal binding of [^{11}C]carfentanil, a selective agonist for mu opiate receptors, has been reported in the temporal neocortex ipsilateral to the seizure focus in patients with TLE (76, 77).

However, [^{11}C]diprenorphine binding was not significantly different between regions in the epileptic and contralateral temporal lobes. Similarly, there is a lack of overall asymmetry of [^{18}F]cyclofoxy (which binds to both mu and kappa opiate receptors) binding, although some patients showed higher binding ipsilateral to the seizure focus (78). Finally, PET studies in TLE patients using the delta-receptor-selective antagonist [^{11}C]methylnaltrindole show a different regional pattern of increased binding as compared to [^{11}C]carfentanil (122). These studies suggest a differential regulation of opiate subtypes in TLE, with greater involvement of mu and delta receptors.

Kumlien et al. (80) reported a 9–34% decrease of (*S*)-[*N*-methyl-^{11}C]ketamine binding (a potential tracer for NMDA receptors) ipsilateral to the seizure focus in eight patients with medial TLE. It remains unclear whether these asymmetries are due to reduced NMDA-receptor density, reduced perfusion, focal atrophy (partial volume effects), or other factors. The same group of investigators have reported increased binding of [^{11}C]deuterium-deprenyl, an irreversible inhibitor of monoamine oxidase type B (MAO-B) with a very high affinity for the enzyme, in the epileptogenic temporal lobe, particularly in the medial temporal structures (124, 125). MAO-B is exclusively localized on astrocytes, and in-vitro studies had shown that its production is increased with gliosis in conjunction with neurodegenerative changes, mainly due to an increased number of reactive astrocytes. Interestingly, [^{11}C]deuterium-deprenyl binding was not increased in neocortical epileptic foci (124).

Thus, [^{11}C]deuterium-deprenyl PET seems to be more sensitive in TLE than in extratemporal epilepsy. This is in contrast to AMT PET, which may show increased uptake in neocortical foci but not in sclerotic hippocampus. These studies illustrate the specificity that PET is capable of providing in various types of epilepsy when appropriate tracers are selected. Finally, in patients with complex partial seizures, [^{11}C]doxepin PET demonstrated an increase of H_1 receptors in the seizure focus, which showed glucose hypometabolism on FDG PET (79) but these findings have not been replicated by other groups.

In summary, ligand/neuroreceptor PET studies provide new insights in the pathophysiology of human epilepsy and show differences in their sensitivity and specificity for temporal versus extratemporal lobe epilepsy. Unlike FDG, which characteristically shows decreased uptake in the region of the seizure focus interictally, some ligand and neuroreceptor tracers (such as AMT, [^{11}C]deuterium-deprenyl and [^{11}C]doxepin) show increased uptake in epileptogenic brain regions even in the interictal state. This represents a clear advantage over other imaging studies, especially when multiple structural lesions are present and potentially confound detection of the epileptogenic zone. The studies reviewed above also demonstrate that various tracers capture different aspects of the epileptic process and can provide

complementary information regarding localization of epileptic foci. Multimodal registration of functional and structural images is a clinically useful tool to accurately delineate anatomical extent of functional abnormalities. Highly accurate software packages that allow detailed comparisons of ligand/neuroreceptor PET studies with scalp and intracranial EEG findings are now available, and their application will further establish the role of these new PET imaging modalities in the presurgical evaluation of intractable epilepsies.

REFERENCES

1. Hoffman EJ, Phelps ME. Positron emission tomography: principles and quantitation. In: Phelps ME, Mazziotta JC, Schelbert HR, eds. Positron emission tomography and autoradiography: principles and applications for the brain and heart. New York: Raven Press, 1986:237–286..
2. Ter Pogossian MM. Positron emission tomography. In: Wagner HN, Szabo Z, Buchanan JW, eds. Principles of nuclear medicine. London: WB Saunders, 1995:342–346.
3. Carson RE. Precision and accuracy considerations of physiological quantitation in PET. *J Cereb Blood Flow Metab* 1991;11:A45–A50.
4. Chugani HT, Phelps ME. Maturational changes in cerebral function in infants determined by ^{18}FDG positron emission tomography. *Science* 1986;231:840–843.
5. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol* 1987;22:487–497.
6. Theodore WH. Antiepileptic drugs and cerebral glucose metabolism. *Epilepsia* 1988;29(Suppl 2):S48–S55.
7. Theodore WH, Bromfield E, Onorati L. The effect of carbamazepine on cerebral glucose metabolism. *Ann Neurol* 1989;25:516–520.
8. Leiderman DB, Balish M, Bromfield EB, Theodore WH. Effect of valproate on human cerebral glucose metabolism. *Epilepsia* 1991;32:417–422.
9. Kuhl DE, Engel J Jr, Phelps ME, Selin C. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of ^{18}FDG and $^{13}NH_3$. *Ann Neurol* 1980;8:348–360.
10. Engel J Jr, Kuhl DE, Phelps ME. Patterns of human local cerebral glucose metabolism during epileptic seizures. *Science* 1982;218:64–66.
11. Engel J Jr, Kuhl DE, Phelps ME, Mazziotta JC. Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes. *Ann Neurol* 1982;12:510–517.
12. Swartz BE, Tomiyasu U, Delgado-Escueta AV, et al. Neuroimaging in temporal lobe epilepsy: test sensitivity and relationships to pathology and postoperative outcome. *Epilepsia* 1992;33:624–634.
13. Gaillard WD, Bhatia S, Bookheimer SY, et al. FDG-PET and volumetric MRI in the evaluation of patients with partial epilepsy. *Neurology* 1995;45:123–126.
14. Knowlton RC, Laxer KD, Ende G, et al. Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy. *Ann Neurol* 1997;42:829–837.
15. Ryvlin P, Bouvard S, Le Bars D, et al. Clinical utility of flumazenil-PET versus [^{18}F]fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. *Brain* 1998;121:2067–2081.
16. Theodore WH, Sato S, Kufta CV, et al. FDG-positron emission tomography and invasive EEG: seizure focus detection and surgical outcome. *Epilepsia* 1997;38:81–86.
17. Engel J Jr, Henry TR, Risinger MW, et al. Presurgical evaluation for partial epilepsy: relative contributions of chronic depth-electrode recordings versus FDG-PET and scalp-sphenoidal ictal EEG. *Neurology* 1990;40:1670–1677.
18. Theodore WH, Sato S, Kufta C, et al. Temporal lobectomy for uncontrolled seizures: the role of positron emission tomography. *Ann Neurol* 1992;32:789–794.
19. Lamusuo S, Jutila L, Ylinen A, et al. [^{18}F]FDG-PET reveals temporal hypometabolism in patients with temporal lobe epilepsy even when quantitative MRI and histopathological analysis show only mild hippocampal damage. *Arch Neurol* 2001;58:933–939.
20. Gaillard WD, Kopylev L, Weinstein S, et al. Low incidence of abnormal ^{18}FDG-PET in children with new-onset partial epilepsy: a prospective study. *Neurology* 2002;58:717–722.
21. Akimura T, Yeh HS, Mantil JC, et al. Cerebral metabolism of the remote area after epilepsy surgery. *Neurol Med Chir (Tokyo)* 1999;39:16–25.
22. Spanaki MV, Kopylev L, DeCarli C, et al. Postoperative changes in cerebral metabolism in temporal lobe epilepsy. *Arch Neurol* 2000;57:1447–1452.
23. Henry TR, Frey KA, Sackellares JC, et al. In vivo cerebral metabolism and central benzodiazepine-receptor binding in temporal lobe epilepsy. *Neurology* 1993;43:1998–2006.
24. Juhász C, Nagy F, Watson C, et al. Glucose and [^{11}C]flumazenil positron emission tomography abnormalities of thalamic nuclei in temporal lobe epilepsy. *Neurology* 1999;53:2037–2045.
25. Van Bogaert P, Massager N, Tugendhaft P, et al. Statistical parametric mapping of regional glucose metabolism in mesial temporal lobe epilepsy. *Neuroimage* 2000;12:129–138.
26. Chugani HT, Shewmon DA, Khanna S, et al. Interictal and postictal focal hypermetabolism on positron emission tomography. *Pediatr Neurol* 1993;9:10–15.
27. Chugani HT, Rintahaka PJ, Shewmon DA. Ictal patterns of cerebral glucose utilization in children with epilepsy. *Epilepsia* 1994; 35:813–822.
28. Bittar RG, Andermann F, Olivier A, et al. Interictal spikes increase cerebral glucose metabolism and blood flow: a PET study. *Epilepsia* 1999;40:170–178.
29. Hong SB, Han HJ, Roh SY, et al. Hypometabolism and interictal spikes during positron emission tomography scanning in temporal lobe epilepsy. *Eur Neurol* 2002;48:65–70.
30. Sperling MR, Alavi A, Reivich M, et al. False lateralization of temporal lobe epilepsy with FDG positron emission tomography. *Epilepsia* 1995;36:722–727.
31. Swartz BE, Halgren E, Delgado-Escueta AV, et al. Neuroimaging in patients with seizures of probable frontal lobe origin. *Epilepsia* 1989;30:547–558.
32. Da Silva EA, Chugani DC, Muzik O, Chugani HT. Identification of frontal lobe epileptic foci in children using positron emission tomography. *Epilepsia* 1997;38:1198–1208.
33. Muzik O, Chugani DC, Shen C, et al. Objective method for localization of cortical asymmetries using positron emission tomography to aid surgical resection of epileptic foci. *Comput Aided Surg* 1998;3:74–82.
34. Drzezga A, Arnold S, Minoshima S, et al. ^{18}F-FDG PET studies in patients with extratemporal and temporal epilepsy: evaluation of an observer-independent analysis. *J Nucl Med* 1999;40:737–746.
35. Kim YK, Lee DS, Lee SK, et al. ^{18}F-FDG PET in localization of frontal lobe epilepsy: comparison of visual and SPM analysis. *J Nucl Med* 2002;43:1167–1174.
36. Chugani HT, Shewmon DA, Peacock WJ, et al. Surgical treatment of intractable neonatal-onset seizures: the role of positron emission tomography. *Neurology* 1988;38:1178–1188.
37. Muzik O, da Silva E, Juhász C, et al. Intracranial EEG vs flumazenil and glucose PET in children with extratemporal lobe epilepsy. *Neurology* 2000;54:171–179.
38. Juhász C, Chugani DC, Muzik O, et al. Is epileptogenic cortex truly hypometabolic on interictal positron emission tomography? *Ann Neurol* 2000;48:88–96.
39. Juhász C, Chugani DC, Muzik O, et al. Relationship of flumazenil and glucose PET abnormalities to neocortical epilepsy surgery outcome. *Neurology* 2001;56:1650–1658.

40. Chugani HT, Shields WD, Shewmon DA, et al. Infantile spasms: I. PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. *Ann Neurol* 1990;27:406–413.
41. Chugani HT, Shewmon DA, Shields WD, et al. Surgery for intractable infantile spasms: neuroimaging perspectives. *Epilepsia* 1993;34: 764–771.
42. Chugani HT, Mazziotta JC, Engel J Jr, Phelps ME. The Lennox-Gastaut syndrome: metabolic subtypes determined by 2-deoxy-2[^{18}F]fluoro-D-glucose positron emission tomography. *Ann Neurol* 1987;21:4–13.
43. Theodore WH, Rose D, Patronas N, et al. Cerebral glucose metabolism in the Lennox–Gastaut syndrome. *Ann Neurol* 1987;21:14–21.
44. Chugani HT, Mazziotta JC, Phelps ME. Sturge–Weber syndrome: a study of cerebral glucose utilization with positron emission tomography. *J Pediatr* 1989;114:244–253.
45. Lee JS, Asano E, Muzik O, et al. Sturge–Weber syndrome: correlation between clinical course and FDG PET findings. *Neurology* 2001;57:189–195.
46. Rintahaka PJ, Chugani HT, Messa C, Phelps ME. Hemimegalencephaly: evaluation with positron emission tomography. *Pediatr Neurol* 1993; 9; 21–28.
47. Lee JS, Juhász C, Kaddurah AK, Chugani HT. Patterns of cerebral glucose metabolism in early and late stages of Rasmussen's syndrome. *J Child Neurol* 2001;16:798–805.
48. Koutroumanidis M, Hennessy MJ, Seed PT, et al. Significance of interictal bilateral temporal hypometabolism in temporal lobe epilepsy. *Neurology* 2000;54:1811–1821.
49. Jokeit H, Seitz RJ, Markowitsch HJ, et al. Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain* 1997;120:2283–2294.
50. Chugani HT, Da Silva E, Chugani DC. Infantile spasms: III. Prognostic implications of bitemporal hypometabolism on positron emission tomography. *Ann Neurol* 1996;39:643–649.
51. Juhász C, Behen ME, Muzik O, et al. Bilateral medial prefrontal and temporal neocortical hypometabolism in children with epilepsy and aggression. *Epilepsia* 2001;42:991–1001.
52. Bachevalier J, Malkova L, Mishkin M. Effects of selective neonatal temporal lobe lesions on socioemotional behavior in infant rhesus monkeys (Macaca mulatta). *Behav Neurosci* 2001;115: 545–559.
53. Sivilotti L, Nistri A. GABA receptor mechanisms in the central nervous system. *Prog Neurobiol* 1991;36:35–92.
54. Verhoeff NP, Petroff OA, Hyder F, et al. Effects of vigabatrin on the GABAergic system as determined by [^{123}I]iomazenil SPECT and GABA MRS. *Epilepsia* 1999;40:1433–1438.
55. Chugani DC, Muzik O, Juhász C, et al. Postnatal maturation of human $GABA_A$ receptors measured with positron emission tomography. *Ann Neurol* 2001;49:618–626.
56. Bertz RJ, Reynolds IJ, Kroboth PD. Effect of neuroactive steroids on [^{3}H]flumazenil binding to the $GABA_A$ receptor complex in vitro. *Neuropharmacology* 1995;34:1169–1175.
57. Blomquist G, Pauli S, Farde L, et al. Maps of receptor binding parameters in the human brain – a kinetic analysis of PET measurements. *Eur J Nucl Med* 1990;16:257–265.
58. Koeppe RA, Holthoff VA, Frey KA, et al. Compartmental analysis of [^{11}C]flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. *J Cereb Blood Flow Metab* 1991;11:735–744.
59. Savic I, Ingvar M, Stone-Elander S. Comparison of [^{11}C]flumazenil and [^{18}F]FDG as PET markers of epileptic foci. *J Neurol Neurosurg Psychiatr* 1993;56:615–621.
60. Koepp MJ, Hand KS, Labbe C, et al. In vivo [^{11}C]flumazenil-PET correlates with ex vivo [^{3}H]flumazenil autoradiography in hippocampal sclerosis. *Ann Neurol* 1998;43:618–626.
61. Nagy F, Chugani DC, Juhász C, et al. Altered in vitro and in vivo flumazenil binding in human epileptogenic neocortex. *J Cereb Blood Flow Metab* 1999;19:939–947.
62. Niimura K, Muzik O, Chugani DC, et al. [^{11}C]flumazenil PET: activity images versus parametric images for the detection of neocortical epileptic foci. *J Nucl Med* 1999;40:1985–1991.
63. Pintor M, Mefford IN, Hutter I, et al. Levels of biogenic amines, their metabolites and tyrosine hydroxylase activity in the human epileptic temporal cortex. *Synapse* 1990;5:152–156.
64. Trottier S, Evrard B, Vignal JP, et al. The serotonergic innervation of the cerebral cortex in man and its changes in focal cortical dysplasia. *Epilepsy Res* 1996;25:79–106.
65. Diksic M, Nagahiro S, Sourkes TL, Yamamoto YL. A new method to measure brain serotonin synthesis in vivo. I. Theory and basic data for a biological model. *J Cereb Blood Flow Metab* 1990; 10:1–12.
66. Cohen Z, Tsuiki K, Takada A, et al. In vivo-synthesized radioactively labelled alpha-methyl serotonin as a selective tracer for visualization of brain serotonin neurons. *Synapse* 1995;21:21–28.
67. Madras BK, Sourkes,TL. Metabolism of α-methyl-tryptophan. *Biochem Pharmacol* 1965;14:1499–1506.
68. Diksic M, Nagahiro S, Chaly T, et al. Serotonin synthesis rate measured in living dog brain by positron emission tomography. *J Neurochem* 1991;56:153–162.
69. Muzik O, Chugani DC, Chakraborty P, et al. Analysis of [C-11]alpha-methyl-tryptophan kinetics for the estimation of serotonin synthesis rate in vivo. *J Cereb Blood Flow Metab* 1997;17:659–669.
70. Nishizawa S, Benkelfat C, Young SN, et al. Differences between males and females in rates of serotonin synthesis in human brain. *Proc Natl Acad Sci USA* 1997;94:5308–5313.
71. Chugani DC, Muzik O, Chakraborty P, et al. Human brain serotonin synthesis capacity measured in vivo with alpha-[C-11]methyl-L-tryptophan. *Synapse* 1998;28:33–43.
72. Saito K, Nowak TS Jr, Suyama K, et al. Kynurenine pathway enzymes in brain: responses to ischemic brain injury versus systemic immune activation. *J Neurochem* 1993;61:2061–2070.
73. Chugani DC, Muzik O. Alpha[C-11]methyl-L-tryptophan PET maps brain serotonin synthesis and kynurenine pathway metabolism. *J Cereb Blood Flow Metab* 2000;20:2–9.
74. Parsey RV, Oquendo MA, Simpson NR, et al. Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT(1A) receptor binding potential measured by PET using [C-11]WAY-100635. *Brain Res* 2002;954:173–182.
75. Toczek MT, Carson RE, Lang L, et al. PET imaging of 5-HT1A receptor binding in patients with temporal lobe epilepsy. *Neurology* 2003;60:749–756.
76. Frost JJ, Mayberg HS, Fisher RS, et al. Mu-opiate receptors measured by positron emission tomography are increased in temporal lobe epilepsy. *Ann Neurol* 23:231–237.
77. Mayberg HS, Sadzot B, Meltzer CC, et al. 1991 Quantification of mu and non-mu opiate receptors in temporal lobe epilepsy using positron emission tomography. *Ann Neurol* 1988;30:3–11.
78. Theodore WH, Carson RE, Andreasen P, et al. PET imaging of opiate receptor binding in human epilepsy using [^{18}F]cyclofoxy. *Epilepsy Res* 1992;13:129–139.
79. Iinuma K, Yokoyama H, Otsuki T, et al. Histamine H_1 receptors in complex partial seizures. *Lancet* 1993;341:238.
80. Kumlien E, Hartvig P, Valind S, et al. NMDA-receptor activity visualized with (*S*)-[*N*-methyl-^{11}C]ketamine and positron emission tomography in patients with medial temporal lobe epilepsy. *Epilepsia* 1999;40:30–37.
81. Koepp MJ, Labbe C, Richardson MP, et al. Regional hippocampal [^{11}C]flumazenil PET in temporal lobe epilepsy with unilateral and bilateral hippocampal sclerosis. *Brain* 1997;120:1865–1876.
82. Friston KJ, Holmes AP, Worsley KJ, et al. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapping* 1995;2:189–210.
83. Koepp MJ, Richardson MP, Brooks DJ, et al. Cerebral benzodiazepine receptors in hippocampal sclerosis. An objective in vivo analysis. *Brain* 1996;119:1677–1687.

84. Bouilleret V, Dupont S, Spelle L, et al. Insular cortex involvement in mesiotemporal lobe epilepsy: a positron emission tomography study. *Ann Neurol* 2002;51:202–208.
85. Richardson MP, Koepp MJ, Brooks DJ, et al. Benzodiazepine receptors in focal epilepsy with cortical dysgenesis: an ^{11}C-flumazenil PET study. *Ann Neurol* 1996;40:188–198.
86. Richardson MP, Koepp MJ, Brooks DJ, Duncan JS. ^{11}C-flumazenil PET in neocortical epilepsy. *Neurology* 1998;51:485–492.
87. Hammers A, Koepp MJ, Labbe C, et al. Neocortical abnormalities of [^{11}C]-flumazenil PET in mesial temporal lobe epilepsy. *Neurology* 2001;56:897–906.
88. Richardson MP Friston KJ, Sisodiya SM, et al. Cortical grey matter and benzodiazepine receptors in malformations of cortical development. A voxel-based comparison of structural and functional imaging data. *Brain* 1997;120:1961–1973.
89. Richardson MP, Hammers A, Brooks DJ, Duncan JS. Benzodiazepine-$GABA_A$ receptor binding is very low in dysembryoplastic neuroepithelial tumor: a PET study. *Epilepsia* 2001;42:1327–1334.
90. Hammers A, Koepp MJ, Hurlemann R, et al. Abnormalities of grey and white matter [^{11}C]flumazenil binding in temporal lobe epilepsy with normal MRI. *Brain* 2002;125:2257–2271.
91. Chevassus-Au-Louis N, Congar P, Represa A, et al. Neuronal migration disorders: heterotopic neocortical neurons in CA1 provide a bridge between the hippocampus and the neocortex. *Proc Natl Acad Sci USA* 1998;95:10263–10268.
92. Von Stockhausen HM, Thiel A, Herholz K, Pietrzyk U. A convenient method for topographical localization of intracranial electrodes with MRI and a conventional radiograph. *Neuroimage* 1997;5:S514.
93. Muzik O, Chugani DC, Shen C, et al. Assessment of the performance of FDG and FMZ PET imaging against the gold standard of invasive EEG monitoring for the detection of extratemporal lobe epileptic foci in children. In: Gjedde A, Hansen SB, Knudsen GM, Paulson OB, eds. Physiological imaging of the brain with PET. San Diego, CA: Academic Press, 2001:381–387.
94. Wellmer J, von Oertzen J, Schaller C, et al. Digital photography and 3D MRI-based multimodal imaging for individualized planning of resective neocortical epilepsy surgery. *Epilepsia* 2002;43:1543–1550.
95. Asano E, Chugani DC, Muzik O, et al. Multimodality imaging for improved detection of epileptogenic lesions in children with tuberous sclerosis complex. *Neurology* 2000;54:1976–1984.
96. Szelies B, Sobesky J, Pawlik G, et al. Impaired benzodiazepine receptor binding in peri-lesional cortex of patients with symptomatic epilepsies studied by [^{11}C]-flumazenil PET. *Eur J Neurol* 2002;9:137–142.
97. Savic I, Persson A, Roland P, et al. In-vivo demonstration of reduced benzodiazepine receptor binding in human epileptic foci. *Lancet* 1988;2:863–866.
98. Szelies B, Weber-Luxenburger G, Pawlik G, et al. MRI-guided flumazenil- and FDG-PET in temporal lobe epilepsy. *Neuroimage* 1996;3:109–118.
99. Juhász C, Nagy F, Muzik O, et al. [^{11}C]flumazenil PET in patients with epilepsy with dual pathology. *Epilepsia* 1999;40:566–574.
100. Ryvlin P, Bouvard S, Le Bars D, Mauguiere F. Transient and falsely lateralizing flumazenil-PET asymmetries in temporal lobe epilepsy. *Neurology* 1999;53:1882–1885.
101. Lamusuo S, Pitkanen A, Jutila L, et al. [^{11}C]Flumazenil binding in the medial temporal lobe in patients with temporal lobe epilepsy: correlation with hippocampal MR volumetry, T2 relaxometry, and neuropathology. *Neurology* 2000;54:2252–2260.
102. Koepp MJ, Hammers A, Labbe C, et al. ^{11}C-flumazenil PET in patients with refractory temporal lobe epilepsy and normal MRI. *Neurology* 2000;54:332–339.
103. Savic I, Thorell JO, Roland P. [^{11}C]flumazenil positron emission tomography visualizes frontal epileptogenic regions. *Epilepsia* 1995;36:1225–1232.
104. Juhász C, Chugani DC, Muzik O, et al. Electroclinical correlates of flumazenil and fluorodeoxyglucose PET abnormalities in lesional epilepsy. *Neurology* 2000;55:825–834.
105. Arnold S, Berthele A, Drzezga A, et al. Reduction of benzodiazepine receptor binding is related to the seizure onset zone in extratemporal focal cortical dysplasia. *Epilepsia* 2000;41:818–824.
106. Juhász C, Muzik O, Chugani DC, et al. Chronic vigabatrin treatment modifies developmental changes of $GABA_A$ receptor binding in young children with epilepsy. *Epilepsia* 2001;42:1320–1326.
107. Savic I, Blomqvist G, Halldin C, Litton JE, Gulyas B. Regional increases in [^{11}C]flumazenil binding after epilepsy surgery. *Acta Neurol Scand* 1998;97:279–286.
108. Hammers A, Koepp MJ, Richardson MP, et al. Central benzodiazepine receptors in malformations of cortical development: a quantitative study. *Brain* 2001;124:1555–1565.
109. Savic I, Pauli S, Thorell JO, Blomqvist G. In vivo demonstration of altered benzodiazepine receptor density in patients with generalized epilepsy. *J Neurol Neurosurg Psychiatr* 1994;57:797–804.
110. Prevett MC, Lammertsma AA, Brooks DJ, et al. Benzodiazepine-$GABA_A$ receptors in idiopathic generalized epilepsy with [^{11}C]flumazenil and positron emission tomography. *Epilepsia* 1995;36:113–121.
111. Prevett MC, Lammertsma AA, Brooks DJ, et al. Benzodiazepine-$GABA_A$ receptor binding during absence seizures. *Epilepsia* 1995;36:592–599.
112. Koepp MJ, Richardson MP, Brooks DJ, et al. Central benzodiazepine/gamma-aminobutyric acid A receptors in idiopathic generalized epilepsy: an [^{11}C]flumazenil positron emission tomography study. *Epilepsia* 1997;38:1089–1097.
113. Chugani DC, Chugani HT, Muzik O, et al. Imaging epileptogenic tubers in children with tuberous sclerosis complex using alpha-[^{11}C]methyl-L-tryptophan positron emission tomography. *Ann Neurol* 1998;44:858–866.
114. Juhász C, Chugani DC, Asano E, et al. Alpha[^{11}C]methyl-L-tryptophan positron emission tomography scanning in 176 patients with intractable epilepsy. *Ann Neurol* Suppl 2002;1:S118.
115. Fedi M, Reutens D, Okazawa H, et al. Localizing value of alpha-methyl-L-tryptophan PET in intractable epilepsy of neocortical origin. *Neurology* 2001;57:1629–1636.
116. Juhász C, Chugani DC, Muzik O, et al. Alpha-methyl-L-tryptophan PET detects epileptogenic cortex in children with intractable epilepsy. *Neurology* 2003;60:960–968.
117. Natsume J, Kumakura Y, Bernasconi N, et al. Alpha-[^{11}C] methyl-L-tryptophan and glucose metabolism in patients with temporal lobe epilepsy. *Neurology* 2003;60:756–761.
118. Simmons ML, Chavkin C. Endogenous opioid regulation of hippocampal function. *Int Rev Neurobiol* 1996;39:145–196.
119. Tortella FC, Long JB, Holaday JW. Endogenous opioid systems: physiological role in the self-limitation of seizures. *Brain Res* 1985;332:174–178.
120. Bartenstein PA, Duncan JS, Prevett MC, et al. Investigation of the opioid system in absence seizures with positro emission tomography. *J Neurol Neurosurg Psychiatry* 1993;56:1295–1302.
121. Koepp MJ, Richardson MP, Brooks DJ, Duncan JS. Focal cortical release of endogenous opioids during reading-induced seizures. *Lancet* 1998;352:952–955.
122. Madar I, Lesser RP, Krauss G, et al. Imaging of delta- and mu-opioid receptors in temporal lobe epilepsy by positron emission tomography. *Ann Neurol* 1997;41:358–367.
123. Kumlien E, Bergstrom M, Lilja A, et al. Positron emission tomography with [^{11}C]deuterium-deprenyl in temporal lobe epilepsy. *Epilepsia* 1995;36:712–721.
124. Kumlien E, Nilsson A, Hagberg G, et al. PET with ^{11}C-deuterium-deprenyl and ^{18}F-FDG in focal epilepsy. *Acta Neurol Scand* 2001;103:360–366.

Reference:

Juhász C, Chugani DC, Muzik O, Chugani HT. Positron-emission tomography in epilepsy. In: Kuzniecky R & Jackson G (eds.), Magnetic resonance in epilepsy - neuroimaging techniques; 2nd edition. Academic Press 2005; 395-411.