

PET Scanning in Partial Epilepsy

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ABSTRACT: Many biologically active tracers are available for positron emission tomography (PET) investigations, but most studies of epilepsy have utilized ^{18}F -fluorodeoxyglucose (FDG) to measure local cerebral metabolic rate for glucose. Over 70% of patients with medically refractory partial seizures demonstrate an interictal zone of hypometabolism corresponding to the epileptogenic region. This metabolic defect commonly involves the temporal lobe in patients with complex partial seizures of mesial temporal origin, and is encountered less consistently with seizures of extratemporal neocortical origin. Although false localization is less likely with FDG-PET than with EEG, the hypometabolic zone merely reflects a focal functional deficit and its epileptogenicity must still be demonstrated electrophysiologically. When hemispherectomy or large multilobar resections are planned in small children, FDG-PET also provides useful supporting evidence that the contralateral hemisphere is functioning normally. It is difficult to obtain FDG-PET scans and to interpret results during spontaneous partial seizures. Ictal scans can be more easily obtained with single photon emission computed tomography (SPECT), which may provide information for planning surgical resections.

RÉSUMÉ: *Pet scan dans l'épilepsie partielle.* En dépit de la disponibilité de plusieurs traceurs radio-actifs pour les études de tomographie par émission de positons (PET), la plupart des études réalisées ont utilisé le ^{18}F -fluorodésoxyglucose (FDG) pour la mesure de métabolisme local du glucose. Chez plus de 70% des patients présentant des crises partielles complexes réfractaires à la médication, on retrouve une zone d'hypo-métabolisme correspondant à la région épileptogène. Cette zone d'hypo-métabolisme implique souvent le lobe temporal chez les patients ayant des crises partielles complexes d'origine méso-temporale; elle est rencontrée de façon plus inconstante chez ceux ayant des crises provenant des structures néo-corticales extra-temporales. Malgré que la possibilité d'une fausse localisation soit moins grande avec les études FDG-PET qu'avec les études électroencéphalographiques, il reste à démontrer électrophysiologiquement que la zone d'hypoperfusion, qui représente tout au plus un déficit fonctionnel localisé est épileptogène. Le FDG-PET peut fournir de précieuses données sur l'intégrité fonctionnelle de l'hémisphère controlatéral lorsqu'une hémisphérectomie ou une large résection multi-lobaire est nécessaire chez de jeunes enfants. Il est difficile d'obtenir des études FDG-PET durant les crises partielles spontanées; de plus, l'interprétation des résultats est problématique. Les mesures du métabolisme cérébral régional en phase ictale sont plus facilement obtenues avec la tomographie par émission de photon unique (SPECT) qui peut fournir de précieux renseignements pour la planification de la résection chirurgicale.

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Experience with the use of positron emission tomography (PET) to evaluate human local cerebral function extends now for well over a decade.¹ The requirements for an on-site medical cyclotron, in particular, have limited the proliferation of PET facilities, and this technique remains largely a research tool. As a result, PET has not enjoyed the same extensive application for clinical diagnosis as has occurred with, for instance, magnetic resonance imaging (MRI). A major focus of clinical PET research, however, has been on partial epilepsy and perhaps the area of greatest demonstrated clinical value for PET at the present time is in the presurgical evaluation of patients with partial seizures who are candidates for resective surgical treatment.² New PET systems are now being developed with self-contained, stand alone cyclotrons which require no shielding, organic chemistry modules for preparation of reagents, and the latest generation tomograph, which can all be operated by a single technician, at a price competitive with structural imaging systems.³ This will facilitate the establishment of clinical PET cen-

ters and should permit the more widespread use necessary to better understand the contributions PET could make to diagnosis of partial epilepsy. At the present time, however, our experience remains limited to patients with severe complex partial seizures who are candidates for surgery.

Interictal Localized Abnormalities

Many PET centers have now confirmed that approximately 70% of patients with severe partial seizures demonstrate an interictal zone of hypofunction corresponding to the epileptogenic region. This has been demonstrated for glucose metabolism, using ^{18}F -fluorodeoxyglucose (FDG),⁴⁻¹⁰ oxygen metabolism using ^{15}O -oxygen,^{8,10,11} and blood flow using ^{13}N -ammonia¹² and ^{15}O -water.^{8,10,11} There is a high degree of correlation between the presence of a zone of hypofunction and the existence of a structural lesion demonstrated by pathological analysis of resected tissue;⁵ however, the PET identified hypofunction extends well beyond the area of morphological abnor-

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mality.⁵ FDG-PET studies have demonstrated that hypometabolism is most commonly encountered in patients with mesial temporal lesions, usually hippocampal sclerosis, but also those with small tumors, hamartomas, and other specific pathological findings in this area,⁵ while localized hypometabolism occurs much less often with small, non-radiologically detected neocortical lesions.^{13,14} Patients with complex partial seizures of mesial temporal origin usually have hypometabolism involving most temporal neocortex, while some also have more distant hypometabolism in other regions,¹⁵ particularly in ipsilateral thalamus.¹⁶ Patients with complex partial seizures of *extratemporal* origin may also demonstrate interictal temporal hypometabolism, presumably due to recurrent projection of ictal discharge into mesial temporal structures.⁷ In these cases, the region of ictal onset has also been hypometabolic interictally, and no patient at UCLA has yet been observed to have only temporal hypometabolism with an extratemporal site of seizure origin. Nevertheless, it is conceivable that this could occur. Therefore, temporal lobe hypometabolism alone should be considered of extremely reliable lateralizing value, but not an absolute indicator of the localization of the primary epileptogenic region.

Although there is excellent correlation between the hemisphere containing the zone of hypometabolism demonstrated by interictal FDG-PET and the hemisphere presumed to contain the primary epileptogenic region demonstrated by electrophysiological means, there is less agreement when the results of FDG-PET are compared with results of individual electrophysiological evaluations (interictal and ictal scalp and sphenoidal EEG, interictal depth electrode EEG). As shown in Table 1, the yield of correctly positive studies (determined by postoperative outcome) is about the same for FDG-PET and individual electrophysiological approaches; however, the incidence of false lateralization is much higher for the latter. False lateralization with FDG-PET has only occurred in two patients at UCLA and this was attributed to artifact induced by depth electrodes in both cases.^{6,18} FDG-PET studies for presurgical diagnostic purposes are now always obtained prior to depth electrode implantation at UCLA and 8 years of experience since have not yielded another case of false lateralization. On the other hand, interictal spike activity and ictal onset from scalp and sphenoidal EEG telemetry recordings have consistently yielded false lateralizing in 10 to 15% of patients.^{18,19} False localizing information is also obtained from scalp and sphenoidal evaluations.¹⁹ Further stud-

ies concerning the incidence of falsely localizing and falsely lateralizing interictal spike activity recorded with depth electrodes have not been carried out.

The low incidence of false lateralization from depth electrode recorded ictal onset seen in Table 1 merely reflects the fact that patients rarely undergo resective surgery at UCLA when depth electrode ictal onsets conflict with most or all other tests of epileptiform excitability and focal functional deficit.²⁰ Since this table includes only those patients who were operated on and benefitted from surgery, it is possible that some patients who did not benefit from surgery, as well as others who did not receive surgery, had falsely lateralized depth electrode recorded ictal onsets. In the one patient where this was documented in the UCLA series,²¹ the seizures that began on the side contralateral to surgery were all atypical and presumed to be due to antiepileptic drug withdrawal. This patient has remained seizure-free, now almost ten years after anterior temporal lobectomy based on scalp and sphenoidal telemetry recording, FDG-PET data, and other studies of focal functional deficit.²⁰

There appears to be no correlation between the presence or degree of interictal localized hypometabolism on FDG-PET, and the frequency of interictal spikes recorded from mesial temporal structures with depth electrodes.²² This clearly demonstrates that FDG-PET measures a different aspect of cerebral function than does EEG. These tests, therefore, should be considered complementary, and both together provide more information concerning the location and nature of dysfunction than either one alone. Interictal EEG spikes, and also apparent ictal EEG onsets, may represent propagation from distant epileptogenic regions which are beyond the recording range of scalp or even depth electrodes. On the other hand, hypometabolism on FDG-PET can occur as a result of ablative lesions that are not epileptogenic. Interictal hypometabolism on FDG-PET has also not correlated well with seizure frequency, recency, or severity²³ and does not necessarily predict the inability of that temporal lobe to support memory with contralateral intracarotid sodium amytal injection.²⁴

Although the demonstration of a localized zone of hypometabolism on FDG-PET is extremely useful for identifying the site of an epileptogenic lesion for surgical purposes, the presence of such a zone has no prognostic value with regard to surgical outcome.¹⁸ FDG-PET scans may be normal in patients with resectable temporal lobe lesions who do well postoperatively, while the presence of hypometabolism may occasionally indicate extensive disturbances that are subsequently incompletely resected. A review of patients in the UCLA series who had no lesions identified in their resected temporal lobes by routine pathological examination indicated that those with negative FDG-PET scans were all seizure-free, while the two patients in this group who had localized interictal hypometabolism on FDG-PET had no worthwhile improvement.²⁵ On quantitative analysis of hippocampal specimens from these patients, those with negative scans who were seizure free all had 30 to 50% pyramidal cell loss; greater than 50% cell loss is usually required for identification by routine pathological evaluation as hippocampal sclerosis. The two patients with localized hypometabolism who did not do well had no hippocampal cell loss, but evidence for incomplete resection. One had more posterior temporal hypometabolism and visual auras which continued postoperatively, and eventually devel-

Table 1: PET and EEG Lateralization for Patients with Good Postoperative Outcome and Greater Than One Year Follow-up

	PET	Scalp		Depth	
		IIS	IO	IIS	IO
I	28 (76%)	27 (74%)	22 (60%)	17 (63%)	26 (96%)
C	1 (3)	5 (13)	5 (13)	6 (22)	1 (4)
O	8 (2)	5 (13)	10 (27)	4 (15)	0
Total	37	37	37	27	27

IIS — interictal spike predominance

IO — ictal onset

I — ipsilateral to resected temporal lobe

C — contralateral to resected temporal lobe

O — nondiagnosis study

From Engel and Henry¹⁷

oped into complex partial seizures again. The other had gelastic seizures and a pneumoencephalogram that suggested a hypothalamic lesion. Consequently, it appeared that the first group of patients who did well had mesial temporal lesions that were missed by the pathologist, while the second group, who did poorly, had lesions that were missed by the neurosurgeon.

A special class of patients with partial seizures are infants and small children with severe unilateral ictal symptoms and large structural lesions, who are candidates for hemispherectomy or multilobar resections. Interictal FDG-PET studies in these patients have revealed marked unilateral hypometabolism on the side of seizure origin.²⁶ One patient also showed localized hypermetabolism in an area demonstrated to be the site of maximal interictal EEG spiking.²⁶ It is uncertain from the EEG and behavioral recordings of this patient whether this reflected a subclinical seizure, or whether energy requirements for interictal spike generation change with cerebral maturation. In over 200 interictal FDG-PET scans of children and adults with more localized partial seizures at UCLA, only one has demonstrated interictal hypermetabolism.²⁷ Behavioral and EEG observation during FDG injection and uptake failed to identify any ictal activity. This patient was six years old, had a previous interictal scan which showed only a zone of hypometabolism, and two ictal FDG-PET scans which showed localized hypermetabolism in a region much larger than that apparently activated during the second interictal study. The reason for this remains unclear.

Ictal Studies

Ictal PET studies are difficult to obtain due to the short half life of positron emitting isotopes. Those that have been reported represent either the fortuitous occurrence of one of more seizures following FDG injection, or seizure induction.^{4,9,27,28} Partial seizures have produced a variety of metabolic patterns. Most commonly there is localized hypermetabolism representing areas involved in seizure onset and early propagation. This may be superimposed on more global hypermetabolism, so far encountered only in patients with simple partial seizures, or superimposed on global hypometabolism, so far only encountered in patients with complex partial seizures.²⁷ Hypometabolism in this latter situation is believed to reflect postictal disturbances, since postictal hypometabolism has been demonstrated following generalized convulsions induced by electroconvulsive treatment.^{28,29} A brief complex partial seizure induced by electrical stimulation of the hippocampus was reported to be associated with lateral temporal localized hypometabolism which might reflect more limited postictal disturbances.²⁷ These studies indicate that ictal FDG-PET might be useful for lateralizing the epileptogenic lesion, but within the involved hemisphere it would be difficult to differentiate the site of ictal onset from areas of propagation. Demonstration that an interictal zone of hypometabolism converts to hypermetabolism during a seizure might be a pathognomonic sign of epilepsy even in the absence of EEG recording; however, localized hypermetabolism has now also been demonstrated in patients who have abused cocaine,³⁰ and the functional significance of this observation has not yet been determined.

Use of PET in presurgical evaluation

At UCLA, FDG-PET has proved to be a valuable diagnostic tool for confirming the location of a resectable epileptogenic

lesion, particularly in patients with complex partial seizures with mesial temporal onset.^{6,8,31} This test remains confirmatory, since demonstration of epileptogenicity using electrophysiological techniques is always a necessary component of the presurgical evaluation protocol. Evidence of focal functional deficit such as local hypometabolism on FDG-PET, localized dysfunction on neuropsychological testing, localized attenuation of thiopental-induced fast activity on EEG, and failure to support memory as well as transfer of language function demonstrated by intracarotid amytal injection,^{2,20} or nonspecific structural disturbances such as atrophy demonstrated by structural imaging, are all important for determining that a temporal lobe that appears to be the site of ictal onset is also abnormal in other ways. At the present time, patients at UCLA are recommended for anterior temporal lobectomy without intracranial EEG recordings when a mesial temporal epileptogenic zone is identified by a focal sphenoidal ictal onset¹⁹ and confirmed by hypometabolism on FDG-PET, and other evidence of focal functional deficit, or nonspecific structural disturbances in that same temporal lobe. Approximately two-thirds of patients undergoing anterior temporal lobectomy at UCLA now do so without extraoperative or intraoperative intracranial recording, as a result of this protocol.

When patients do not meet the electrophysiological criteria for surgery without intracranial evaluation, but a localized resectable epileptogenic region is still suspected, a positive FDG-PET scan is useful for planning the subsequent investigation. Patients with complex partial seizures suspected of being of mesial temporal origin are studied with depth electrodes, and will also have extratemporal depth or strip electrodes placed when there is evidence that an extratemporal ictal onset is a possibility. On the other hand, when seizures are believed to originate from lateral neocortex, particularly in patients with simple partial seizures, subdural grid electrodes may be used.³² In this case, the location and extent of hypometabolism on FDG-PET may determine the size and location of the subdural grid placement. FDG-PET abnormalities also help in interpreting the results of intracranial electrode recording and in making the final decisions regarding resective surgery. For instance, patients that demonstrate occasional contralateral ictal onsets, or regional onsets from mesial temporal depth electrodes,^{20,33} can be operated on with a higher degree of confidence when a zone of hypometabolism on FDG-PET corresponds with the presumed epileptogenic region.

Diffuse hemispheric hypometabolism on FDG-PET confirms the abnormal side in infants and young children who are candidates for hemispherectomy. Although this is usually obvious from electrophysiological studies and behavioral observations, structural imaging studies may be normal and additional evidence of diffuse dysfunction provides additional security.³⁴ More importantly, however, FDG-PET in these patients provides information that the contralateral hemisphere is functionally normal. The role of FDG-PET identified hypometabolic areas in determining the extent of multilobar resections still requires substantiation. It has also been suggested that interictal FDG-PET of patients with Lennox-Gastaut syndrome may reveal focal abnormalities that would respond to localized resection, or unilateral dysfunction that would respond to corpus callosum section,³⁴ but this remains speculation.

Single photon emission computed tomography (SPECT) is becoming increasingly available as a clinical diagnostic tool. A number of tracers are being used to image cerebral blood flow. Most studies have consistently reported localized interictal hypoperfusion and ictal hyperperfusion corresponding to the epileptogenic region.³⁵⁻⁴⁰ This technique offers the advantage that single photon emitting isotopes have relatively long half lives and an on-site medical cyclotron is not necessary. On the other hand, spatial resolution is considerably less with SPECT than with PET, quantitative studies cannot be carried out at the present time, and blood flow is the only cerebral function that can be studied. Because tracers can be easily mixed at the bedside, however, ictal or postictal studies can be much more easily obtained with SPECT than with PET. Since localized hypermetabolism is reported to persist into the postictal period, perhaps for hours even when partial seizures become secondarily generalized,³⁹ SPECT has potential for playing a unique role in presurgical evaluation. It must be demonstrated, however, that ictal and/or postictal SPECT-demonstrated regions of hyperfusion can differentiate between cerebral sites of ictal onset and sites of propagation, which does not appear to be the case with ictal FDG-PET-induced hypermetabolism.

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