Positron Emission Tomography and Single Photon Emission Computed Tomography in Epilepsy Care

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Radiopharmaceutical brain imaging is clinically applied in planning resective epilepsy surgery. Cerebral sites of seizure generation-propagation are highly associated with regions of hyperperfusion during seizures, and with glucose hypometabolism interictally. For surgical planning in epilepsy, the functional imaging modalities currently established are ictal single photon emission computed tomography (SPECT) with [99mTc]technetium-hexamethylpropyleneamine oxime (HMPAO) or with [99mTc]technetium-ethylene cysteine dimer (ECD), and interictal positron emission tomography (PET) with 2-[18F]fluoro-2-deoxyglucose (FDG). Ictal SPECT and interictal FDG PET can be used in presurgical epilepsy evaluations to reliably: 1) determine the side of anterior temporal lobectomy, and in children the area of multi-lobar resection, without intracranial electroencephalographic recording of seizures; 2) select high-probability sites of intracranial electrode placement for recording ictal onsets; and, 3) determine the prognosis for complete seizure control following anterior temporal lobe resection. Coregistration of a patient's structural (magnetic resonance) and functional images, and statistical comparison of a patient's data with a normal data set, can increase the sensitivity and specificity of these SPECT and PET applications to the presurgical evaluation.
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FUNCTIONAL IMAGING WITH various radioligands and single photon emission computed tomography (SPECT) or positron emission tomography (PET) has demonstrated many types of blood flow, glucose metabolic and neurochemical dysfunctions in a variety of neurological conditions,[1] including epilepsy.[2] Seizures are among the most common of neurologic symptoms. Seizures, or paroxysmal spells of transitory alteration in consciousness or other cortical function, may reflect episodic neurologic, psychiatric, or extracerebral (particularly cardiovascular) dysfunction. Epileptic seizures are distinguished from other paroxysmal spells by their abnormally synchronized electrical discharges of localized or widely distributed groups of cerebral neurons. Many individuals will suffer a single unprovoked generalized tonic-clonic seizure some time in life, or one or more epileptic seizures associated with recurring hypoglycemia, electrolyte disturbances or other extracerebral conditions; these individuals do not have epilepsy, despite occurrence of one or more epileptic seizures. Epilepsy is diagnosed when persisting cerebral dysfunction causes recurring epileptic seizures. Approximately 5% of Americans have at least 1 epileptic seizure during their lifetimes. At any point in time 1-2% of Americans have epilepsy; cumulative lifetime incidence exceeds 3%.[3]

The epilepsies are diverse conditions with little in common save the tendency for epileptic seizures to occur at variable intervals and usually at unpredictable times. Functional imaging research in the epilepsies requires full classification of the subjects' seizures and epilepsies. Partial-onset seizures begin electrophysiologically in one cerebral region before ceasing at that site or propagating to other sites. Some degree of bihemispheric propagation is required for a partial-onset seizure to cause globally altered consciousness (a complex partial seizures), and spread over the entirely of both cerebral hemispheres causes a generalized convulsive (grand mal) seizure. Grand mal seizures also can begin without any behavioral or EEG changes to suggest a focal onset. Such generalized-onset seizures probably begin with pathological, synchronous discharges of thalamocortical neurons, which "pace" the simultaneous onset of ictal discharges over the entire cortex.[4] Generalized-onset seizures sometimes involve all areas of cortex, but only a minority of neurons in each area, to cause behavioral and cognitive arrest, without convulsive activity (an absence seizure). High quality imaging research in the epilepsies requires that the investigators exclude subjects who have "pseudoseizures." Pseudoseizures are paroxysmal events in which behaviors closely mimic those of epileptic seizures, but occur due to organic or psychiatric dysfunction in the absence of electrographic ictal

discharges. Video-EEG monitoring is routinely used to diagnose epileptic versus non-epileptic seizures.[3]

Epilepsy is diagnosed only when persisting cerebral dysfunction causes recurring epileptic seizures. Epilepsies are classified in two domains, as localization-related (with partial-onset seizures) versus generalized (with generalized-onset seizures), and as primary versus secondary in etiology. In primary epilepsies, seizures are the only clinical manifestations of the cerebral dysfunction, epidemiological evidence points to variably penetrant autosomal inheritance, and no post-conceptional cerebral insult appears necessary for initiation of epileptogenesis. Secondary generalized epilepsies and most partial epilepsies are acquired secondary to cerebral insult, although the precise nature of the insult cannot always be determined. Frequently, this etiologic insult causes interictal cerebral dysfunction, as in the mental retardation usually seen in secondary generalized epilepsies, and the deficits of delayed recall that typify the interictal hippocampal dysfunction of limbic temporal lobe epilepsy. Many types of seizures are followed by transitory (minutes or hours) postictal dysfunction, which is more severe or affects different functions than those that characterize the interictal state.

Brain imaging research with PET and SPECT has provided a great deal of new information concerning ictal and interictal epileptic dysfunctions.[2,5] The productivity of emission tomographic research in the epilepsies is in part attributable to the wide range of functions that can be anatomically mapped with radioligands. Regional brain functions can be mapped with PET or SPECT at different points in time, to: 1) localize and measure functional differences between ictal and interictal states, and to determine the sites of dysfunction in the interictal state; 2) assess effects of epilepsy therapies; and 3) analyze regional changes in synaptic activity during motor, sensory or cognitive processing, which may be abnormal interictally in epilepsy. Detailed discussion of emission tomographic research in the epilepsies is beyond the scope of this review. The interested reader can find a current summary of this research in a recently published monograph.[6]

EMISSION TOMOGRAPHIC METHODOLOGY IN EPILEPSY

Epilepsy poses several unique problems for PET and SPECT performance and analysis. First, a variety of structural lesions and neurochemical disturbances are associated with the epilepsies, with greater heterogeneity of underlying structural lesions than occurs in many other neurological diseases and conditions.

Many lesions associated with epilepsy are readily characterized with MRI, and correlation of the individual's MRI findings with PET and SPECT abnormalities is essential to adequate interpretation for epilepsy surgery evaluation. Second, functional differences among the ictal, postictal, and interictal states increase the complexity of PET and SPECT image acquisition and interpretation in the epilepsies, compared with other neurologic conditions. Some PET ligands and their corresponding kinetic models do not support imaging of a particular function over a period of time as short as that of a typical complex partial or absence seizure. Clinical PET usually is performed in the interictal state, but it may be difficult to exclude seizure occurrence, even when scalp EEG recordings are made before and during PET. Subclinical electrographic seizures in small cerebral volumes or deep structures may not be detected with extracranial EEG[7], but may increase glucose metabolism sufficiently to alter ^{18F}2-fluoro-2-deoxyglucose (FDG) images, as shown in Fig 1. Acquisition and analysis of ictal SPECT is difficult for these same reasons, in addition to difficulties in timing injection of the radioligands during a seizure, which often is quite brief. Further, antiepileptic drug therapy alters many cerebral functions, so the PET and SPECT images do not reflect only dysfunction due to the epilepsy itself, but also dysfunction due to the effects of AEDs. Decreased global cerebral glucose metabolism is more severe after barbiturates are initiated than occurs with phenytoin, carbamazepine or valproate.[9]

Several reviews have covered general and epilepsy-related aspects of PET methodology in detail,[10-12] but a few points should be re-emphasized. Different PET ligands not only produce different functional maps of the brain (based on their different biochemical activities), but also generate image sets that reflect different periods of time. In particular, FDG kinetics generate a non-linear temporal resolution, in that metabolism is averaged over about 40 minutes, with earlier periods during scanning weighted more heavily in this average. The tracer kinetic model of FDG requires steady-state conditions for absolute measurements of glu-

Fig 1. Ictal (prolonged auras) and interictal FDG PET images of a mesial TLE patient. These transaxial images of two FDG scans of the same patient were obtained interictally (lower row) and during a period of repetitive auras without behavioral changes (upper row). The left hippocampus shows markedly greater FDG uptake during the ictal scan (at the arrowhead and on the adjacent image planes), compared with the interictal scan. The interictal scan shows the typical anterior mesial-lateral temporal lobe hypometabolism of unilateral mesial temporal lobe epilepsy. Imaging was performed with the ECAT Exact (Siemens, Hoffman Estates, IL), with intrinsic resolution of 5.8 mm in plane and 4.2 mm axially (full width at half maximum). On each row the transaxial images are arranged with the most superior plane to the left and 3.4 mm spacing, with the same levels displayed on each row. Subject left is displayed on image right. (Images supplied courtesy of Dr. John M. Hoffman, Emory University PET Center).

cose metabolic rate, so only relative comparison of metabolism within different regions of the image set can be made if a single seizure occurs during FDG imaging.[13] Each dimension of a volume of tissue must be at least twice the linear resolution of the imaging system for the volume to be accurately resolved in space and functional intensity on the image.[14] Structures smaller than this will have their functional activity averaged with those of adjacent structures (the partial volume effect). The higher spatial resolution of current PET tomographs, compared with those reported in earlier FDG imaging research, has been shown to generate more sensitive and accurate detection of hypometabolism, with greater ability to correlate FDG image coordinates with brain MRI locations.[15]

Several reviews have covered general and epilepsy-related aspects of SPECT methodology in detail,[16] but a few points should be re-emphasized. It is critical to fully analyze the temporal relationships between radioligand injection and ictal semiology. Interpretation of delayed positictal injection

as representing injection during the ictus may cause false lateralization of interhemispheric asymmetries of CBF, due to the "postictal switch" phenomenon,[17] as discussed below. Both interictal and ictal CBF images must be compared in the same patient, as unrecognized interictal abnormalities might lead to false localization of ictal hyperperfusion if it is wrongly assumed that ictal perfusion patterns are changed from normal interictal CBF distributions.[18] A considerable increase in sensitivity and specificity is afforded by coregistration and subtraction of ictal and interictal SPECT images, followed by superimposition on the individual's MRI scan, and statistical analysis of CBF differences.[16] While stabilized HMPAO and ECD often are considered as equivalent for ictal SPECT, one study found that the dynamic range of ictal hyperperfusion on HMPAO images was greater than that afforded by ECD.[19]

Full co-registration of an individual's FDG and MRI scans, followed by registration of the MRI to a set of normal MRI studies, permits comparison of
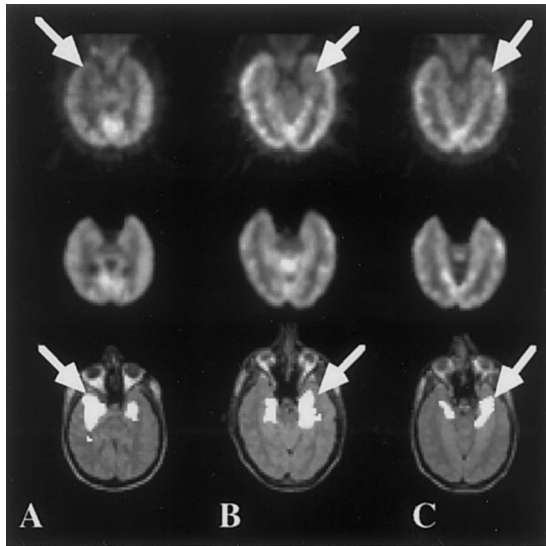
Fig 2. Statistical parametric mapping of interictal hypometabolism in three patients with unilateral mesial TLE. The upper row shows a single axial image of FDG activity for each patient, which includes temporal neocortex anteriorly and laterally, and the amygdala (patient A) or hippocampal formation (patients B and C) mesially. The middle row shows the corresponding axial plane of the normal FDG atlas, as coregistered to the image in the upper row. The lower row shows the coregistered MR image for the patient, with voxels of decreased (by Z-score of 2 or greater) FDG activity shown in white. Several areas of visually apparent hypometabolism over lateral temporal regions on the FDG images in the upper row were not significantly hypometabolic on comparison with the normal data. These patients had asymmetric bilateral temporal hypometabolism on parametric mapping, with small volumes of hypometabolism over mesial temporal regions that were contralateral to the ictal onset zone, and larger volumes of significant hypometabolism on the epileptogenic side; the contralateral hypometabolic regions were not apparent on visual analysis of the FDG activity images. (The phenomenon of asymmetric bilateral temporal hypometabolism interictally in unilateral TLE is discussed in the text). The epileptogenic temporal lobe is indicated with an arrow for patients' FDG images and parametric images. (Images supplied courtesy of Dr. Tracy L. Faber, Emory University PET Center).

anatomically specific metabolic measurements of the individual with normal subjects' means and variances of regional metabolism.[20] Statistical parametric imaging detects some abnormalities that cannot be appreciated with qualitative interpretation. For example, bilateral temporal hypometabolism with marked asymmetry of temporal metabolism can be accurately described with statistical parametric imaging techniques, but usually appears as unilateral temporal hypometabolism on visual interpretation (see Fig 2). Quantitative analyses that determine an asymmetry index also will

fail to detect bilateral temporal hypometabolism, although the temporal lobe with relatively greater metabolic decrease will be accurately noted as hypometabolic. Issues regarding the construction of regions of interest, for regional sampling of FDG activity, have been previously discussed.[21] Despite the advantages of statistical parametric imaging techniques, visual interpretation and quantification of asymmetry remain useful in current clinical applications, as unilateral TLE typically has asymmetric, bilateral temporal hypometabolism interictally.

Acquisition of ictal and interictal SPECT usually is performed during in-patient video-EEG monitoring, so availability of both behavioral observations and EEG is not an issue. Many centers also perform continuous scalp EEG monitoring immediately prior to and following FDG administration, including for out-patient PET. Continuous EEG monitoring immediately prior to and following FDG administration is useful in determining wake-sleep state, frequency of interictal epileptiform discharges, and occurrence of electrographic seizures. Scalp electrodes do not significantly attenuate or scatter the high energy (511 keV) photons that are produced by positron annihilation. However, intracranial electrodes have been suspected of producing spurious regional hypometabolism on FDG imaging.[22] Some centers do not routinely perform EEG monitoring, which slightly increases the cost of FDG scanning, on the bases that subclinical or unreported seizures rarely occur in the imaging suite and that single seizures do not alter FDG images.[23] The latter point has been disproved (see, e.g., the case presented in 21), but the cost-benefit ratio of continuous EEG during FDG studies has not been established.

EMISSION TOMOGRAPHIC FINDINGS IN CLINICAL EPILEPSY STUDIES

Ictal Imaging of Single Seizures in Partial Epilepsies

Intense increases in regional cerebral blood flow (rCBF) and glucose metabolism are hallmarks of partial-onset seizures. Paroxysmal changes in rCBF and regional cerebral metabolic rate for glucose ($rCMR_{Glc}$) probably are due mainly to increases and decreases in regional synaptic activity. Increased ictal rCBF and $rCMR_{Glc}$ could be due mainly to increased excitatory neurotransmis-

sion, to increased inhibitory neurotransmission, or to increases in excitatory and inhibitory neurotransmission, with hypersynchrony of synaptic activities. Thus, imaging of ictal changes in rCBF and $rCMR_{Glc}$ can be used to localize increased synaptic neurochemical activity, although without specificity for particular types of neurotransmission.

Single seizures usually last for less than 90 seconds (and often are much briefer), and occur less than once per day (and often far less than that) for most individuals with epilepsy. Seizure frequency (and duration) can be significantly increased by taking hospitalized patients off their antiepileptic drugs (AEDs). Tapering or discontinuation of AEDs usually is performed to make a complete diagnosis of seizures types, or to localize regions of ictal onset in consideration of resective surgical therapy, with EEG-videomonitoring. In the setting of an epilepsy monitoring unit, with AEDs reduced or discontinued, injection of [99mTc]HMPAO or [99mTc]ECD can be accomplished during or within seconds following termination of a complex partial seizure. Peri-ictal SPECT imaging of CBF has excellent accuracy in determining the region of ictal onset and predominant propagation in refractory partial epilepsies.[17,18,24-31] When the radiopharmaceutical is injected during the electrographic seizure or within 30 seconds after the seizure, over 90% of patients with unilateral temporal lobe epilepsy (TLE) have regional hyperperfusion over mesial and lateral portions of the temporal lobe of ictal onset.[18] Ictal hyperperfusion also frequently extends to contiguous areas of ipsilateral extratemporal cortex and to ipsilateral basal ganglia.[27] Bilateral temporal hyperperfusion occurs in some ictal SPECT studies in TLE,[18] but the epileptogenic temporal lobe has greater CBF increase from the interictal to the ictal scan than occurs contralaterally. Resolution of ictal and early postictal hyperperfusion occurs at different rates in different brain regions. Ictal HMPAO SPECT also is useful in determining the region of ictal onset and predominant propagation in extratemporal partial epilepsies.[26,30]

Ictal SPECT studies can clarify the anatomical substrates of ictal semiology. Partial seizures that cause greater impairment of consciousness (without causing a full generalized tonic-clonic seizure) are more likely to show hyperperfusion of the thalami and midbrain, in addition to cortical hyperperfusion, than are simple partial seizures.[32,33] Greater degrees of ictal impairment of consciousness and motor phenomena are associated with greater propagation of CBF increases to the contralateral hemisphere.[34] Newton and colleagues examined the ictal hemidystonia that often occurs late in complex partial seizures in TLE.[28] They demonstrated unilateral basal ganglia hyperperfusion during seizures with hemidystonia of the opposite limbs, which was consistently ipsilateral to the temporal lobe of ictal onset, but found no basal ganglia CBF changes during complex partial seizures without dystonia. In the rare epileptic syndrome of hypothalamic hamartoma with gelastic seizures, a complex partial seizure was associated with hypothalamic hyperperfusion, in the absence of temporal lobe or other cortical CBF changes,[35] thus supporting other lines of evidence that focal seizures can originate in the hypothalamus. It is well known that ictal semiology can be altered by changes in AED regimens. A further question that might be addressed with ictal SPECT is how different AEDs affect ictal onset-propagation CBF distributions.

Ictal [18F]FDG PET studies cannot be quantified because glucose metabolism is not at steady-state.[13] Dynamic [15O]H2O PET imaging of cerebral blood flow (CBF) is in theory superior for ictal scanning of single seizures to either FDG PET or SPECT techniques, owing to its superior temporal resolution and the possibility of fully quantifying CBF (without requirement of correction for nonlinear activity-CBF relationships, as occur with SPECT agents). In practice, the short half-life of 15O and the usually unpredictable timing of seizure onsets render ictal [15O]H2O impossible, except for the study of reflex seizures. Relative increases and decreases in ictal regional metabolism have been observed with [18F]FDG PET. Ictal [18F]FDG studies are most useful when the duration of continuous seizure activity approximates the duration of FDG uptake and phosphorylation following bolus FDG injection, i.e., when seizures last 10 minutes or longer. Occurrence of a brief complex partial seizure shortly after FDG injection may actually be associated with false normalization of apparent FDG activity, presumably due to averaging of interictal hypometabolism and ictal hypermetabolism in the same region.[21]

SPECT and PET Imaging of Postictal States

Peri-ictal SPECT studies of TLE have shown a characteristic evolution in regional CBF, as the region of ictal hyperfusion declines to severe hypoperfusion for several minutes postictally, then within about 20 minutes perfusion rises back to a milder degree of interictal hypoperfusion. This phenomenon has been called the "postictal switch".[17] Resolution of ictal and early postictal hyperperfusion and of later postictally enhanced hypoperfusion occurs at different rates in different brain regions. This "postictal switch" phenomenon is extremely important to recognize in clinical applications of ictal SPECT, because false lateralization of the ictal onset zone might occur if a "switched" postictal CBF asymmetry is mis-interpreted as representing an ictal CBF asymmetry.

Peri-ictal $[^{18}F]$FDG PET studies have shown a rather different time course of regional CMR_{Glc} changes following seizures. In a group of patients with complex partial seizures who had PET at different intervals following the most recent seizure, quantified regional metabolic changes evolved for more than 48 hours after a single complex partial seizure.[36] The most severe regional hypometabolism occurred more than 48 hours after the seizure, the least severe hypometabolism occurred at 24–48 hours postictally, and metabolism was intermediate in the first 24 hours postictally. In a study in which $[^{18}F]$FDG studies were performed on average less than 60 hours after the most recent seizure, the type of seizures that preceded the scan had a strong influence on the regional distribution of hypometabolism.[37] In general, the most localized ictal discharges preceded scans with the smallest volumes of hypometabolism, and secondarily generalized seizures preceded scans with the most widespread patterns of unilateral hypometabolism.

Interictal FDG PET in Mesial Temporal Lobe Epilepsy

Interictal FDG PET usually demonstrates hypometabolism of one temporal lobe, or bilateral temporal hypometabolism with more severe hypometabolism of one temporal lobe, in adults and children with refractory mesial TLE.[6,9,15,21,38-64] Qualitative visual analysis of FDG scans, obtained with high performance tomographs, currently detects unilateral (or bilateral, but asymmetric) temporal lobe hypometabolism in over 70% of refractory TLE patients. Higher resolution tomographic systems produce a higher detection rate for hypometabolism and greater concordance in scan interpretation, in qualitative interpretation of FDG imaging in localization-related epilepsies.[15] With quantitative analysis, detection of significant temporal hypometabolism may reach or exceed 90% in this group.

Temporal lobe hypometabolism usually extends over mesial and lateral portions of an interictally dysfunctional temporal lobe, on FDG scans in mesial TLE.[46,47,55,64] Regional hypometabolism in mesial TLE typically is diffuse, with graded demarcations from adjacent areas of normal metabolism, and with a relatively large area of hypometabolism. Even in the presence of a temporal lobe foreign-tissue lesion, patients with refractory mesial temporal seizures usually have widespread temporal lobe hypometabolism, rather than focal hypometabolism restricted to the site of the lesion. The lateral temporal hypometabolism often appears more severe than the mesial temporal hypometabolism of an affected temporal lobe, on qualitative scan interpretation. Two quantitative investigations also demonstrated more severe hypometabolism of lateral temporal than mesial temporal areas in many mesial TLE patients.[47,55] Using an ultra-high resolution tomograph, one study of mesial TLE found that small volumes of anterior mesial temporal structures were more severely hypometabolic than were any other temporal or extratemporal areas in many mesial TLE patients.[64] This suggests that partial-volume averaging of severe hypometabolism in the epileptogenic amygdala-hippocampus together with less depressed metabolism of adjacent basal temporal areas may cause the mesial temporal areas to appear less severely hypometabolic than they actually are, using clinical PET systems. Normal interictal metabolism also occurs in refractory mesial TLE, but normal FDG scans are more common in non-refractory than in refractory mesial TLE.

Many TLE patients have unilateral frontal, parietal, thalamic or basal ganglial hypometabolism ipsilateral to temporal hypometabolism, but occipital hypometabolism is rare in mesial TLE.[46,47,56,57] The temporal hypometabolism is nearly always more severe than is any extratemporal hypometabolism. The cortical hypometabolic area typically is

contiguous across its entire temporal and extratemporal extent and bilateral cerebellar hypometabolism is common. Thus, interictal FDG PET in refractory mesial TLE usually reveals unilateral diffuse regional hypometabolism of one mesial-lateral temporal area, with or without ipsilateral extratemporal cortical hypometabolism or contralateral temporal hypometabolism; ipsilateral extratemporal and contralateral temporal hypometabolism appears less severe than is the temporal lobe hypometabolism.

The pathophysiological basis of regional hypometabolism, imaged with FDG interictally in TLE, currently is unclear. Ablative structural lesions must contribute to localized decreases in glucose metabolism. Nonetheless, it has been recognized for some time that the volume of hypometabolism is greater than the volume of associated structural lesions, in localization-related epilepsies.[40] Acute-subacute cerebral infarction is associated with hypometabolism at the site of neuronal loss, and additional extra-infarctional sites of hypometabolism are considered to represent "diaschisis", as passive and usually impersistent effects of a focal insult on remote brain regions that receive projections from the insulted area.[65] Neuronal loss and diaschisis were considered the causes of the anatomically distributed interictal hypometabolism in TLE patients with hippocampal sclerosis. However, this hypothesis was refuted by a study of quantified preoperative FDG PET in patients whose resected temporal tissue underwent quantitative neuronal volumetric densitometry.[48] While neuronal loss and diaschisis probably cause some of the disseminated glucose metabolic depression in mesial TLE, other factors must also influence regional metabolism interictally. Several alternative such factors have been proposed.[2,66] At present, the diagnostically robust patterns of interictal glucose hypometabolism are not fully explained by macrostructural and microstructural alterations in temporal lobe epilepsy.

Focal mesial temporal hypermetabolism sometimes occurs interictally in children with mesial TLE, but rarely occurs in adults with localization-related epilepsies.[41,62,67] Continuous or repetitive focal mesial temporal seizures, which are subclinical and not detectable with scalp electrodes, may cause "interictal" deep temporal hypermetabolism.[8] Alternatively, there may be interictal epileptogenic processes that are peculiar to childhood

and that generate greater glucose metabolism interictally. The latter speculation is encouraged by the presence of interictal regional hypermetabolism is some young children with the Sturge-Weber syndrome or with infantile spasms, which does not occur in older children with the Sturge-Weber syndrome or with the Lennox-Gastaut syndrome (a common "endpoint" for patients with infantile spasms earlier in life), the older children having exclusively hypometabolism or normal metabolism interictally.

Ictal or peri-ictal (mixed ictal-postictal-interictal) FDG scans are difficult to obtain and to interpret. True ictal imaging with FDG is restricted to status epilepticus, due to the relatively poor temporal resolution of the FDG method. Occurrence of a single complex partial seizure during the FDG uptake period may be associated with the usual interictal findings of unilateral temporal hypometabolism. In one reported case, a partial seizure occurred about 2 minutes after FDG injection and the scan appeared normal; the same patient later had marked hypometabolism of the epileptogenic temporal lobe on an interictal FDG scan.[21] Presumably, ictal hypermetabolism was averaged with interictal-postictal hypometabolism over the temporal lobe to cause "normalization" of FDG activity on the peri-ictal scan. In another case, a TLE patient had repeated complex partial seizures following FDG injection, and the scan showed hypermetabolism over the epileptogenic temporal lobe, with ipsilateral frontal and thalamic metabolic increases.[68] Alterations on ictal and peri-ictal FDG images likely reflect ictal dysfunction at the site of ictal onset and in areas of ictal propagation, and interictal and postictal dysfunction in these areas, but it is impossible to sort out the relative contributions of these various dysfunctions to a single set of FDG images.

Interictal CBF imaging with PET often shows "diffuse" regional hypoperfusion, consisting of a relatively large area of hypoperfusion with indistinct boundaries from adjacent areas of normal CBF, and with inhomogeneous severity of hypoperfusion.[50,51,69,70] Interictal regional CBF decreases often occur predominantly contralateral to the ictal onset zone in mesial TLE.[51,71] Ictal CBF imaging of complex partial seizures with $[^{15}O]H_2O$ is nearly impossible to obtain, given the 2-minute half-life of oxygen-15, except with seizure induction by proconvulsant drugs or during complex
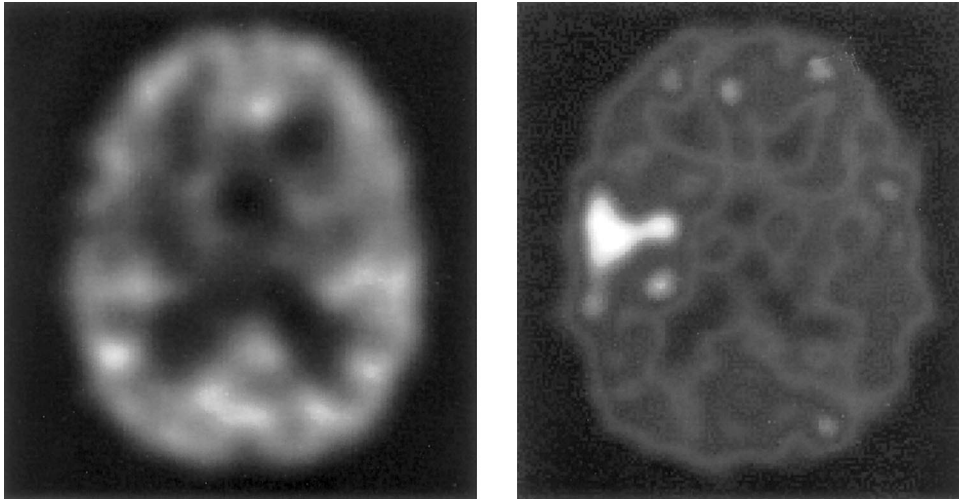
Fig 3. Ictal and interictal SPECT images of a patient with seizures of right insular origin. Inter-ictal (left) and ictal (right) transverse plane Tc-99m ECD brain SPECT images demonstrate an ictal seizure focus in the right insular cortex that is hypoperfused on the inter-ictal study.

partial status epilepticus.[72] For these reasons, ictal imaging and resting interictal imaging with [^{15}O]H$_2$O have no clinical role in presurgical evaluation.

Interictal FDG PET in Other Localization-Related Epilepsies

Interictal FDG PET often demonstrates a region of pathological hypometabolism, in adults and children with refractory partial seizures of extra-temporal origin or of neocortical (extra-limbic) temporal origin.[6,21,44,45,57,60,73-75] In patients with a single neocortical site of ictal onset, interictal FDG PET usually demonstrates a single region of hypometabolism, but normal metabolism also is frequently observed (Fig 3). Compared with non-lesional limbic TLE, non-lesional neocortical epilepsies are much more likely to have normal interictal FDG PET studies.[73,74] Interictal focal neocortical areas of hypermetabolism may occur in early childhood epilepsies,[67] but have not been reported in adults. In many lesional neocortical epilepsies, the hypometabolic region is small, sharply circumscribed, and co-localized with a focal structural lesion detected with MRI (see Fig 4); a similar relationship of "matching" focal PET hypometabolism and focal MRI lesion rarely is observed in limbic TLE.[73] Many individuals with lesional or non-lesional neocortical localization-related epilepsies have a more widespread hypo-metabolic zone, that has graded transitions from

areas of severe hypometabolism to areas of normal metabolism, similar to patterns of hypometabolism in limbic TLE. When associated with a lesion, a diffuse hypometabolic area of neocortex often is much larger than any associated structural imaging abnormality and any histopathological lesion, as also observed in limbic TLE. In the absence of a structural lesion on MRI, the volume of diffuse regional hypometabolism sometimes is fairly small in neocortical epilepsies. Larger areas of hypometabolism often include mesial temporal, thalamic, and basal ganglial hypometabolism ipsilateral to the neocortical site of hypometabolism. Hypometabolism over an entire hemisphere is rare, as is symmetric bilateral hypometabolism, in unilateral neocortical epilepsies. The degree of hypometabolism usually varies across a region of diffuse hypometabolism. The zone of most severe hypometabolism, excluding the site of a foreign-tissue lesion, usually contains the electrophysiologically defined ictal onset zone.[21]

Ictal or peri-ictal FDG imaging during simple partial seizures of neocortical frontal origin demonstrate patterns of increased and decreased FDG uptake, which likely reflect neuronal activity at the site of ictal onset, in areas of ictal spread, and in regions involved in post-ictal depression. Epilepsia partialis continua can be associated with a small volume of cortical hypermetabolism or hypometabolism when the ictal discharge remains limited, or more diffuse unilateral cortical and thalamic
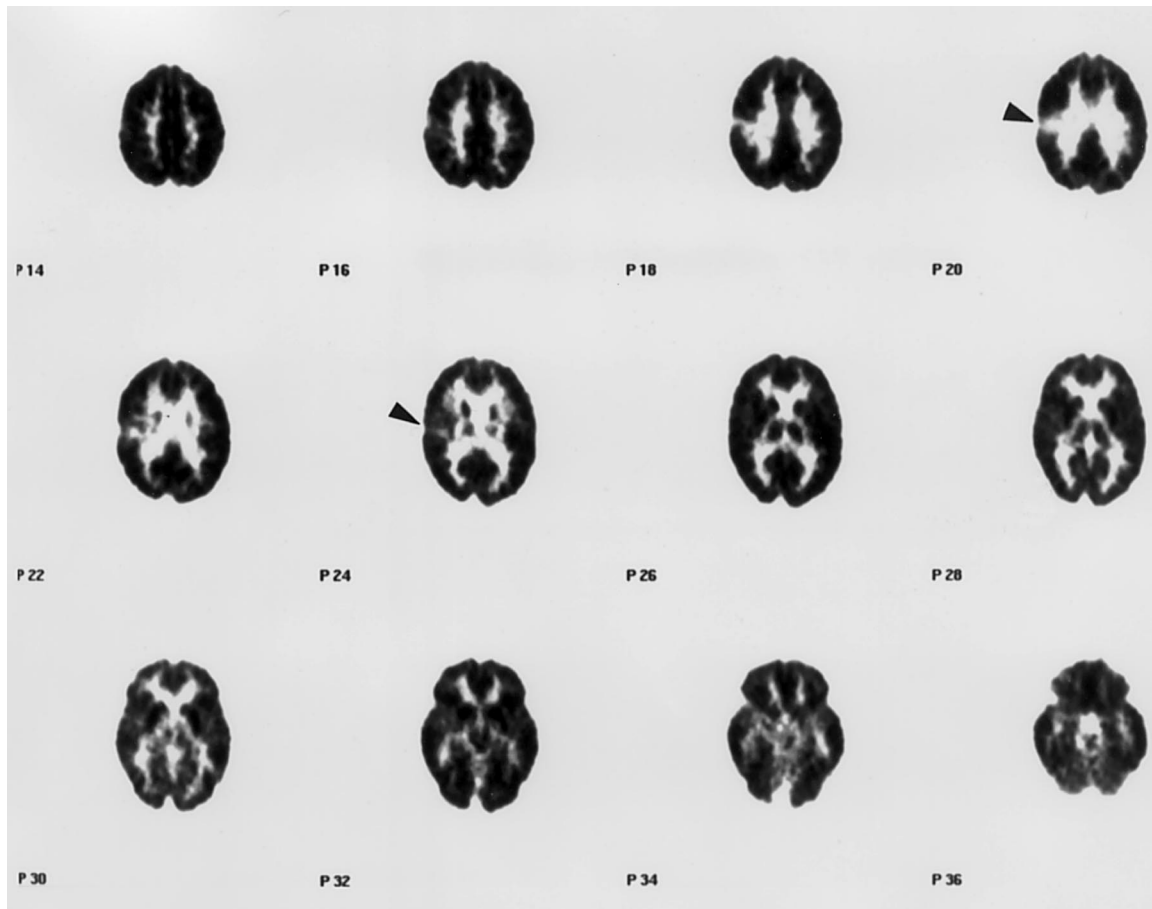
Fig 4. Interictal FDG PET images of a patient with seizures of neocortical frontal origin. The highly focal defect in the metabolic image (at the arrowhead on plane P20, at the upper right) was at the site of a cavernous angioma, which was visible on MRI. Intracranially recorded ictal onsets occurred superior to the lesion, in the region of structurally normal cortex that was most severely hypometabolic (at the arrowhead on plane P24). Imaging was performed with the ECAT Exact. Transaxial images are arranged with the most superior plane to the left and 6.75 mm spacing. (Images supplied courtesy of Dr. John M. Hoffman, Emory University PET Center).

hypermetabolism or hypometabolism when intra-hemispheric spread occurs.[2,68,70,76] In one patient with epilepsia partialis continua manifested as left arm and leg clonus, right frontal hypermetabolism and other bilateral regions of hypermetabolism were present.[68,76] In other cases of epilepsia partialis continua, FDG scans have revealed focal frontal hypermetabolism with ipsilateral thalamic or contralateral cerebellar hypermetabolism, or widespread hypometabolism without detectable areas of hypermetabolism. In several patients with epilepsia partialis continua, $[^{15}O]O2$ scans showed increased blood flow, increased oxygen metabolism and decreased oxygen extraction fraction in widespread areas of one cerebral hemisphere, which was contralateral to the focal motor seizure;

frontal lobe abnormalities were quantitatively more severe than those of other regions.[70]

Interictal FDG PET in Primary Generalized Epilepsies

Presurgical evaluations with PET have not been used to exclude primary generalized epilepsy patients from consideration of surgery; because clinical histories, and interictal and ictal scalp EEG recordings usually have established the diagnosis. Even when history and EEG might not entirely distinguish an atypical primary generalized epilepsy from a secondary generalized epilepsy, interictal FDG imaging would not be helpful. Interictal FDG studies are normal in primary generalized epilepsies.[22,77-79] Some patients with secondary

generalized epilepsies, and some with localization-related epilepsies, also have normal interictal FDG imaging,[47,80,81] so the finding of normal interictal cerebral glucose metabolism is not useful in syndromic classification.

Interictal FDG PET in Symptomatic ("Secondary") Generalized Epilepsies

West Syndrome

Patients with infantile spasms have been extensively studied with FDG imaging, in both research applications and presurgical evaluation. Unilateral cortical metabolic dysfunctions (hypo- or hypermetabolism) are relatively common in West's syndrome.[82-85] Bitemporal hypometabolism is less common, occurring in approximately 15% of infants with spasms in Chugani's series. In this series, bitemporal hypometabolism was never associated with a single predominant zone of structural imaging or electrophysiological abnormality, so surgery was never performed; most of these infants later developed autism.[85] (Bitemporal hypometabolism also has been reported in autistic children who had partial status epilepticus early in life,[86] but these children had evidence of hippocampal sclerosis on MRI.) By contrast, approximately 20% of infants with refractory spasms had FDG studies showing unilateral cortical regions of metabolic dysfunction; those who underwent unilateral cortical resection, which usually included large volumes of cortex, often had cessation of seizures, and normal or near-normal cognitive development.[49,87]

Many infants with West's syndrome have both unilateral cortical metabolic dysfunction, and bilateral lenticular and brainstem metabolic dysfunction.[83] Chugani has hypothesized that infantile spasms begin with a focal cortical abnormality, which induces brainstem activities that are projected symmetrically to the basal ganglia and spinal cord.[83] This theory is consistent with the observations that infantile spasms are generalized from onset, and that unilateral cortical resection can result in cessation of the spasms.[82] Such patients often have cortical dysplasias in resected tissue, and in some of these cases brain MRI did not detect the malformation.[87,88]

High-resolution PET tomographs permit detection of focal cortical regions of decreased or increased glucose utilization in many infants who previously were diagnosed as idiopathic West's

syndrome. Chugani reported a series of 140 cases of infantile spasms, including 7 who had neurogenetic syndromes and 29 who had lesions on structural imaging; among the patients without lesions or neurogenetic syndromes, FDG imaging detected regional metabolic dysfunction at one cortical site in 30 cases and at multiple cortical sites in 62 cases.[84] The subjects in this study were biased by referral pattern towards infants with refractory spasms and without a structural lesion on MRI. Nonetheless, one might logically conclude that infantile spasm-associated malformations of cortical development are more likely to be detected as metabolic dysfunction than as structural lesions, during infancy. Chugani has suggested that in infants the normal absence of myelination of subcortical white matter may render MRI less sensitive in detecting subtle neuronal heterotopia and other dysplastic features, compared with the high MRI sensitivity to dysplasias in children and adults with completed myelination.

Lennox-Gastaut Syndrome and Related Conditions

Patients with the Lennox-Gastaut syndrome usually have multiple regions of bilateral cortical hypometabolism interictally on FDG scans, but sometimes have predominantly unilateral hypometabolism, when patients with structural lesions are included.[80,89] When only Lennox-Gastaut patients with no lateralizing findings on neurological examination and with normal cranial x-ray CT scans were imaged with FDG interictally, most patients had symmetric generalized cortical and thalamic hypometabolism, although a few had symmetric generalized cortical hypermetabolism.[81]

A series of 32 children with "cryptogenic epileptic encephalopathies", which presumably included mainly children with secondary generalized epilepsies, demonstrated generalized metabolic dysfunction in most cases (usually hypometabolism, but hypermetabolism in some), regional metabolic dysfunction in some cases, and normal metabolism in only two cases.[90] The FDG scans in this series detected thalamic hypometabolism in 90% of cases, which was usually bilateral, but thalamic metabolism was lower on the side of more severe cortical hypometabolism.

Unilateral focal or multifocal sites of hypermetabolism during sleep, with more nearly normal cerebral glucose metabolism during waking, are

typical of electrical status of slow wave sleep.[91] The sites of metabolic dysfunction mainly were found in association cortex. This childhood syndrome of continuous generalized spike-and-wave discharges during slow wave sleep, usually with dementia or progressive aphasia, and with clinically evident epileptic seizures, thus provides another example of a secondary generalized epilepsy where generalized EEG phenomena are associated with focal or multifocal cortical metabolic dysfunction.

EMISSION TOMOGRAPHIC IMAGING IN PRESURGICAL EVALUATION OF PARTIAL EPILEPSIES

Imaging of ictal CBF with SPECT and of interictal CMR_{Glc} with PET have similar roles in evaluations for epilepsy surgery. Both ictal CBF SPECT and interictal FDG PET can detect definite abnormalities when structural imaging is normal or nonspecifically altered.[53,92,93] Overall sensitivity and specificity of ictal SPECT and interictal FDG PET are similar; studies of the two techniques, in the same sets of patients, report sensitivity to functional abnormality in excess of 70% (and usually much greater than 70%), with specificity to the ictal onset zone above 90%.[92,94,95] Single regions of interictal hypometabolism on FDG PET are highly associated with the region that can be resected to control seizures in localization-related epilepsies. In the syndrome of limbic TLE, interictal FDG PET and ictal SPECT that shows most severe abnormality in one temporal lobe strongly supports anterior temporal lobectomy without prior intracranial EEG monitoring, if other non-invasively acquired data support this localization (specifically; when 1) extracranial EEG recordings show unilateral temporal ictal onsets; 2) MRI is normal, or non-specifically abnormal, as in the case of puncta of subcortical white matter abnormalities, or abnormal in the same temporal lobe; and, 3) other non-invasively acquired data are not discordant with this localization.[43] In the syndrome of limbic TLE, interictal FDG PET and ictal SPECT that shows most severe abnormality in one temporal lobe does not alone establish that all seizures are arising from that temporal lobe (as discussed further below), so intracranial monitoring will be necessary when FDG abnormalities are not supported by ictal EEG localization, and when FDG abnormalities contradict other localizing abnormalities.

In extratemporal epilepsies and in localization-related epilepsies that cannot be fully characterized by electroclinical manifestations, FDG abnormalities cannot be used to determine the margin of cortical resection, but can be used with other data to determine sites that should be monitored with intracranial electrodes.[73] Current evidence demonstrates that PET and SPECT data are not redundant with electrophysiological data nor with structural imaging data. These functional imaging modalities sometimes provide evidence of falsely localized extracranial ictal EEG data, or evidence that EEG and MRI falsely suggested unifocal ictal onsets in patients who actually have two independent ictal onset zones. However, the cost effectiveness of performing one of these functional imaging modalities in all patients before resective epilepsy therapy is unknown. Based on currently available information, it is reasonable to perform either interictal FDG PET or ictal SPECT in all patients with localization-related epilepsies before resective surgery, in addition to ictal recordings with extracranial EEG, MRI and neuropsychometric studies.

Unilateral temporal lobe hypometabolism is "falsely lateralized" (located contralateral to the intracranially recorded site of ictal onset, in patients with single ictal onset zone) in approximately 1–2% of patients, in series in which potential sources of imaging artifact and unreliable forms of quantitative analysis were excluded. Prior intracranial surgery, including depth electrode placement, can produce temporal hypometabolism that is falsely lateralized with respect to intracranially recorded temporal lobe ictal onsets and to the side of subsequent, efficacious resection.[43] Imaging artifacts also can be produced by unrecognized errors in cranial positioning, errors in computerized image reconstruction and other aspects of imaging; visual image analysis should be used to exclude these artifacts, prior to any automated quantitative image analysis. Volume-of-interest-based quantitative analysis should sample regions whose volumes are in the range of the usual volume of the interictally hypometabolic area of TLE, and techniques which do not use predefined volumes of interest, such as statistical parametric mapping, should use a volume threshold to avoid detection of potentially misleading,

tiny foci of statistically significant hypometabolism, at least for application in presurgical evaluation. Continuous EEG monitoring can be performed during FDG scanning and sometimes can exclude unintentional ictal scanning that could lead to misinterpretation of FDG images.[21] Sperling[8] reported a patient who did not have subjective or objective clinical changes or scalp EEG changes during "interictal" FDG scanning, which appeared to show falsely lateralized temporal hypometabolism. In fact, the scan probably showed correctly lateralized ictal hypermetabolism. Subsequent intracerebral recordings showed frequently recurrent seizures confined to one hippocampus (without subjective or objective behavioral change and without scalp EEG change). Visual interpretation relies on detecting asymmetry, so hypermetabolism on one side may appear to represent hypometabolism on the other side. Sperling suggested that relative quantification of temporal lobe and occipital lobe metabolism may support distinction of temporal hypermetabolism on one side from temporal hypometabolism on the other side. As is true of all noninvasive means of localizing the epileptogenic zone, presurgical application of interictal FDG PET in partial epilepsies should be limited to correlation with other studies used to regionalize the ictal onset zone.

Neuroimaging abnormalities of the ictal onset zone can be reliably detected with MRI, peri-ictal single photon emission computed tomography (SPECT), or interictal FDG PET. Many groups use one or more such abnormalities, when concordant with ictal EEG and other data, to direct temporal lobectomy without prior intracranial EEG monitoring. The relative sensitivities of MRI, peri-ictal SPECT, and interictal FDG PET in various situations of presurgical evaluation remain unclear.[93] When MRI was performed with a high-performance 1.5-Tesla system, but without quantitative volumetric or T2-relaxometric analysis, 39 TLE patients in the UCLA series did not have localizing MRI abnormalities; among these 39 patients, 24 (62%) had temporal lobe hypometabolism on qualitative analysis of FDG PET and surgical outcome was consistent with correct PET lateralization.[15] Ryvlin reported that among 19 TLE patients with normal X-ray computed tomography, 8 had hippocampal T2 increase on MRI and these 8 also had widespread temporal hypometabolism ipsilaterally on interictal FDG PET; 8 had normal MRI but had temporal hypometabolism on PET; 3 had normal MRI and normal PET.[53] Therefore, it can be useful to perform FDG PET for localization based on concordance with ictal scalp EEG, even when qualitatively or quantitatively analyzed MRI is normal.

Cerebral MRI is essential in detection of neoplasia, vascular malformations and other foreign-tissue lesions.[96] Cerebral structural abnormalities are highly but not completely correlated with the epileptogenic zone. For this and other reasons, Spencer has recommended that whenever possible functional imaging should also be performed and compared with the other data prior to surgery.[93] With increased knowledge of the sensitivity and specificity of the various imaging techniques in particular clinical situations, it is possible that in the future, interictal FDG PET will be reserved for those cases in which MRI is non-localizing or in which MRI provides localization discordant with ictal EEG and other routinely acquired data in refractory partial epilepsy. Currently many surgery programs send selected patients to an outside PET center for FDG imaging, if MRI is normal or nonlocalizing, ictal SPECT cannot be obtained successfully, and PET is not available at the center.

Optimal choice of intracranial electrode placements is necessary for successful localization of the electrophysiological ictal onset zone, when non-invasive data do not suffice. Interictal metabolic information may be combined with other data to direct intracranial electrode placement to sites of possible ictal onset. Regional hypometabolism can suggest otherwise unsuspected possible sites of ictal onset, to avoid intracranial monitoring procedures that record ictal propagation patterns but fail to record earliest ictal onset patterns (evidenced by absence of ictal discharges recorded during earliest behavioral manifestations). The absence of any hypometabolism obviously does not rule out localization-related epilepsy. Similarly, regional hypometabolism strongly suggests that seizures may begin somewhere within the region of hypometabolism, but does not rule out multiple areas of ictal onset both within and beyond the hypometabolic cortex. Unilateral temporal hypometabolism has been reported in patients who have intracranially recorded bilateral independent hippocampal ictal onsets of complex partial seizures, most of whom also have exclusively unilateral MRI abnormality.[97] It is the author's experience that ictal scalp-

sphenoidal EEG recordings are much more likely than are MRI or PET images to show evidence of bilateral TLE, among patients who subsequently have intracranial recording of bilateral independent hippocampal ictal onsets during complex partial seizures. The author also has seen several patients who had bilateral independent temporal ictal onsets on extracranial EEG, with unilateral temporal abnormalities on MRI and PET or on PET only, but had exclusively unilateral hippocampal intracranial EEG onsets that were on the side of the imaging abnormality (and of efficacious temporal lobectomy). All focal ictal onset patterns on extracranial EEG, all focal cerebral gray matter lesions on MRI, and all regions of cortical hypometabolism on PET should be considered when determining intracranial electrode placements.

Interictal regional hypometabolism is useful in predicting the outcome of temporal lobectomy with respect to seizures. Greater severity of preoperative hypometabolism of the resected temporal lobe is associated with significantly better postoperative seizure control, using either qualitative or quantitative definitions of severity of hypometabolism.[52,63,98] The high correlation of temporal hypometabolism and seizure outcome is independent of the pathological diagnosis. Uncal metabolism, analyzed quantitatively, may provide the most accurate correlation with seizure outcome.[98] Qualitatively, severe extratemporal hypometabolism is associated with a higher incidence of postoperative seizures.[59] Symmetric, severe, bilateral temporal hypometabolism also is associated with a higher incidence of postoperative seizures, even when other data suggest that all seizures originate in one temporal lobe.[39] A site of reduced FDG activity that is distinct and non-contiguous with a cavernous angioma is highly associated with recurrent seizures after lesionectomy.[59,99] Interictal CBF imaging with [^{15}O]H$_2$O PET is not useful in predicting seizure outcome.[71] One study found ictal SPECT highly predictive of surgical outcome in extratemporal epilepsies.[100]

Future investigations may establish CBF activation PET studies as useful in avoiding iatrogenic injury to essential cortical processing zones during resective epilepsy surgery, although functional MRI studies provide similar information without exposure to ionizing radiation.[101] Both activation PET and fMRI appear likely to be able to lateralize hemisphere language specialization, based on

functional imaging studies of normal subjects who did not undergo Wada tests. Full application of activation PET or fMRI in presurgical evaluation will require many studies to determine the answers to many areas of uncertainty, including: 1) whether fMRI techniques can be developed to permit speech-related cranial motion during imaging, and whether it is essential to assess patient effort with analysis of verbal responses (given that patients may not comply with instructions during silent cognitive task performance, as apparently do paid, healthy volunteers in studies of normal cognitive activation); 2) how results of activation PET and fMRI compare with current clinical tools such as the Wada test and direct cortical electrical stimulation mapping; and, 3) whether modification of resection based on functional imaging results actually improves functional outcome of surgery.

EMISSION TOMOGRAPHIC IMAGING IN PRESURGICAL EVALUATION OF SYMPTOMATIC GENERALIZED EPILEPSIES

Single regions of interictal hypometabolism on FDG PET are highly associated with the region that can be resected to control seizures in the West syndrome, in the Sturge-Weber syndrome with generalized-onset seizures, and in other secondary generalized epilepsies of early childhood.[82,83,87] In addition to the generalized interictal and ictal EEG phenomena, these early childhood secondary generalized epilepsies frequently have focal scalp EEG abnormalities,[87] that often correspond to the PET focus in patients with infantile spasms. When a single region of abnormal glucose utilization is apparent on PET, corresponding to the EEG focus, and the seizures are intractable, surgical removal of the PET focus results not only in seizure control, but also in complete or partial reversal of the associated developmental arrest. This is in contrast to the expectation of moderate to severe retardation based on their preoperative developmental decline.

Neuropathological examination of the resected tissue in the West syndrome who underwent surgery reveals that the epileptogenic zone is typically a previously unsuspected area of cortical dysplasia.[82,87] It is now recommended that any patient considered to have cryptogenic medically refractory infantile spasms following extensive evaluation, including metabolic studies and structural neuroimaging, should have a PET study of glucose metabolism. About 20% of these refractory cases

will show a single focal lesion and be candidates for cortical resection. The remainder will show multifocal abnormalities on PET, usually corresponding to bihemispheric epileptogenicity on the EEG.

In Sturge-Weber syndrome patients with refractory epilepsy, PET has been useful both in guiding the extent of focal cortical resection (i.e., correlating better with intraoperative electrocorticography than CT or MRI) and in assessing candidacy for early hemispherectomy. Children with cutaneous anomalies similar to those of Sturge-Weber syndrome, but without intracranial angiomata, have normal cerebral FDG PET. Therefore, PET provides a sensitive measure of the extent of early cerebral involvement in Sturge-Weber syndrome patients, a means of monitoring disease progression, and information useful in guiding resective surgery.

Normal metabolism or complex regional metabolism bilaterally on FDG PET might be proposed as indirect support for corpus callosotomy. Further investigation will be required to establish a specific role for PET in pre-callosotomy evaluation.

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