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The role of PET in presurgical assessment of partial epilepsies

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ABSTRACT – In the presurgical assessment of drug refractory partial epilepsies PET represents a privileged means for investigating glucose metabolism and neurotransmission in the functional-deficit zone, defined as the region of cortex that is functioning abnormally in the interictal period. Another aim of PET investigation is to produce images of neurotransmission abnormalities underlying neuronal hyperexcitability, and thus to allow direct visualization of the epileptogenic zone. This approach has been mostly based on the binding of various radio-ligands on specific receptors (GABA-A, opiate and serotonin receptor) and on brain uptake of serotonin precursors. These attempts have not yet been fully validated, in spite of promising studies of serotonin synthesis and receptors. Consequently, at the present state of their development, most of the PET techniques routinely used, reflect changes that are not directly related to the epileptogenic process itself. The lack of large multicentric controlled studies, evaluating the impact of PET, represents the main limitation to a better understanding of the clinical role and utility of PET in epilepsy. We review the basic aspects and limitations of the technique, the various radiopharmaceuticals that have been tested in epilepsy, the sensitivity of the different types of PET investigations, the pathophysiolgy of PET abnormalities and discuss the practical utility of PET imaging in presurgical assessment of partial epilepsies.

KEY WORDS: PET, ^{18}FDG, presurgical evaluation, epilepsy surgery, partial epilepsies

Positron emission tomography (PET) has been the first functional neuroimaging technique applied to pre-surgical evaluation of drug-resistant partial epilepsies in the late seventies, using the fluoro-deoxyglucose labeled with ^{18}F isotope (^{18}FDG) to obtain quantified images of interictal brain glucose metabolism. At that time magnetic resonance imaging (MRI) was not yet available in clinical settings, and ^{18}FDG PET represented a major breakthrough in non-invasive exploration of partial epilepsies by showing a focal interictal glucose hypometabolism, particularly in patients with temporal lobe epilepsy and a normal brain CT scan. Another target of PET investigation has progressively developed, which is to get images of neurotransmission abnormalities underlying neuronal hyper-excitability, and thus to give access to a direct visualization of the epileptogenic zone. These attempts have not yet been fully validated, so that, at the present state of their development, most of routinely used PET techniques reflect changes that are not directly related to the epileptogenic process itself. The basic aspects and limitations of the technique, the various radiopharmaceuticals that have been tested in epilepsy, the sensitivity of the diffe-

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rent types of PET investigations, and the practical utility of PET imaging in pre-surgical assessment of partial epilepsies are discussed.

PET tracers: relevance and application in epilepsy

A list of PET tracers and related abnormalities that have been reported in functional imaging of interictal state in partial epilepsies is given in *Table 1*. In what follows we will focus on tracers that have demonstrated some clinical utility in the pre-surgical assessment of epilepsies.

^{18}FDG

^{18}FDG has been the most widely used PET tracer in epilepsy studies. It crosses the blood-brain barrier before being phosphorylated in the cell compartment at a rate, which is that of glycolysis. Contrary to glucose-6-phosphate the FDG-6-phosphate does not enter into further steps of Krebs glycolysis cycle, but accumulates in the intracellular compartment. Thus the measured radioactivity directly reflects the energetic demand of brain cells. This method permits to quantify the glucose metabolic rate by applying the model developed by Sokolow [1] in autoradiographic animal studies of deoxyglucose accumulation. This model requires a 45 minutes period of ^{18}FDG accumulation, during which the functional state of the brain is assumed to remain stable [2]. In patients with epilepsy the occurrence of ictal discharges, with or without clinically detectable manifestations in the condition of PET data acquisition, is able to increase the rate of glucose consumption in the discharging area (*figure 1*). The programming of an ictal FDG-PET, though feasible in some patients, has been rarely attempted [3]. In fact, the basic finding in partial epilepsies is represented by an interictal hypometabolism, of which characteristics and diagnostic significance are detailed below.

Table 1. Interictal PET abnormalities in partial epilepsies (mostly TLE).

1)	Focal glucose hypometabolism
2)	Decreased BZD-GABA$_A$ receptors (^{11}C-FMZ)
3)	Increased BZD receptors (focal dysplasia, normal MRI)
4)	Increased opiate receptors μ
5)	Decreased opiate kappa receptors
6)	Increased opiate delta receptors
7)	Increased Histamine H1 receptors
8)	Decreased muscarinic receptors
9)	Increased uptake of ^{11}C-Deprenyl (MAOB ihibitor)
10)	Decreased N-Methyl D aspartate receptors
11)	Increased serotonin synthesis
12)	Decreased serotonin (HT1A) receptors

$H_2{}^{15}0$, ^{15} O2, $C^{15}02$ and $^{13}NH3$

Used individually or in combination these markers permit to get quantified images of cerebral blood flow, brain blood volume, oxygen extraction ratio and oxygen consumption rates. PET studies of interictal cerebral blood flow in groups of patients with partial epilepsies, in which mesial TLE predominates, have generally shown regional hypo-perfusion in the same areas as regional glucose hypo-metabolism [4]. However regional hypo-perfusion proved to be uncoupled to glucose hypometabolism, the former being less sensitive and associated with more frequent false lateralization than the latter [5-7]. Intravenous injection of a $H_2{}^{15}0$ bolus can be used to obtain blood flow images, with a data acquisition time of about two minutes. Injections and data acquisitions can be repeated at intervals equal or superior to five times the radioactive half-life of $^{15}0$ (≥ 10 minutes). This technique is well adapted for comparing a "resting state" with a state of sensory, motor or cognitive activation. In epilepsy studies, the method can be used under EEG monitoring to compare interictal versus ictal states. This can be achieved on the condition that discharges do not provoke head movements, and occur during the data acquisition period. These limitations render the technique poorly applicable in routine studies to epilepsy patients. Exceptions are, episodes of non motor status epilepticus [8], or when very focal discharges can be provoked by either a proconvulsant drug [9], or direct cortical stimulation in patients with chronically implanted depth electrodes [10] (*figure 2*). Because of these limitations, when studying changes in cerebral blood flow between ictal and interictal periods, SPECT using markers of cerebral perfusion which allow a delay of a few hours between tracer injection (performed at bedside during a spontaneous video-EEG monitored seizure) and data acquisition is currently preferred to the $H_2{}^{15}0$ or other blood flow PET techniques.

Radio-ligands of receptors

General principles and difficulties of PET receptors studies

Based on the assumption that changes in neurotransmission could be one of the basic mechanisms of cortical hyper-excitability, one of the most promising applications of PET in epilepsy study consists in imaging the distribution of brain receptors in the interictal state. Quantification problems, as well as functional interpretation of images, are peculiarly delicate in receptors studies. Two methods are currently used to extract specific fixation from raw PET images [11]. The first one consists in evaluating the non-specific binding by studying the kinetics of radioactivity in a brain region known as deprived of specific receptors. The second consists in performing data acquisition in two conditions, one in which specific receptors are free for binding with the injected radio-labeled ligand and the other in which specific receptors are occupied by the non

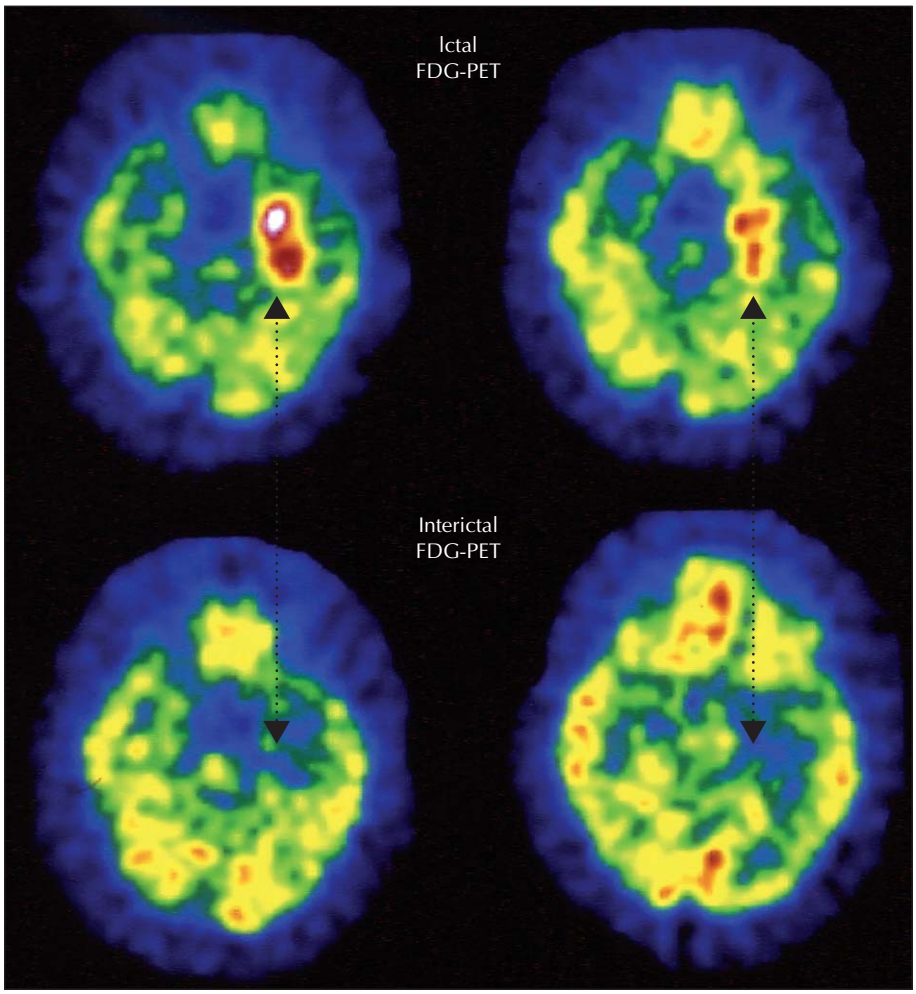

Figure 1. ***Ictal [^{18}F]FDG-PET***. *An ictal FDG-PET was obtained in a patient who presented several epigastric auras during the 10 minutes following FDG injection, showing a clear-cut left mesial temporal glucose hypermetabolism. The latter was replaced by a left mesial temporal hypometabolism on a second FDG-PET performed interictally.*

labeled ligand injected at a high and pharmacologically active dose, prior to radio-labeled ligand injection (saturation method). This second method requires that the injection of the cold non-labeled ligand has no adverse pharmacological effects, a condition that is not fulfilled, for instance, for some opiate receptors agonists. Thus quantification of specific receptors binding may require very heavy protocols that cannot be implemented routinely in patients for diagnostic use.

When specific cerebral binding represents a high percentage of the measured activity on uptake images (for instance 90% for [^{11}C]-flumazenil binding to $GABA_A$ receptors) the volume of distribution of the ligand (Vd) reflects the receptors availability (Bmax). Voxel based images of the labeled ligand Vd can then be produced from the brain uptake and plasma input functions using spectral analysis [12]. Simplified protocols that do not necessitate arterial blood sampling have been proposed for clinical studies, such as the use of late ligand uptake images, for instance images acquired between 20 and 40 minutes post injection in ^{11}C-flumazenil studies [13-15]. The rationale for using such non-modeled approaches relies on correlations demonstrated between late uptake and distribution volume images [16-21], or quantified parametric images reflecting the receptors density [13, 22].

Another practical limitation to the use of PET receptors studies in patients with epilepsy is that any treatment susceptible to interfere with the specific binding of the radio-ligand must be interrupted before the study. For instance benzodiazepines, gamma-vinyl GABA and tiagabine must be interrupted at least for two weeks before a PET study of GABA receptors binding.

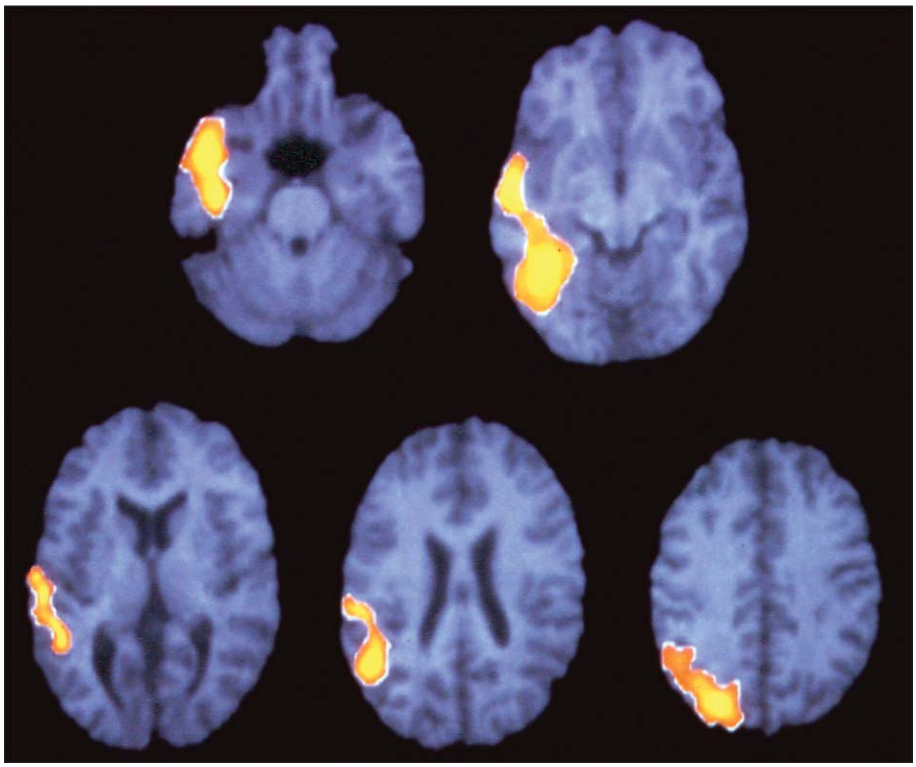

Figure 2. ***[^{15}O]H$_2$0-PET coupled with intra-cerebral stimulation****. An increased cerebral blood flow was elicited over the temporal and parietal lobes by an electrically induced sub-clinical discharge arising from the fusiform gyrus, and propagating to the temporo-parietal structures.*

Physiological interpretation

Physiological interpretation of PET receptors data is often equivocal, even when the problems of modeling and correction for partial volume effect have been resolved. Indeed, the same quantified image of a change of receptors density in brain tissue may reflect different biological changes. For instance, changes in receptors binding can merely reflect changes in the density of neurons per volume of cortex. Alternatively a given change in receptors binding can theoretically be explained by opposite abnormalities of neurotransmission. For instance an increase of specific receptors binding can be due either to an up-regulation of receptors in response to increased synthesis and release of the endogenous ligand, or to an increase in the proportion of receptors that are unoccupied as a consequence of decreased endogenous ligand concentration in the synaptic cleft. Moreover binding changes can also reflect a change in receptors characterictics affecting the ligand affinity. Since several of these mechanisms can combine in the same individual to produce the observed binding changes, it is not possible to distinguish between them without quantitative correlation studies between in vivo PET data and in vitro evaluations of neuronal density and receptors number. For instance, by comparing, in the same group of patients, pre-operative PET with post-operative autoradiographic evaluation of the density of benzodiazepine receptors and of neurons in sclerotic epileptogenic hippocampus Koepp *et al.* [23] showed a similar reduction of receptors in vivo and in vitro, which was over that of neuronal density.

$GABA_A$ – benzodiazepine (BZD) receptors

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in mammalian brain. The GABA type A ($GABA_A$) receptor is a pentameric structure functioning as a chloride ion selective channel that contains binding sites for GABA, picrotoxin, neurosteroids, barbiturates and benzodiazepines. The central benzodiazepine (BZD) receptor is an allosteric modulatory site dependent on the presence of both alpha and gamma subunits. In human epileptogenic atrophic hippocampus reduced $GABA_A$ and BZD binding has been demonstrated and electrophysiological studies have suggested a decrease of $GABA_A$ mediated inhibition. The most widely used ligand in epilepsy is ^{11}C-flumazenil ([^{11}C]-FMZ), which is a selective antagonist of $GABA_A$ - BZD receptors [24]. The BZD receptors labeled with [^{11}C]-FMZ represent modulatory sites of the $GABA_A$ receptors, which are primarily expressed post-synaptically on the apical dendrites of neurons. A reduced FMZ binding, as observed in patients with partial epilepsies is thought to largely reflect an underlying neuronal loss, as demonstrated in temporal lobe epilepsy (TLE) associated with mesial temporal sclerosis [14, 17,

25]. Most attention has been directed toward focal abnormalities in drug resistant partial epilepsies, with the hope to better delineate non invasively the epileptogenic zone [13-16, 21, 24]. As a matter of fact, patients with refractory partial seizures often demonstrate a localized reduction of [^{11}C]-FMZ binding, which closely correlates with the side and site of seizure onset [13, 16, 21, 24, 26]. This issue will discussed below.

Opiate receptors

The interest for opiate receptors in epilepsy stems from several arguments suggesting the existence of an endogenous opiate-receptor mediated anticonvulsant system in human beings. The release of opioid peptides is involved in the termination of epileptic seizures [27-31]. CSF concentrations of leuenkephalin are increased in epileptic patients [32]. The number of delta opioid receptors is increased in animals after a seizure [30]. Several ligands of opiate receptors have been used in epilepsy since the late eighties and early nineties. The first ones were [^{11}C]-carfentanil, which is an agonist of mu-opiate receptors [33], and [^{11}C]-diprenorphine, which binds less selectively than [^{11}C]-carfentanil onto delta and kappa opiate receptors and, to a lesser degree, to mu-receptors [34, 35]. A ligand binding to mu and kappa opiate receptors, the ^{18}F-cyclofoxy, has been tested by Theodore *et al.* [36]. [^{11}C]-carfentanil PET studies in the inter-ictal state showed an increased mu-opiate receptors binding in the epileptogenic temporal lobe in patients with TLE [33, 35]. This change is located in the temporal neocortex adjacent to the mesial temporal focus; it has been interpreted as reflecting an up-regulation of receptors limiting the discharge spreading in the inter-ictal state. Conversely [^{11}C]-diprenorphin studies only showed a slight decrease of binding in a small proportion of TLE patients [34-36]. A more recent study using a selective antagonist of delta receptors ([^{11}C]-MeNTI) demonstrated an increased uptake with a different distribution, as compared to that of mu receptors increase, in the temporal cortex of TLE patients suggesting distinct roles of different opiod-receptor subtypes in seizure phenomena [37].

Endogenous opioids can displace [^{11}C]-diprenorphine from receptors more easily than other sub-type specific ligands. With this ligand it has been shown that opioid receptors binding can be modified differently by specific brain activity in epileptic patients and normal subjects [38]. The model used by these authors was that of reading epilepsy. The finding was that, during reading, opioid receptor binding increases in the left parieto-temporo-occipital cortex of normal subjects, while it decreases in the same area in patients. This reduction of binding in patients during reading was interpreted as reflecting a release of endogenous opioids limiting the seizure spread, but other physiological explanations are possible (see above).

Serotonin receptors

5-hydroxy-tryptamine (5HT) or serotonin is a monoamine transmitter produced in brainstem raphe nuclei and released at cortical level through widely distributed ascending pathways. Among the 17 subtypes of serotonin receptors identified to date, the 5-HT$_{1A}$ receptor is the most widely studied [39]. While some authors described a convulsant effect of 5-HT$_{1A}$ agonists in absence type epilepsies [40, 41] a majority of studies suggest that serotonin might have, on the contrary, an anticonvulsant and anti-epileptic effect via 5-HT$_{1A}$ receptors. Serotonin was shown to delay the kindling process [42-44], to decrease the frequency of seizures induced by kainic acid [45] or bicuculline [46] and to inhibit the epileptiform activity induced by a Mg^{2+} free medium on rat hippocampal slices [47]. Moreover, agents that increase the concentration of endogenous serotonin, such as the inhibitors of serotonin re-uptake (fluoxetine) were shown to have an anticonvulsant effect mediated by 5-HT$_{1A}$ receptors on several animal models of partial epilepsies. In humans, immunohistochemical studies have revealed increased levels of serotonin in cortical dysplasia with focal epilepsy [48]. An anticonvulsant effect of fluoxetine was also suggested in a group of 17 patients suffering from partial epilepsy [49].

Two antagonist ligands of 5-HT$_{1A}$ receptors, recently developed for PET studies, have been tested in epilepsy. The first one is the [^{18}F]trans-4-fluoro-N-2[4-(2-methoxyphenyl)-1-piperazinyl)ethyl]-N-(2-pirydyl) cyclohexanecarboxamide known as [^{18}F]FCWAY, which presents a much higher affinity than endogenous serotonin for 5-HT$_{1A}$ receptors, comparable to that of the original WAY100635 labeled with ^{11}C [50, 51]. The second one is the 4-(2′-methoxyphenyl)-1-[2′-(N-2′′-pirydynyl)-p-fluorobenzamido]ethylpiperazine labeled with F18 [52] known as [^{18}F]MPPF, which has an affinity close to that of endogenous serotonin for 5-HT$_{1A}$ receptors and is thus sensitive to endogenous serotonin variations [53] (*figure 3*). Thus a decrease of [^{18}F]MPPF binding can be interpreted as reflecting either a decrease in receptor density or an increase of endogenous serotonin, resulting in a competition for receptor binding by the radioligand. PET studies with either of these two ligands of 5-HT$_{1A}$ receptors show a high level of tracer uptake in limbic (hippocampus, amygdala, parahippocampal gyrus) and paralimbic (temporal pole, insula, anterior and posterior cingulate gyri) regions as compared with other neocortical areas [54]. This selective distribution and the relation between serotoninergic neurotransmission and epileptogenic processes make these tracers peculiarly attractive in mesial temporal or frontal lobe epilepsies. Only three PET studies of 5-HT$_{1A}$ receptors have been reported to day in temporal lobe epilepsies, one with [^{18}F]FCWAY [55], the others with [^{18}F]MPPF [56, 57]. Both concluded that 5-HT$_{1A}$ receptors availability is decreased in the epileptogenic

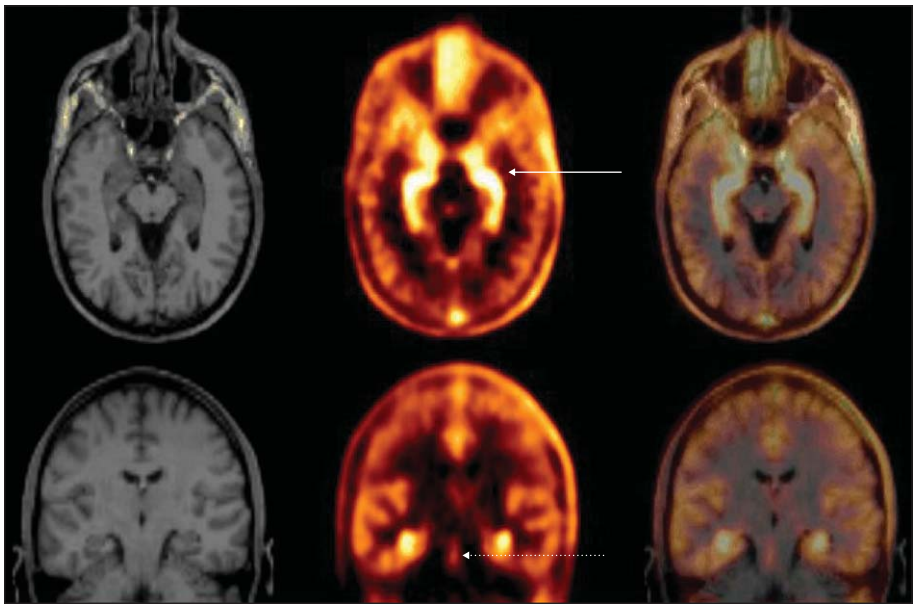

Figure 3. ***[^{18}F]MPPF-PET*** *in a normal subject showing the brain distribution of 5-HT1A serotoninergic receptors, particularly concentrated in the mesial temporal structures (arrow). The raphe nuclei are also well disclosed within the upper brainstem (dotted arrow).*

temporal lobe, with one of the two studies showing a correlation between the degree of [^{18}F]MPPF binding reduction and cortical epileptogenicity as evaluated by intra-cranial EEG recording [56] (*figure 4*).

Serotonin synthesis

Alpha-^{11}C-methyl-L-tryptophan (^{11}C-AMT) is the only precursor of a neurotransmitter that has been applied to the study of epilepsy. It has been used as a PET marker of brain serotonin synthesis and first proved promising for characterization of lesional epileptogenicity. This proved pecu-

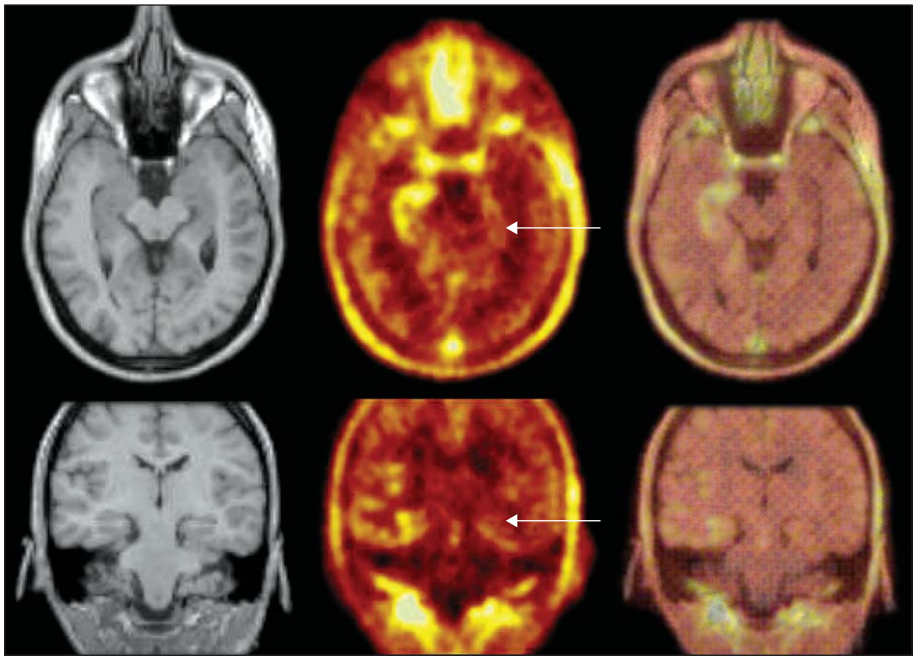

Figure 4. ***[^{18}F]MPPF-PET*** *in a patient with a left mesial temporal epilepsy, showing a decreased binding potential of 5-HT1A receptors over the epileptogenic zone. More subtle abnormalities are observed in the ipsilateral temporal neocortex and insula.*

liarly useful in patients with Bourneville's disease for identifying, in the interictal state, the epileptogenic tuber where ^{11}C-AMT uptake is increased [58, 59]. Focal increased uptake of ^{11}C-AMT congruent with the epileptogenic area was also reported more recently; 1) in 57% of patients with neocortical epilepsy and cortical dysplasia and in 27% of patients with normal MRI and ^{18}FDG PET [60]; 2) in 80% of chidren with severe epilepsy and cortical developmental malformations [61] and; 3) in the hippocampus ipsilateral to the focus in all (7) TLE patients with normal hippocampal volume, but not in TLE patients with hippocampal atrophy [62]. In this latter study increased uptake of ^{11}C-AMT correlated with glucose hypometabolism in lateral temporal neocortex, suggesting that serotoninergic mechanisms could be involved in interictal inhibitory processes causing glucose hypometabolism and controlling onset or propagation of ictal discharges. Another explanation for increased ^{11}C-AMT uptake in epileptogenic cortex is that of an upregulated production of tryptophan metabolites produced through the kynurenine pathway. Quinolinic acid is one of these metabolites, which is a known epileptogenic molecule through its action as an agonist on the NMDA receptor [63, 64].

Abnormal PET findings in the functional deficit zone: relation with the epileptogenic and irritative zones

Being performed mostly during the interictal period, PET is a priori better adapted to the assessment of the region of cortex that is functionally abnormal between seizures, known as the functional deficit zone [65], than to that of the epileptogenic zone, of which total resection or disconnexion is necessary and sufficient to obtain seizure-freedom. It is however obvious that the challenge of PET research is not primarily to evaluate the functional deficit zone, but rather to delineate the epileptogenic zone. Apart from the few promising data recently reported in studies of serotonin receptors binding and precursor uptake, it is obvious that, up to day, no specific marker of epileptogenicity has been validated. Relation between abnormalities of receptors and neuronal hyperexcitability is most often indirect, because several confounding factors are blurring the physiological interpretation of PET data (see above). It is uncertain whether demonstrating the presence of a "functional deficit zone" using PET is a priority of crucial relevance for planning the surgical procedure in epilepsy. This issue, per se, does not justify the implantation of a PET facility in epilepsy surgery departments, where alternative means of assessing preoperative deficits, such as neuropsychological testing and functional MRI, are available. Conversely prediction of postoperative outcome in terms of seizure control can benefit from PET investigation.

In what follows we will focus on interictal changes in glucose metabolism and $GABA_A$ receptors for three reasons; i) literature is abundant because these two methods have been widely used in epilepsy centers; ii) $GABA_A$ receptor studies have been developed mostly with the purpose of marking selectively neurons deprived of inhibitory control, while glucose hypometabolism has never been thought to reflect neuronal hyperexcitability, iii) interictal decrease in $GABA_A$ receptors is usually more focal than glucose hypometabolism, in the same way as the epileptogenic zone may involve only a limited portion of a larger functional deficit zone. This parallel between the concepts of epileptogenic and functional deficit zones and PET data remains to-date speculative, but the purpose of PET research is to make it realistic.

Focal interictal glucose hypometabolism

The interictal state

Focal interictal glucose hypometabolism has been reported in ^{18}FDG PET studies of patients with partial epilepsies, mostly with TLE, since the early eighties [66]. Main literature data obtained with this method are given in Tables 2 to 5. In most of the early studies there was no EEG monitoring during PET data acquisition, so that there is no certitude that no patient presented subclinical ictal discharges in these series. In our experience the prevalence of such discharges is of 4% of patients included in routine ^{18}FDG PET evaluation of their epilepsy. Barrington *et al.* [67] observed the occurrence of spontaneous seizure during tracer uptake in 6 of 236 ^{18}FDG PET studies in patients with intractable epilepsy. They reported that the occurrence of a single complex partial seizure (23s to 4 min) did not induce a focal increase of glucose metabolism sufficient to influence the interpretation of PET, and concluded that monitoring the EEG may be unnecessary. In any case the occurrence of an incidental seizure, which may have some importance for interpretation of individual data, does not influence group results and does not question the conclusion from converging studies, with or without EEG monitoring during PET data acquisition, that the functional deficit area shows a reduced glucose metabolism between seizures.

Sensitivity

The sensitivity of this ^{18}FDG PET abnormality has been estimated at about 65-80% in the early studies [66, 68-71]. The higher sensitivity of glucose hypometabolism on ^{18}FDG PET over that of interictal reduction of cerebral blood flow, as assessed by SPECT, has been demonstrated by early comparative studies of the two methods [72, 73]. This is explained by the better spatial resolution of PET [74] and by the fact that cerebral blood flow is less decreased than glucose metabolism in the interictal period [6, 77]. However ^{18}FDG PET sensitivity differs according to the location of the epileptic focus and to the nature of the underlying lesion, if any. It was close to 100% in

Table 2. Interictal glucose hypometabolism in partial epilepsies: Sensitivity according to published studies.

Sensitivity	References
70% to 80% (mean values in all type of partial epilepsies)	Khul [66], Engel [68, 70], Theodore [69, 71, 76, 77]
61% to 77% in patients with normal brain MRI	Ryvlin [80], Henry [82]
	Sperling [85], Theodore [71], Hajek [86]
85% to 100% in temporal lobe epilepsy (TLE)	Ryvlin [80], Sadzot [87], Theodore [78], Hajek [86], Henry [16, 82], Debets [14], Ryvlin [15]
40% to 96% in frontal lobe epilepsies (FLE)	Swartz [88, 89, 90], Henry [83, 84], Franck [91], Ryvlin [15]
92% in children with FLE and normal CT and MRI, restricted to FL in 60%	Da Silva [92]
33% (visual analysis) to 67% (automated analysis) in extra-TL epilepsies	Drzezga [93]
36% in FLE with normal MRI, 73% in FLE with structural lesion on MRI	Kim [94]
Not found in benign TLE (3 to 50 seizures in 0.5 to 27 years)	Franceschi [95]
Absent in benign childhood epilepsy with centrotemporal spikes	Van Bogaert [96]
20%in children with new-onset partial epilepsies	Gaillard [97]
30% in newly diagnosed TLE	Matheja [98]
Similar in adolescents and adults with partial complex seizures	Gaillard [99]
89% versus 94% for HMPAO ictal SPECT in patients with complex partial seizures	Markand [100]
Identical for FDG PET & HMPAO interictal SPECT	Coubes [101]
Better than that of HMPAO interictal SPECT	Stefan [72], Ryvlin [73], Nagata [102], Gaillard [6], Lamusuo [103]
Correlated with age at epilepsy onset	Ryvlin [80], Sadzot [87], Theodore [78], Hajek [86]
Correlated with epilepsy duration	Theodore [79]
No correlation with epilepsy duration	Abou-Khalil [104], Ryvlin [80]
No correlation with the frequency of seizures or interictal spikes	Engel [105], Theodore [69], Abou-Khalil [104]
No correlation with epileptogenicity of cavernous angiomas	Ryvlin [81]
Test-retest reproducibility	
Excellent with some variations in spatial extent	Kuhl [6], Theodore [69]

patients with temporal lobe epilepsy and hippocampal sclerosis in a prospective study of 100 consecutive cases carried out in our department [15], while it did not reach 50% in frontal lobe epilepsy patients whose brain MRI was considered as normal. This lower sensitivity in frontal lobe epilepsies has been reported by several converging studies (*Table 2*) but literature data show a wide range of variation between studies. It has also been recognized for long that major antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, sodium valproate) globally depress brain glucose metabolic rate [5, 76], but this has little or no influence on the detection of focal hypometabolism in the functional deficit zone.

The fact that ^{18}FDG PET sensitivity differs according to the site of the epileptogenic area is a strong argument against a causal relationship between hypometabolism and epileptogenicity. A second argument is that, if the epileptogenic zone surrounding a lesion can be hypometabolic, it can also be normo-metabolic (*figure 5*). This was demonstrated for cavernous angiomas, which are surrounded by a hypometabolic zone only when located in the temporopolar region, independently of their association with epileptic seizures [81]. In children with new-onset partial epilepsies the sensitivity of ^{18}FDG PET is rather low [97], it is also low at the onset of cryptogenic TLE [98], and no temporal hypometabolism has been detected in drug naive TLE patients with a low seizures frequency. This may suggest that, if hypometabolism is not directly related to the mechanism underlying epilepsy, it could have some link with the structural consequences of repeated seizures, in spite of conflicting results concerning its correlation with epilepsy duration, age at epilepsy onset and frequency of seizures or interictal spikes (*Table 2*).

Lateralizing value

Data given in *Table 4* show that, when present, glucose hypometabolism is ipsilateral to the epileptogenic area, as assessed by scalp or intracranial recordings, in a vast majority of patients. This conclusion is based on routine clinical studies in which ^{18}FDG PET was analyzed visually with evaluation of asymmetry indexes. This approach certainly overviews the possibility of less intense meta-

Table 3. Interictal glucose hypometabolism in partial epilepsies: reported lateralizing and localizing values.

LATERALIZING VALUE (as compared to that of the epileptogenic area)	
Scalp interictal EEG abnormalities ipsilateral in 90%,	Engel [68, 70], Theodore [69, 71, 78], Sperling [86], Abou-Khalil [104]
Bilateral in 8%, strictly contralateral in 2%	Swartz [88, 116], Henry [82, 83], Ryvlin [80], Chee [117], Hajek [86]
Ipsilateral to intracranial or depth EEG (SEEG) seizure onset zone in 92% to 100% of cases	Engel [68], Sadzot [87], Ryvlin [15]
Better than that of MRI, ictal SPECT & proton MR spectroscopy	Knowlton [118], Won [119]
False lateralization reported in a few single case studies	Sperling [85], Nagarajan [120]
Bilateral areas of hypo- and hypermetabolism as compared to global metabolism in TLE	Rubin [121]
Also present contralaterally to epileptogenic TL in 32% of TLE (SPM analysis)	Kim [106]
Bi-temporal hypometabolism is predictive of bilateral independent seizure onset	Koutroumanidis [107]
LOCALIZING VALUE	
Restricted to the temporal lobe (TL) in most cases of TLE, including the temporal pole and lateral neocortex in most cases, possibly spreading to the frontal or parietal lobe, and involving thalamus.	Engel [68, 70], Theodore [69, 71, 78], Yamamoto [123], Abou-Khalil [104], Sperling [85], Holmes [122], Swartz [116], Ryvlin [80], Chee [117], Hajek [86], Savic [13], Valk [124], Debets [14], Ryvlin [15]
Involving insular cortex in 60% of TLE	Bouilleret [125], Dupont [126]
Involving the dorsomedial thalamic nucleus in TLE	Juhasz [127]
Occasionally restricted to frontal lobe in TLE	Engel [105], Henry [82]
Restricted to frontal lobe, or fronto-temporal in FLE	Swartz [88, 89], Henry [83], Franck [90], Sadzot [87]
Absent in FLE with synchronous bilateral spike-waves & normal MRI	Ryvlin [15]
In favor of a frontal focus when absent in patients with complex partial seizures	Swartz [88, 89], Henry [83], Sadzot [87]
More mesial than lateral in mesio-temporal epilepsies,	Engel [68], Stefan [72], Sackellares [127], Henry [82], Sadzot [87]
Larger and more severe in mesial than in lateral TLE	Hajek [86], Valk [124], Kim [106]
More lateral and less severe in lateral than in mesial TLE	Hajek [86], Henry [82], Sadzot [87], Kim [106]
Spreading to adjacent TL, but higher in occipital cortex in occipital lobe epilepsies. Useful for epileptic focus lateralization	Henry [83], Kim [129]
Matched in space with sources of interictal EEG or MEG spikes	Merlet [130], Lamusuo [94], Pozzo [131]
Does not match when the irritative zone spreads outside the temporal lobe	Hong [132]
Poor agreement with intracranial recordings with false negativities in pediatric epilepsy	Snead [133]
Predictive of intracranial EEG focus localization when sphenoidal recordings are congruent	Engel [70]
Predictive of intracranial EEG focus localization when surface EEG is nonlocalizing	Henry [83], Theodore [134]
Correlated with interictal regional slow EEG activty	Koutroumanidis [135]
Occurrence of contralateral dystonia in TLE seizures linked with striatal hypometabolism	Dupont [136]
Occurrence of somatosensory ictal symptoms linked with perisylvian and thalamic hypometabolism	Wunderlich [137], Bouilleret [125]
Unrelated with Stereo-EEG activity (ictal onset, irritative or lesional activity)	Lucignani [108]
Co-extensive with SEEG ictal onset in a majority of mesial TL seizures	Ryvlin [15]
Localizing value	
Detection of seizure onset area in 8/10 children with extra-TL epilepsy	Muzik [138]
Ictal onset zone better correlates with the transition areas between the hypometabolic and normometabolic cortex, than with the hypometabolic zone proper	Juhasz [109]
Poor localizing value in cryptogenic neocortical epilepsies	Hong [111], Lee [110]

Table 4. Interictal glucose hypometabolism in partial epilepsies : prediction of postoperative seizure free outcome.

No prognostic value	Chee [117]
Predictive of good outcome when present in TLE,	Theodore [78], Radtke [139], Manno [140], Van Bogaert [96]
peculiarly if associated with MRI hippocampal atrophy	Salanova [141]
No correlation with outcome in the lateral temporal cortex in TLE	Manno [140]
Predictive of good outcome when surface EEG is non localizing	Theodore [134]
Predictive of bad outcome when spreading out of the temporal lobe in TLE	Holmes [122], Sadzot et coll. [87], Choi [114]
Predictive of good outcome when congruent with MEG modeling of spikes sources	Lamusuo [141]
Bad prognosis of direct and crossed thalamic hypometabolism	Newberg [143]
Extent not predictive of outcome in neocortical partial epilepsy	Juhasz [144]
Extent and severity not correlated with surgical outcome (SPM analysis)	Lee [115]
Prediction independent from that of MRI signs of hippocampal sclerosis	Choi [114]

Table 5. Interictal glucose hypometabolism in partial epilepsies: mechanisms, relation with hippocampal atrophy and neuropsychology, reversibility after surgery

Mechanisms	
Responsive (metabolic increase) to GABA- A receptors activation	Peyron [147, 148]
Uncoupled with cerebral blood flow	Gaillard [6]
Linked to reduced hexokinase activity with preserved blood flow	Fink [75]
Correlated with reduced blood-brain barrier glucose transporter activity	Cornford [152]
Correlated with glutamate/glutamine concentration	Pfund [153]
Relation with hippocampal atrophy	
No relation between lateral temporal hypometabolism and hippocampal atrophy or neuronal loss as measured with MRI volumetry and histological studies, respectively	Sackellares [128], Theodore [71], Radtke [139], Henry [154], Semah [155], Debets [14], O'Brien [156], Ryvlin [15], Salanova [141], Dlugos [157], Foldvary [158], Choi [159], Lamusuo [160], Theodore [161]
Mesial temporal hypometabolism correlates with reduced hippocampal volume in TLE	Knowlton [162]
Temporo-polar hypometabolism correlates with reduced hippocampal volume in TLE	Semah [155]
Thalamus & putamen metabolism correlate with dentate granule cell density	Dlugos [157]
Lateral temporal hypometabolism correlates with white matter change on MRI in TL as well as microscopic cortical dysplasia in the lateral temporal cortex	Latack [163], Stefan [72], Theodore [71], Ryvlin [80], Choi [159], Diehl [164], Chassoux [165]
Relation with neuropsychological testing	
Correlated in the left temporal lobe with decreased verbal IQ and memory scores in TLE	Raush [166]
Correlated in prefrontal region with decreased verbal and performance intelligence	Jokeit [167]
Correlated with ipsilateral memory impairment on intracarotid amobarbital test	Salanova [168], Hong [150], Salanova [151]
Predictive of less severe verbal memory decline after lobectomy in left TLE	Griffith [149]
Reversibility after surgery	
Bilateral metabolic increase after surgey in mesial TLE	Hajek [169]
Decrease in the contralateral mesial TL after surgey in mesial TLE	Hajek [169]
Reversible in temporal neocortex after surgery in mesial TLE	Hajek [169]
Reversible in lateral TL cortex after temporomesial radiosurgey in TLE	Régis [170]
Reversible in inferior frontal lobe and thalamus after surgery in TLE	Spanaki [171]

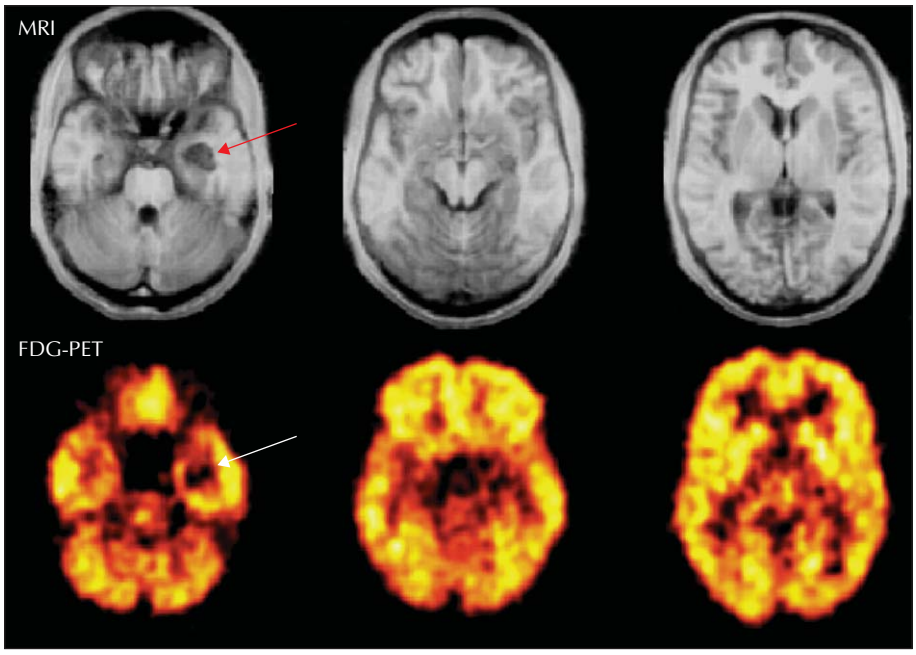

Figure 5. ***[^{18}F]FDG-PET*** *in a patient with an epileptogenic left amygdala cavernoma. Apart from the signal void observed at the location of the vascular malformation, no metabolic abnormality is detected in the surrounding epileptogenic cortex.*

bolic reduction on the opposite side, as recently shown by Kim *et al.* [106] who, using statistical parametric mapping (SPM) analysis to compare individual TLE patients against a normative data set, observed decreased metabolism contralateral to the epileptogenic lobe in 32 % of cases. Statistical parametric mapping is a statistical process that is used to characterize any regionally specific effect in imaging data. This statistical analysis is voxel-based; it is used to produce images of significant differences either between groups of subjects or between a given individual and a control group. In PET studies of epilepsy SPM analysis can be used to perform a voxel-by-voxel statistical comparison between each patient and a group of normal control subjects. The detection of bi-temporal hypometabolism is of particular interest in TLE, where it was found to be predictive of bilateral independent seizure onset in 53% of 15 patients with either normal or unilateral MRI findings [107].

Localizing value

Apprehending the localizing value of hypometabolism by analyzing the literature data given in *Table 4*, is a much more difficult issue, mostly because the concept of "epileptogenic zone localization" has different meanings according to authors. Some progress can be made in this analysis by accepting the fundamental assumption that, due to the large distribution of hypometabolism, peculiarly in TLE (*figure 6*), and to its spread to subcortical structures such as thalamus or striatum, no author would support the view that resection surgery can be tailored according to the limits of ^{18}FDG PET hypometabolism. Moreover, attempt made to correlate, region by region, the degree of glucose metabolism with the stereo-EEG recording of ictal discharges (epileptogenic zone) brought negative results [108]. This result was not unexpected knowing that epileptogenicity and glucose metabolism are not directly related one with the other (see above).

• *^{18}FDG PET and localization of the epileptogenic zone*

Most data converge on the conclusion that the epileptogenic zone, as assessed by intracranial EEG recordings, is usually included in the hypometabolic area (*Table 3*). This is particularly true in TLE, as well as in symptomatic epilepsy, but does not apply to cryptogenic neocortical epilepsies. Indeed, using grids in patients with non lesional neocortical epilepsy, Juhasz *et al.* [109] showed that the ictal onset zone better correlated with the transition areas between the hypometabolic and normometabolic cortex, than with the hypometabolic zone proper. More recently, Lee *et al.* [110] investigated 33 patients with a cryptogenic neocortical epilepsy, and found that FDG-PET provided a correct localization of the ictal onset zone, as assessed by intra-cranial EEG recordings, in only 55% of cases. Most of the falsely localizing metabolic abnormalities were encountered in patients with extra-temporal seizures. Accordingly, another series of 41 patients with cryptogenic neocortical epilepsy found a correctly localizing FDG-PET abnormality in only 43% of cases [111]. The better localizing value offered by FDG-PET in patients with TLE and a clearcut MRI abnormality, might be considered superfluous [112, 113]. In such patients,

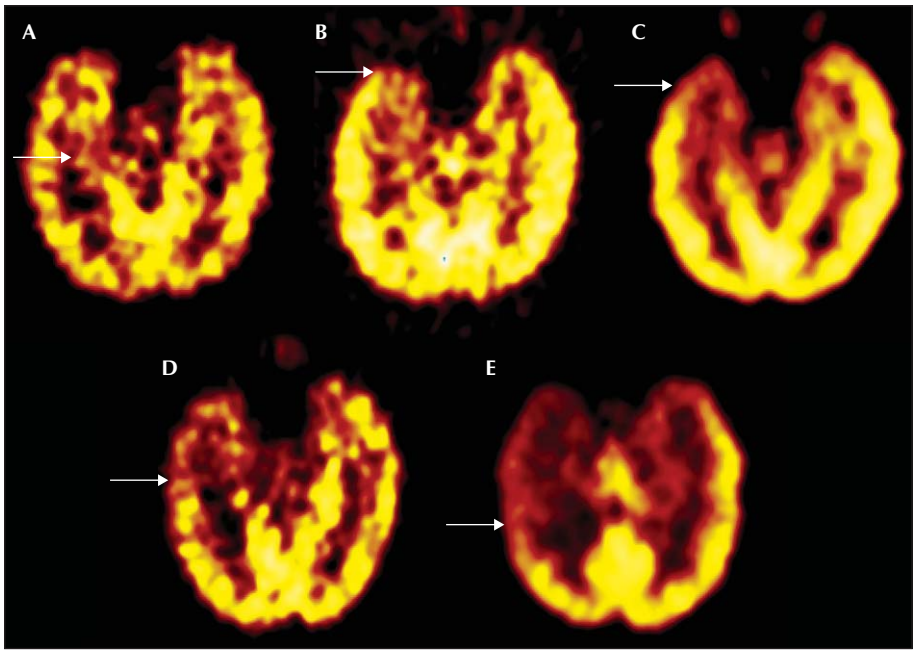

Figure 6. ***[^{18}F]FDG-PET****. The various form of interictal temporal hypometabolism in TLE, which may include : A) the hippocampal region, B) the entire mesial temporal structures, C) the mesial temporal and temporo-polar regions, D) the latter as well as the anterior portion of the lateral temporal cortex, and E) the all temporal lobe.*

however, the combination of FDG and flumazenil-PET might help to better delineate the extension of the epileptogenic zone, and to offer the possibility of more tailored temporal cortectomies [15] (*figure 7*). Another way to assess the localizing value of ^{18}FDG PET is to determine whether the presence (and/or the site) of a focal hypome-

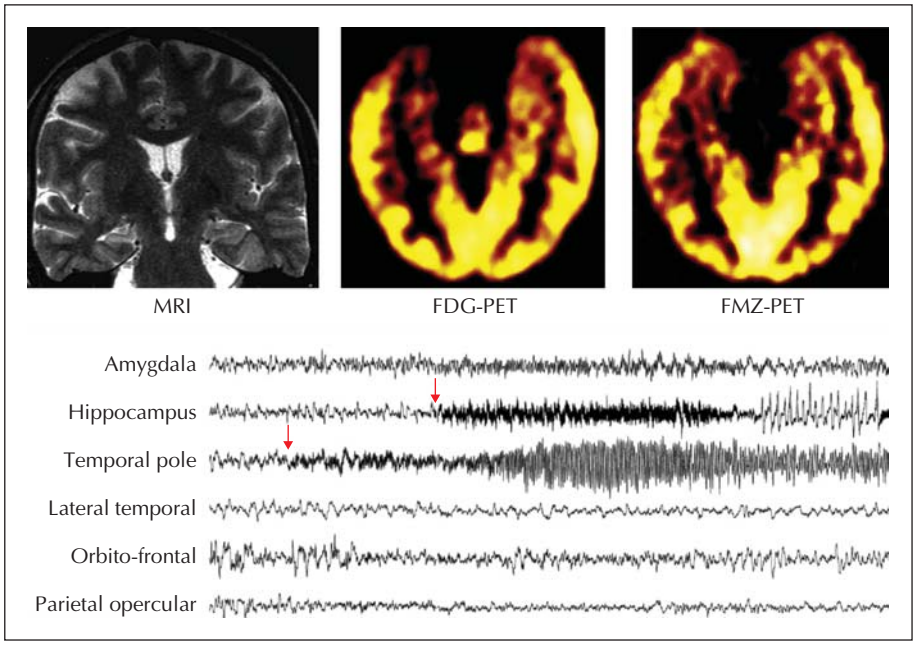

Figure 7. ***FDG-PET and FMZ-PET*** *in a patient with a right TLE and mesial temporal sclerosis on MRI. FDG-PET demonstrates right mesial temporal and temporo-polar hypometabolism, whereas FMZ-PET abnormality is restricted to the mesial temporal structures. Intra-cerebral EEG recording shows that the ictal discharge originate in the temporal pole and then rapidly propagate to the hippocampus and amygdala.*

tabolism predicts a postoperative seizure free outcome. As shown in *Table 4*, most studies agree on the conclusion that, in TLE, a focal hypometabolism limited to the temporal lobe predicts a good outcome of anterior temporal lobectomy. Importantly, this prognostic factor appears to be independent from that of MRI signs of hippocampal sclerosis [114]. A more pragmatic conclusion from these studies is that the absence of temporal lobe hypometabolism, or its extension to extra-temporal cortex, entails a less optimistic postoperative prognosis. However, this view has been challenged by a recent study of TLE patients, which failed to demonstrate a significant relation between pre-operative FDG-PET data and seizure-freedom after temporal lobe surgery [115].

• *^{18}FDG PET and localization of the irritative zone*

The irritative zone is defined as the cortical area generating interictal epileptiform discharges in the EEG or MEG [65]. If interictal glucose hypometabolism is ipsilateral to the epileptogenic zone in most cases, interictal spikes also occur on the side of the hypometabolic area in nearly 90% of cases, suggesting that hypometabolism represents a reliable marker of the irritative zone (*Table 3*). A clear discordance between the side of interictal spiking and that of hypometabolism is observed in less than 10% of cases, but unilateral hypometabolism can be associated with bilateral spiking. A few studies have attempted to compare the location and extent of glucose hypometabolism with those of spikes sources, as assessed by dipole modeling of EEG or MEG data, in temporal lobe epilepsies [130, 142, 131]. When spikes can be modelled by unilateral temporal sources, the latter are located within the hypometabolic zone. In this condition the hypometabolic area is more widespread than the network involved in interictal spiking activity, whereas glucose hypometabolism is not significantly more pronounced in regions where spike sources are localized. In case of congruence between ^{18}FDG PET abnormalities and sources of MEG spikes, intracranial EEG usually confirms the localization of the irritative zone. When multiple sources are needed to obtain the optimal fit between the observed and modeled data some of these sources may be located outside the temporal lobe. In that condition the hypometabolic area is usually restricted to the temporal cortex, and even to mesiotemporal areas. In frontal lobe epilepsies, the spatial relationships between glucose hypometabolism and spike sources can be extremely diverse. Dipole sources can then be located either in the hypometabolic area when this latter involves several lobes, or outside of it in cases where the metabolic abnormality is restricted to a very focal area. All together, the above studies converge on the conclusion that when spike sources are localized within one temporal lobe,[18] FDG images tend to confirm the dipole locations and this could suggest some functional link between the metabolic dysfunction and the processes involved in generating interictal spikes. Conversely, when the irritative zone spreads outside the temporal lobe the metabolic and electrophysiological processes seem to be partly independent, as also shown for the ictal onset zone [132].

• *^{18}FDG PET and localization of the ictal symptomatogenic zone*

The idea that the topography of decreased glucose metabolism in the interictal period could be congruent with that of areas generating the ictal symptomatology has not been extensively investigated. Dupont *et al.* [136] reported that the occurrence of dystonia contralateral to the discharging area in TLE seizures correlated with the presence of interictal hypometabolism in the striatum on the seizure side. More recently the same team [125, 126] reported first: that the insular cortex ipsilateral to the epileptogenic TL was hypometabolic in 60% of patients with mesial TLE, a result which fits well with the high frequency of ictal insular involvement in intracerebral recordings of TLE seizures, and second: that the occurrence of emotional and somatosensory symptoms correlated with interictal hypometabolism in the anterior and posterior parts of the insula, respectively. Accordingly, others have found a correlation between somatosensory ictal symptoms and perisylvian as well as thalamic interictal hypometabolism [137].

Mechanisms of interictal glucose hypometabolism

Several mechanisms, which can combine one with another, can theoretically contribute to produce interictal glucose hypometabolism, which are the following: 1) atrophy and partial volume effect; 2) neuronal loss in the functional deficit zone; 3) hypometabolic macro- or microscopic lesions; 4) decreased synaptic activity (diaschisis), 5) deafferentation with reduced numbers of synapses; 6) post-ictal metabolic depression; 7) inhibitory mechanisms of seizures. Pertinent data from literature regarding this issue are given in *Table 5*, which are globally converging in spite of a few contradictions.

From analysis of these data no doubt persists regarding the conclusion that hypometabolism is a reversible functional state [146]. The increase of glucose consumption observed during seizures was the earliest finding supporting this view. Later on, Peyron *et al.* [147, 148] brought the first experimental demonstration that the interictal hypometabolic area was responsive to the pharmacological action of a $GABA_A$ receptor agonist. Paradoxically the cognitive slowing induced by this agent was associated with a global increase of brain glucose metabolism. Furthermore this increase was higher in the hypometabolic area than anywhere else in the cortex of TLE patients. Besides demonstrating the reversibility of hypometabolism this finding also suggested that $GABA_A$-mediated inhibition increases the neuronal energetic demand. Consequently the parallel between inhibition and hypometabolism looks questionable. Lastly the preoperative interictal hypometabolic surrounding the epileptogenic zone

returns to a normal metabolic state after successful surgery (*Table 5*).

A second conclusion from *Table 5* data is that the hypometabolic area represents a zone of functional deficit, associated with impaired scores on neuropsychological testing of involved area specific cognitive functions. The practical consequence of this finding for TLE surgery is that ^{18}FDG PET may have some predictive value regarding postoperative language and memory deficits [149], which are expected to be less severe when the temporal lobe was hypometabolic before operation. In fact, recent studies could correlate FDG-PET findings with the result of the intra-carotid amobarbital test [150, 151].

A more controversial issue is that of the relation between the degree of hypometabolism and that of hippocampal atrophy, or hippocampal neuronal loss, in mesial TLE. The prevalent opinion is that there is no relation between lateral temporal hypometabolism and hippocampal atrophy or neuronal loss, as measured with MRI volumetry and histological studies, respectively [14, 15, 71, 128, 139, 141, 151-158]. However, the degree of hippocampal atrophy correlates with mesial temporal and temporopolar metabolic abnormalities [155, 162].

The idea that part of the extra-hippocampal hypometabolism in mesial TLE could be due to other structural abnormalities than hippocampal sclerosis was first supported by early studies showing some correlation between the interictal hypometabolic state, or reduced blood flow, and the presence of white matter MRI changes and volume loss in the affected temporal pole and lateral cortex [71, 72, 80, 163, 172]. Most of these white matter changes consist in blurred gray-white matter demarcation of which underlying pathology remains uncertain, though significantly associated with temporo-polar atrophy [54, 172]. The alternative roles of an increased number of heterotopic neurons and of a dysmyelination have been disputed, with no final consensus [159, 174, 175]. According to the group of Milano, this type of anterior temporal MRI abnormality is associated with architectonic dysplasia in the underlying neocortex [176], a finding consistent with the neocortical microscopic dysplasia recently reported in patients with temporal lobe atrophy [164]. Overall, the temporo-polar T2 white matter changes, as well as the associated atrophy and microscopic dysplasia, are associated with lateral temporal hypometabolism [159, 164, 165] (*figure 8*). A similar association was previously demonstrated in temporo-polar cavernomas, regardless of their epileptogenicity, suggesting a deafferentation or deactivation mechanism [81].

Abnormalities of $GABA_A$ BZD receptors binding

Distribution and sensitivity of decreased [^{11}C]-FMZ binding

Contrary to glucose hypometabolism, which has uncertain relation with the epileptogenic process, the interictal decrease in BZD receptors density has been extensively studied because of its potential link with an altered

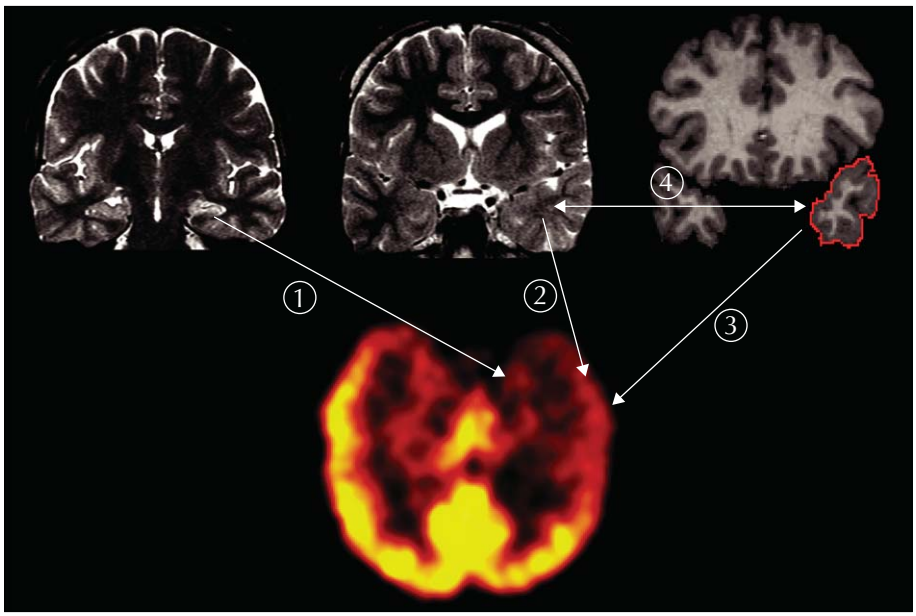

Figure 8. *Schematic representation of the relation between MRI and FDG-PET abnormalities in the temporal lobe, according to Table 5.*
1) Hippocampal atrophy was found to correlate with mesial temporal hypometabolism, but not with lateral temporal hypometabolism.
2-3) Conversely, the latter appears to be associated with the presence of anterior temporal white matter hyperintense T2 signal, as well as with anterior temporal atrophy.
4) Anterior temporal atrophy is also associated with the presence of anterior temporal white matter hyperintense T2 signal.

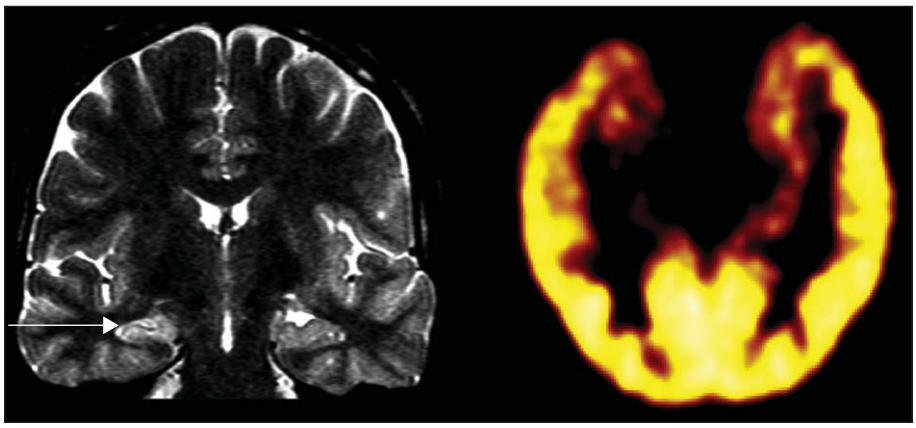

Figure 9. ***[11C]flumazenil-PET (FMZ-PET)*** *in a patient with right TLE and mesial temporal sclerosis on MRI, showing a typical decreased FMZ binding over the atrophic hippocampal region.*

$GABA_A$ inhibition in the epileptogenic cortex. PET studies of ^{11}C-flumazenil ([^{11}C]-FMZ) binding have been carried out with the hope to better delineate non invasively the epileptogenic zone [13, 14, 16, 21, 24, 26]. As a matter of fact, in early series, almost all reported patients with refractory partial seizures demonstrated a localized reduction of [^{11}C]-FMZ binding, which closely correlated with the side and site of seizure onset. The reduced [^{11}C]-FMZ binding observed in epileptic patients was thought to largely reflect an underlying neuronal loss, as demonstrated in temporal lobe epilepsy (TLE) associated with mesial temporal sclerosis [14, 17, 25] (*figure 9*). However functional changes of the BZD receptor system, some of which related to the occurrence of seizures, also seem to contribute to the abnormalities observed on [^{11}C]-FMZ PET images [18-20, 177-179], and individual test-retest variations of binding, with possible false lateralization, have been reported [180] (*figure 10*).

[^{11}C]-FMZ PET sensitivity is close to 100% in TLE patients with MRI signs of hippocampal sclerosis [13-17, 19, 21, 24] and was estimated at 73% (versus 75% for FDG-PET) in our series of 100 consecutive patients with all types of refractory partial epilepsies including 52 TLE and 27 frontal lobe epilepsy (FLE) patients [15].

Decreased binding of [^{11}C]-FMZ can be larger than MRI changes. This has been observed in patients with MRI signs of hippocampal sclerosis, where the decreased [^{11}C]-FMZ binding can spread to temporo-polar, lateral temporal, and extra-temporal structures [13, 15, 16, 177, 179], as well as in patients with epileptogenic mass lesions, where the peri-lesional PET abnormalities appear to reflect the extent of the epileptogenic zone [109, 182]

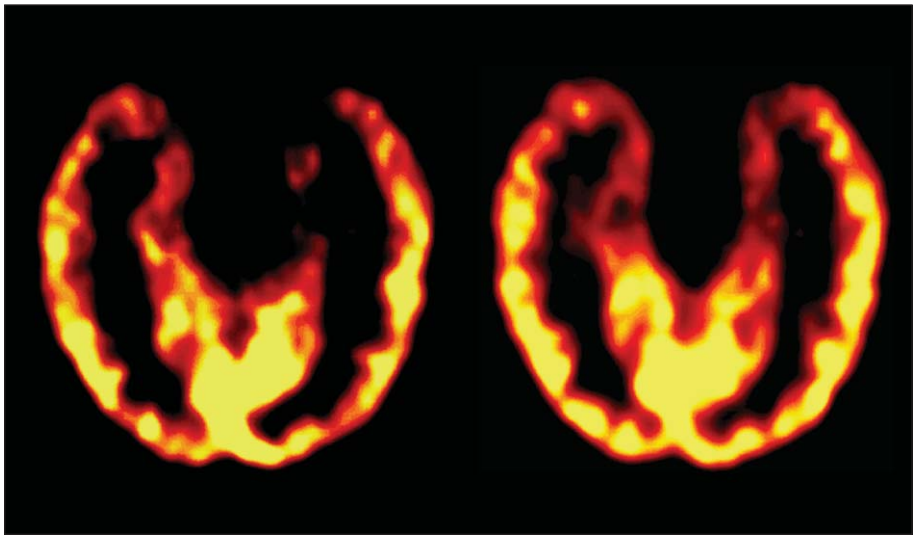

Figure 10. ***[11C]flumazenil-PET (FMZ-PET)*** *was repeated twice at one week interval in the same TLE patient whose MRI was normal. The first FMZ-PET showed a clearcut left mesial temporal decreased FMZ binding, which has vanished at the second investigation.*

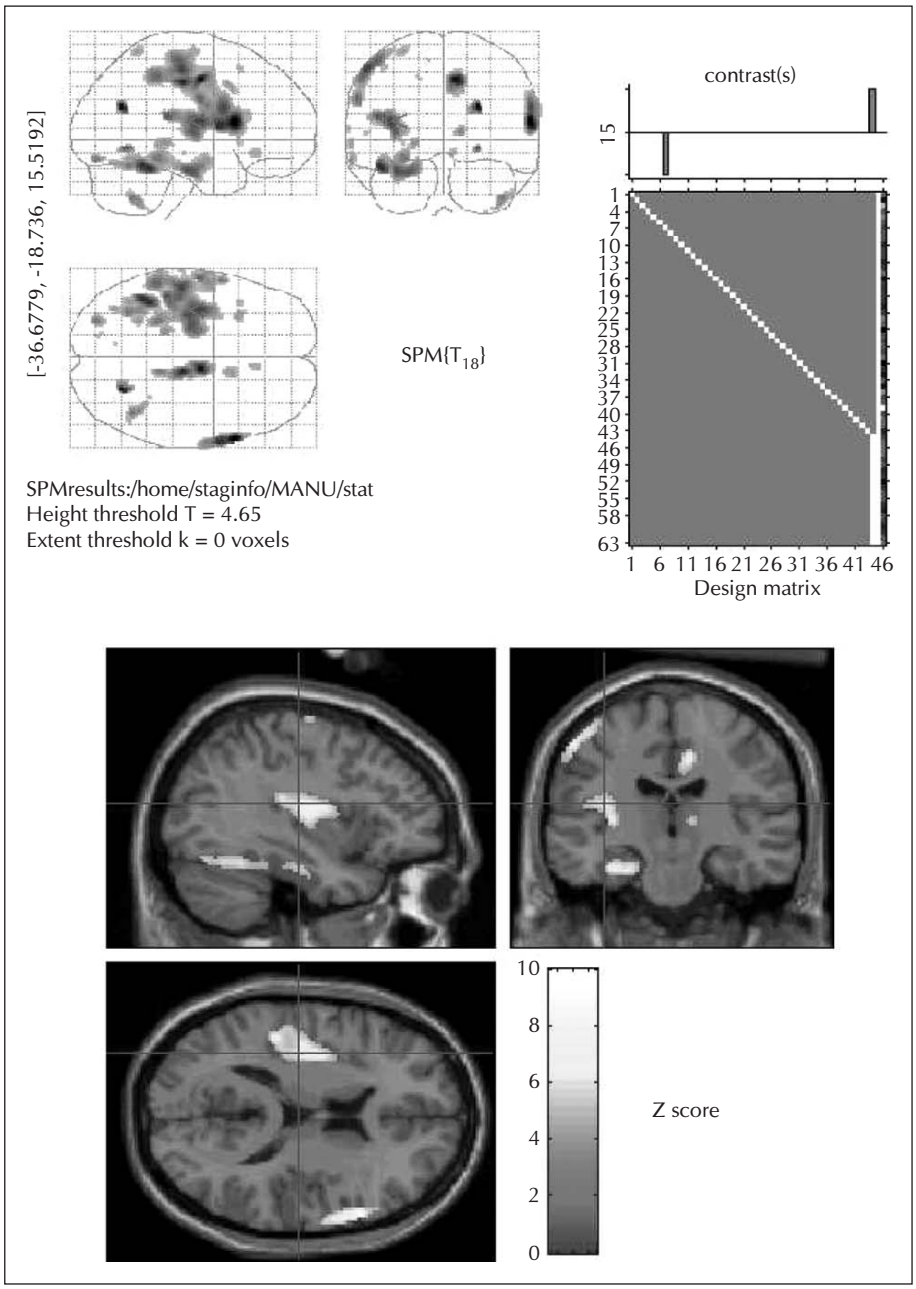

Figure 11. ***Statistical parametric mapping (SPM) analysis of [^{11}C]flumazenil-PET (FMZ-PET)*** *in a patient with TLE and left mesial temporal sclerosis. The SPM map has detected a significant decreased FMZ binding within the atrophic hippocampus, but also over the ipsilateral temporal, insular, and frontal regions, as well as in the contralateral thalamus, mesial and lateral frontal structures.*

(*figure 11*). In addition, a decreased [^{11}C]-FMZ binding can also be observed in patients with temporo-limbic or neocortical epilepsy, and a normal MRI [15, 175, 182-185]. Such PET abnormalities might reflect a MRI occult epileptogenic dysplasia [186, 187], but were also found to be falsely lateralizing in patients with TLE [180, 178].

Decreased [^{11}C]-FMZ binding as a marker of the epileptogenic area

All authors agree on the conclusion that the area of reduced BZD receptors density is either congruent with, or smaller than, that of glucose hypometabolism in TLE patients. This was taken as an argument supporting the view that [^{11}C]-FMZ PET abnormalities more closely correlate

with the epileptogenic zone than do metabolic abnormalities [13, 16, 21, 24]. This view has been supported by some studies correlating intracranial EEG data (subdural EEG or intraoperative electrocorticography) with both ^{18}FDG and [^{11}C]-FMZ PET findings [26, 109, 138]. These studies converged to conclude that [^{11}C]-FMZ abnormalities show a better spatial congruence than glucose hypometabolism with the epileptogenic area. Other studies were contradictory, showing that in TLE the [^{11}C]-FMZ abnormalities may not cover the whole extent of the seizure onset area [14, 15] and concluded that [^{11}C]-FMZ PET does not prove superior to ^{18}FDG PET in localizing the origin of temporal lobe seizures. For example, TLE patients with a decreased [^{11}C]-FMZ binding restricted to the hippocampal formation, and a hypometabolic zone covering the mesial temporal and temporo-polar structures, often presented with seizures originating in the amygdalo-hippocampal complex and the temporal pole, concomitantly [15] (*figure 7*). Similarly [^{11}C]-FMZ PET was moderately informative in patients with unilateral frontal lobe epilepsy (FLE) and normal MRI, showing an abnormality in 55% (compared with 45% for ^{18}FDG-PET). Part of the discrepancies between studies pertains to methodological differences (timing of data acquisition, correction of partial volume effect, spatial resolution of the scanner...), others are related to differences in patients' populations in children and adults series.

Increased [^{11}C]-FMZ binding

Comparison, at a voxel level, between the [^{11}C]-FMZ volumes of distribution (FMZVd) in individual patients and a normal group using statistical parametric mapping (SPM) revealed subtle reductions of FMZVd in the hippocampus contralateral to the epileptogenic hippocampal atrophy [19]. Moreover this approach revealed that not only decreases, but also increases, of BZD-receptors density could be observed in partial epilepsies. This was first demonstrated in patients with cortical dysgenesis, whose FMZVd changes were often more extensive than MRI changes [20, 185, 186, 188, 189], then in patients with mesial TLE [181], TLE and extratemporal neocortical epilepsy with normal MRI [178, 185, 186, 189]. In TLE with normal MRI Hammers *et al.* [185] observed increased FMZVd in the temporal lobe white matter in 56% of cases (11/18). In extra-temporal neocortical epilepsy (14 unilateral FLE, 6 parietal lobe epilepsy, 5 occipital lobe epilepsy and 19 without clear lobar origin) these authors [186] recently reported areas of increased FMZVd in 57% of cases (25/44), either isolated (16/44) or in combination with areas of FMZVd decrease (9/44). Interestingly the rate of focal FMZVd decreases in this series was comparable to that reported in an earlier study that included patients with neocortical epilepsies with similar inclusion criteria and similarly stringent definition of normal MRI [15]. Therefore the FMZVd increases revealed by SPM analysis actually represents a new information that was not accessible to conventional analysis based on region of interest analysis and asymmetry index calculation. The pathophysiological signification of this finding might be that FMZVd increases reflect the presence of microdysgenesis with ectopic neurons bearing $GABA_A$ receptors, especially when located in the white matter of the periventricular area. Ectopic white matter neurons are known to contribute to epileptogenesis [190-193] and their revelation by [^{11}C]-FMZ PET imaging represents an important addition to the non-invasive presurgical evaluation of partial epilepsies.

Summary and conclusions

Based on ^{18}FDG data the utility of PET has long been considered either as a means to explore the interictal functional deficit zone in patients with partial epilepsies, or as a means to reveal functional abnormalities in cortical areas with normal MRI presentation. The prevailing opinion was that PET could be included as an ancillary technique that may be helpful for surgical outcome prognosis in TLE, and for guiding the placement of intracranial electrodes in extra-temporal neocortical epilepsies. Advances in MRI technology have considerably reduced the percentage of patients with so-called "cryptogenic" partial epilepsies. In parallel recent progresses in PET technology permitted to revisit the pathophysiology of interictal glucose hypometabolism, to develop biological markers of focal brain dysgenesis unseen by MRI at its present sate of development, and to explore neurotransmission abnormalities that are closely related to epileptogenesis. Obviously no epilepsy center has the capacity of developing all tracers and software to be at the edge of all possible PET methodologies, and no PET technique has proved its capacity to map the epileptogenic zone with enough of preciseness to guide cortical resection. The lack of large multicentric controlled studies, aiming at evaluating the impact of PET on the overall outcome of patients undergoing an epilepsy surgery program, currently represents the main limitation to a better understanding of the clinical role and utility of PET in epilepsy. Future studies should be directed towards this objective, taking advantage of the recent large dissemination of PET instrumentation. □

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