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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

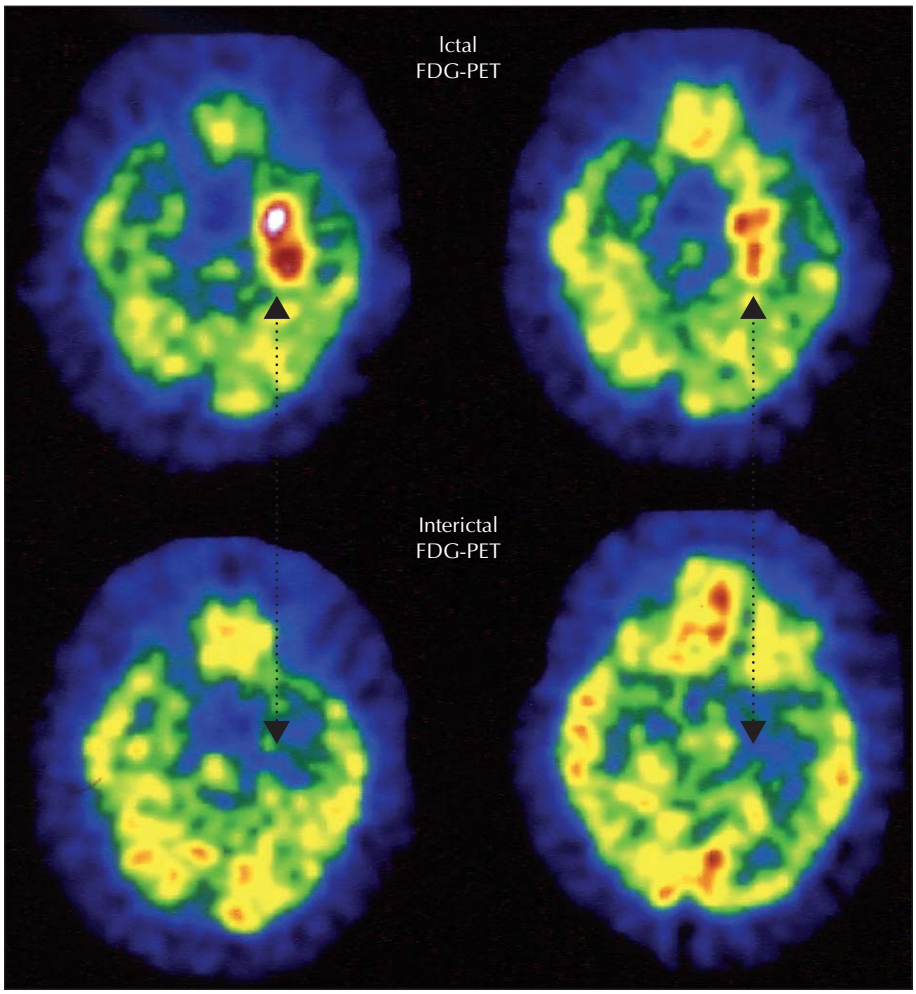

Figure 1. ***Ictal [^{18}F]FDG-PET***. *An ictal FDG-PET was obtained in a patient who presented several epigastric auras during the 10 minutes following FDG injection, showing a clear-cut left mesial temporal glucose hypermetabolism. The latter was replaced by a left mesial temporal hypometabolism on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

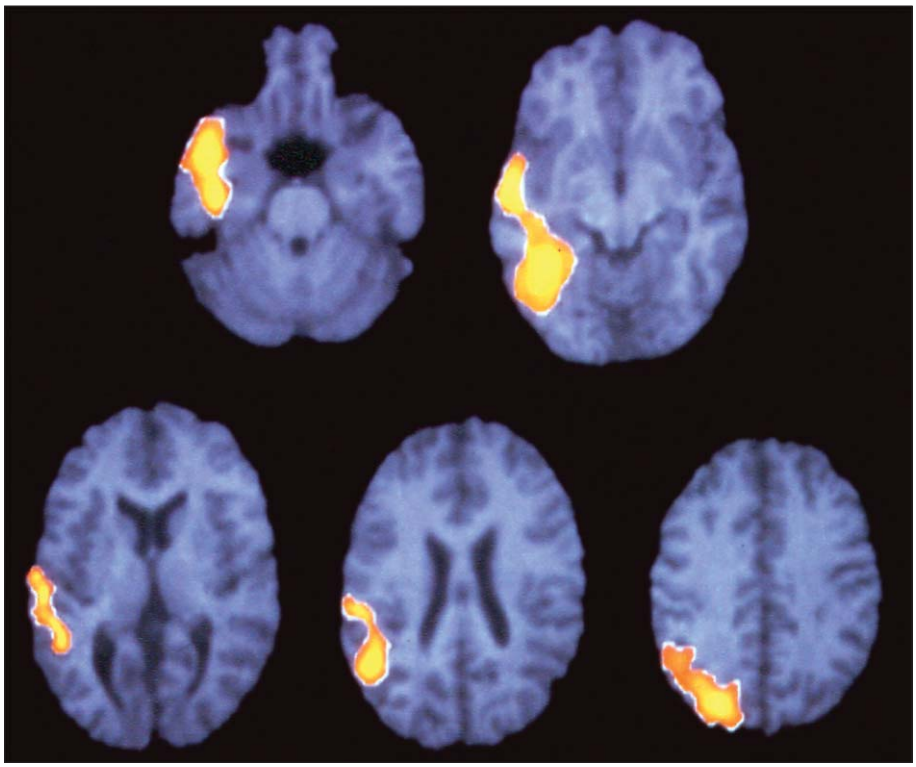

Figure 2. ***[^{15}O]H$_2$0-PET coupled with intra-cerebral stimulation****. An increased cerebral blood flow was elicited over the temporal and parietal lobes by an electrically induced sub-clinical discharge arising from the fusiform gyrus, and propagating to the temporo-parietal structures.*

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 antiepileptic 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

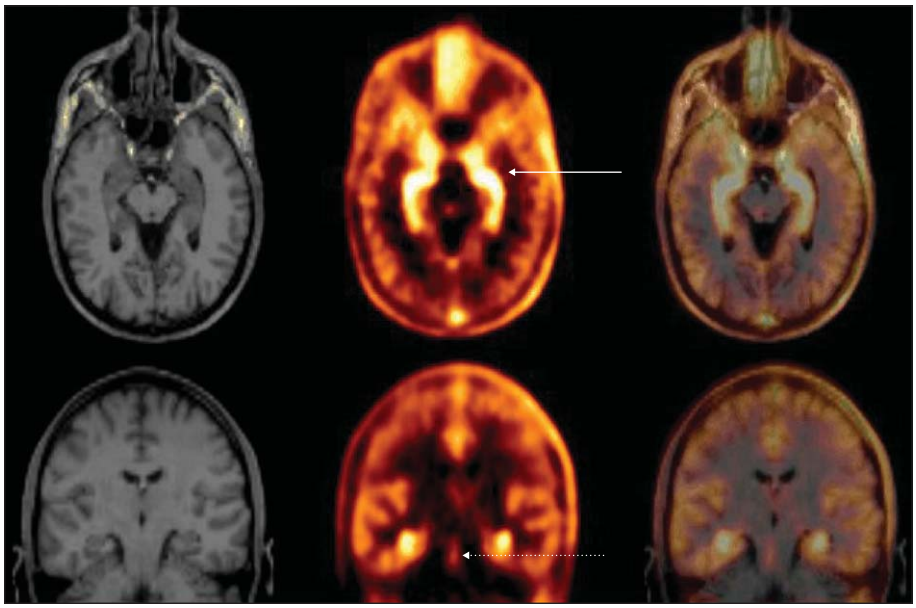

Figure 3. ***[18F]MPPF-PET*** *in a normal subject showing the brain distribution of 5-HT1A serotoninergic receptors, particularly concentrated in the mesial temporal structures (arrow). The raphe nuclei are also well disclosed within the upper brainstem (dotted arrow).*

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-

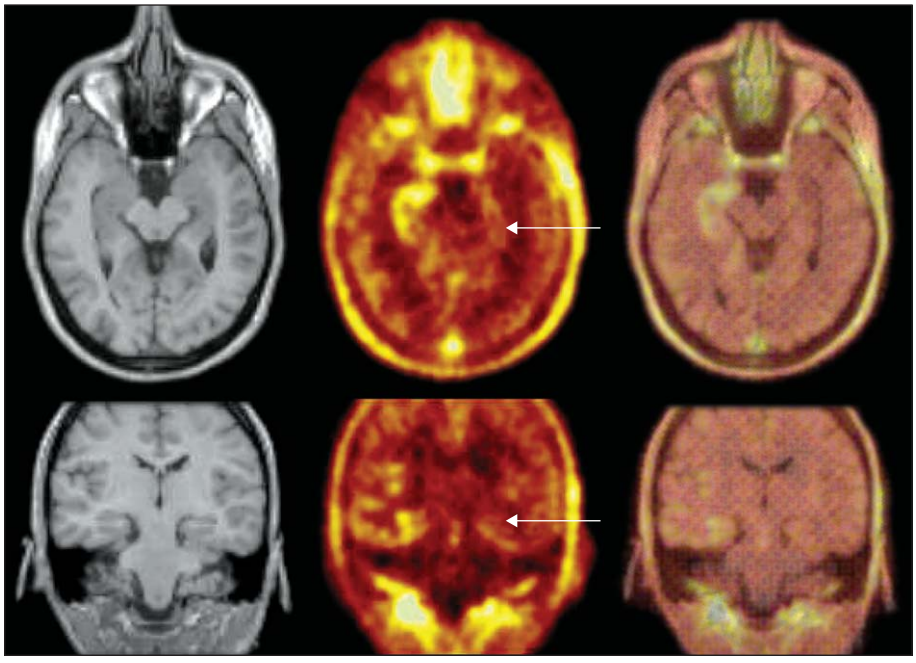

Figure 4. ***[18F]MPPF-PET*** *in a patient with a left mesial temporal epilepsy, showing a decreased binding potential of 5-HT1A receptors over the epileptogenic zone. More subtle abnormalities are observed in the ipsilateral temporal neocortex and insula.*

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]

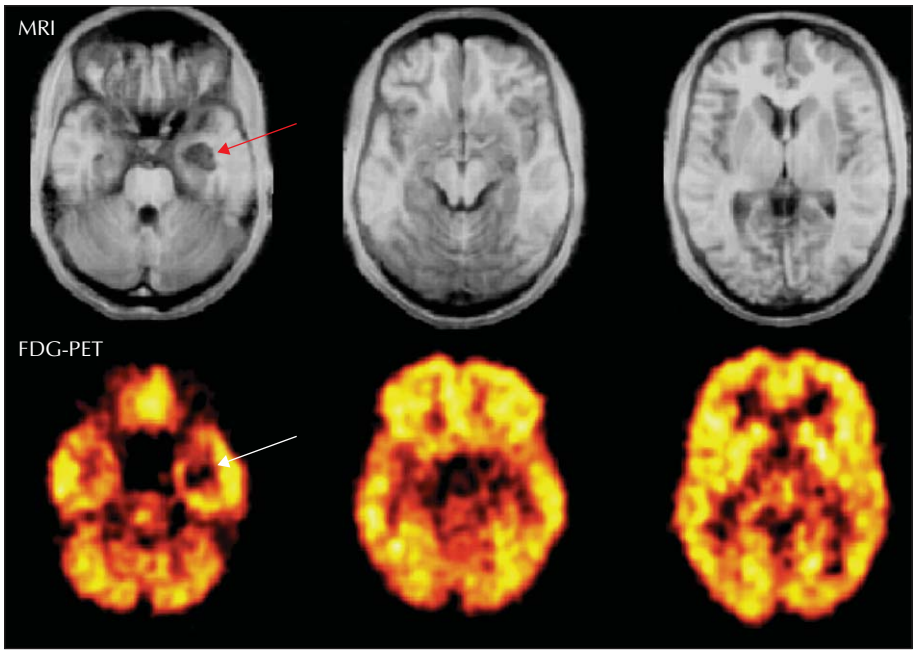

Figure 5. ***[^{18}F]FDG-PET*** *in a patient with an epileptogenic left amygdala cavernoma. Apart from the signal void observed at the location of the vascular malformation, no metabolic abnormality is detected in the surrounding epileptogenic cortex.*

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,

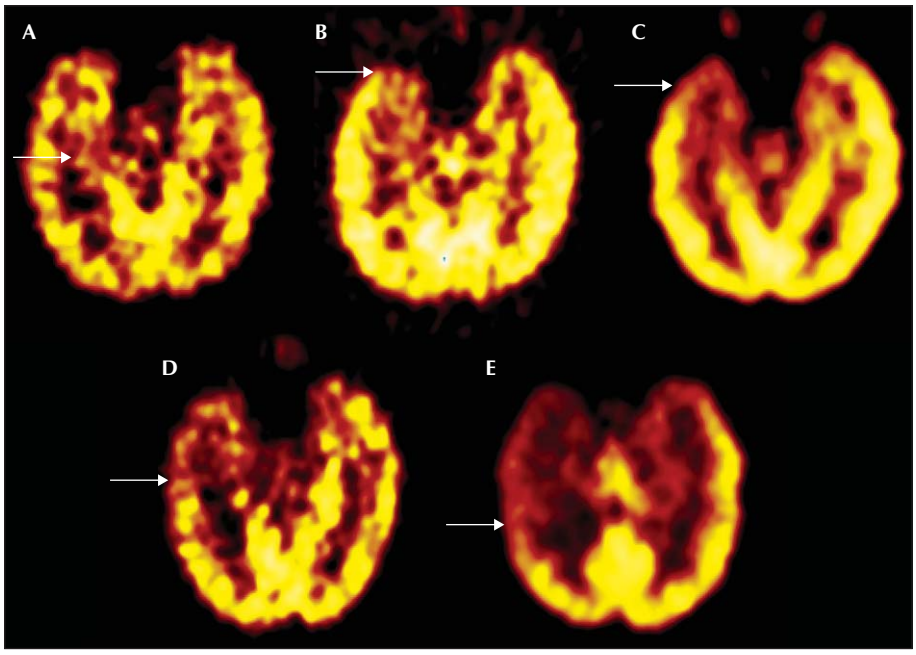

Figure 6. ***[^{18}F]FDG-PET****. The various form of interictal temporal hypometabolism in TLE, which may include : A) the hippocampal region, B) the entire mesial temporal structures, C) the mesial temporal and temporo-polar regions, D) the latter as well as the anterior portion of the lateral temporal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

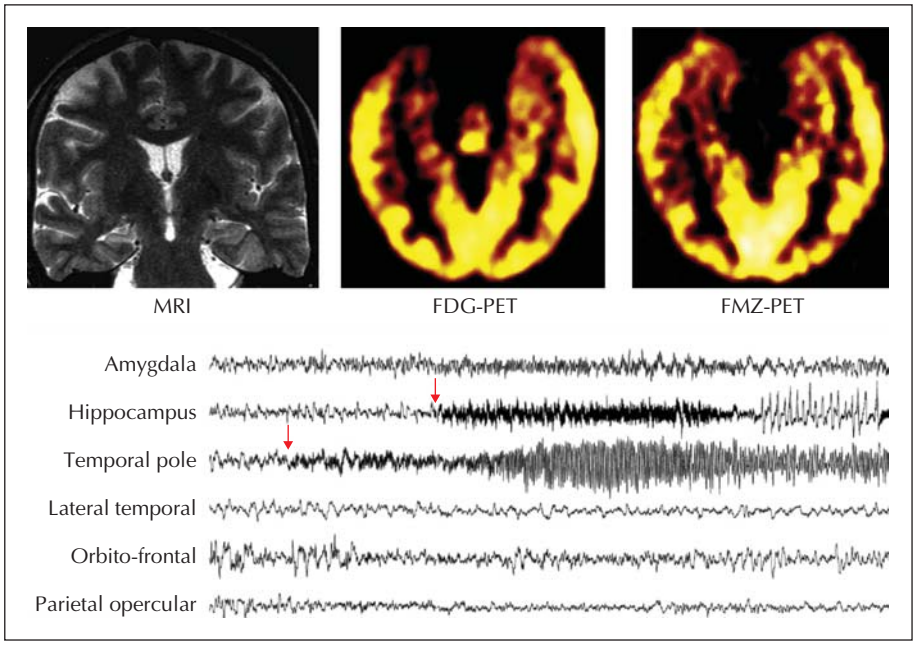

Figure 7. ***FDG-PET and FMZ-PET*** *in a patient with a right TLE and mesial temporal sclerosis on MRI. FDG-PET demonstrates right mesial temporal and temporo-polar hypometabolism, whereas FMZ-PET abnormality is restricted to the mesial temporal structures. Intra-cerebral EEG recording shows that the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

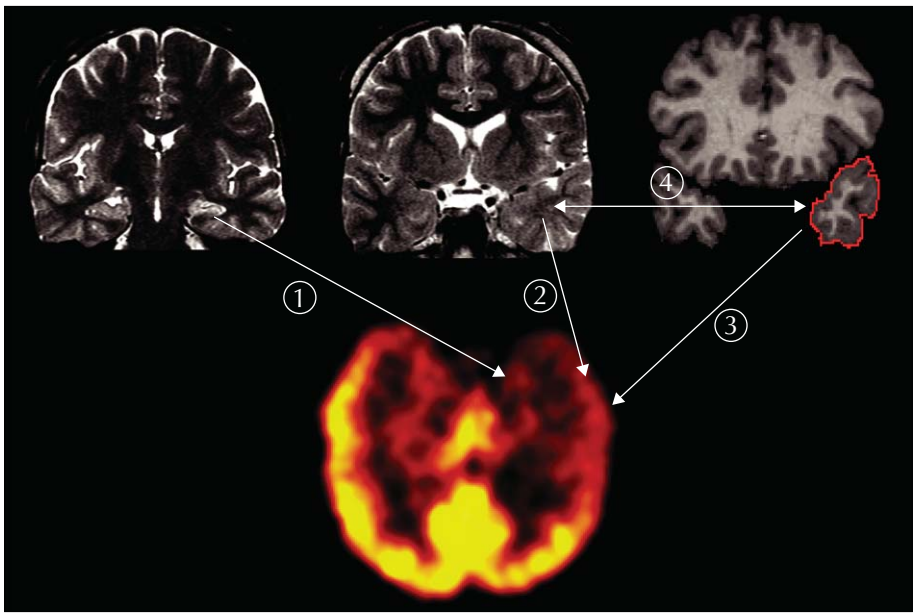

Figure 8. *Schematic representation of the relation between MRI and FDG-PET abnormalities in the temporal lobe, according to Table 5.*
1) Hippocampal atrophy was found to correlate with mesial temporal hypometabolism, but not with lateral temporal hypometabolism.
2-3) Conversely, the latter appears to 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.

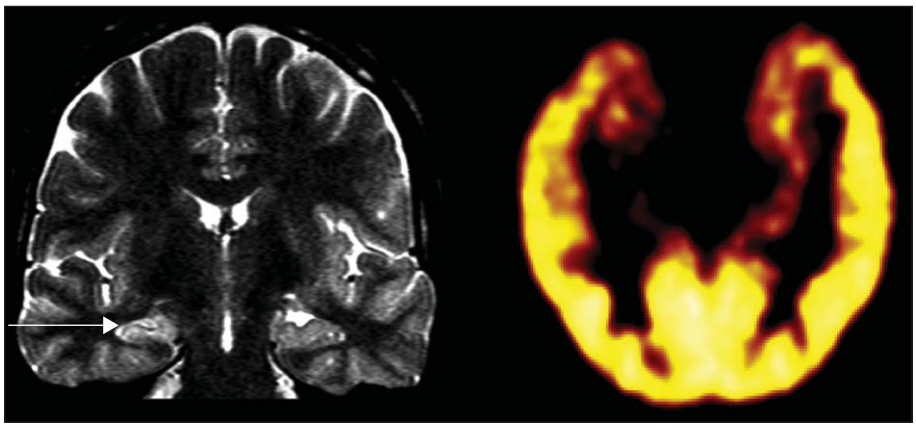

Figure 9. ***[11C]flumazenil-PET (FMZ-PET)*** *in a patient with right TLE and mesial temporal sclerosis on MRI, showing a typical decreased FMZ binding over the atrophic hippocampal region.*

$GABA_A$ 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]

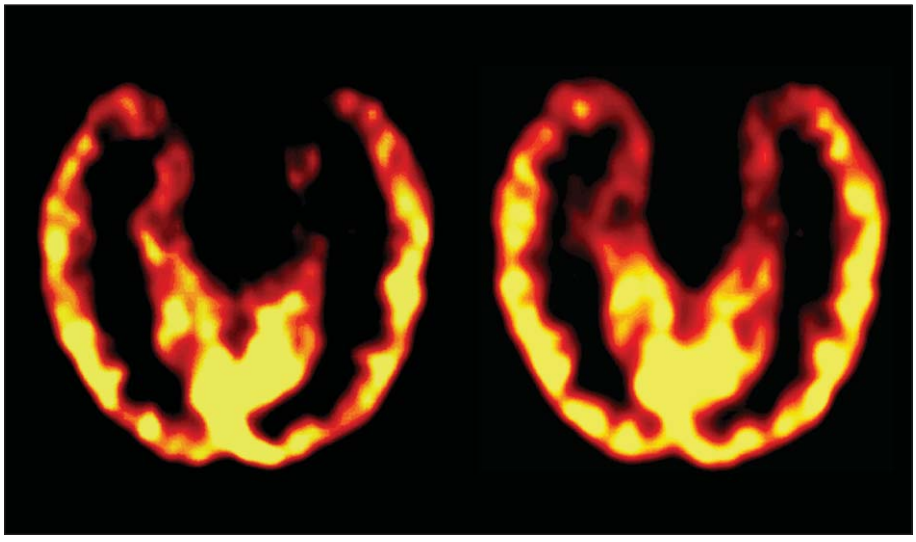

Figure 10. ***[11C]flumazenil-PET (FMZ-PET)*** *was repeated twice at one week interval in the same TLE patient whose MRI was normal. The first FMZ-PET showed a clearcut left mesial temporal decreased FMZ binding, which has vanished at the second investigation.*

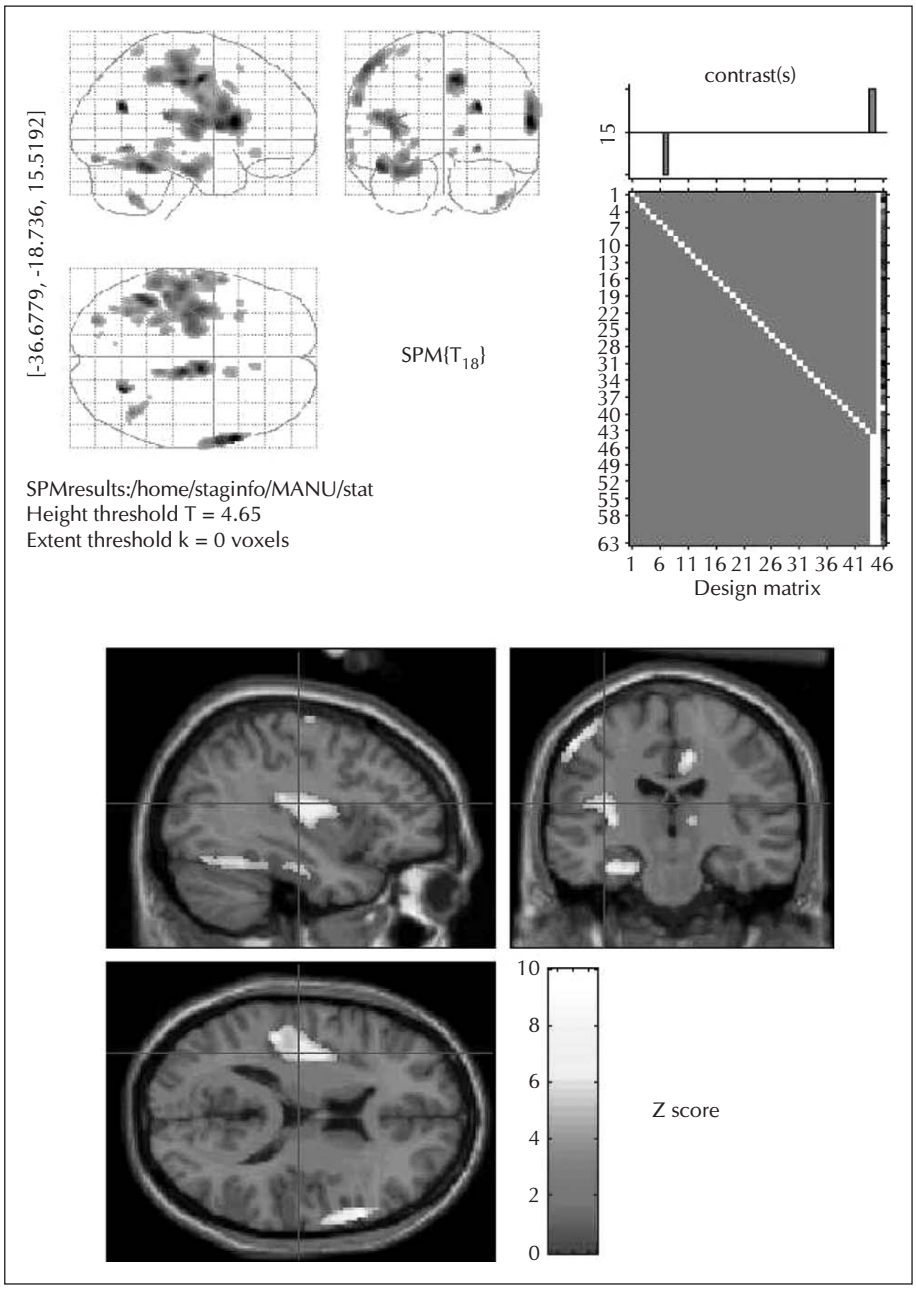

Figure 11. ***Statistical parametric mapping (SPM) analysis of [^{11}C]flumazenil-PET (FMZ-PET)*** *in a patient with TLE and left mesial temporal sclerosis. The SPM map has detected a significant decreased FMZ binding within the atrophic hippocampus, but also over the ipsilateral temporal, insular,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

References

1. Sokoloff L. Measurement of local cerebral glucose utilization and its relation to local . functional activity in the brain. *Adv Exp Med Biol* 1991; 291: 21-42.

2. Phelps ME, Huang SC, Hoffman EJ, Salin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F 18)2-fluoro-2-deoxy-D-glucose: Validation of method. *Ann Neurol* 1979; 6: 371-88.

3. Meltzer CC, Adelson PD, Brenner RP, *et al.* Planned ictal FDG PET imaging for localization of extratemporal epileptic foci. *Epilepsia* 2000; 41: 193-200.

4. Henry TR, Chugani HT, Abou-Khalil BH, Theodore WH, Swartz BE. Positron emission tomography. In: Engel J (Ed), *Surgical treatment of the epilepsies*. Second Edition, New York, Raven Press, 1993, p. 211-32.

5. Leiderman DB, Balish M, Bromfield EB, Theodore WH. Effect of valproate on human cerebral glucose metabolism. *Epilepsia* 1991; 32: 417-22.

6. Gaillard WD, Fazilat S, White S, *et al.* Interictal metabolism and blood flow are uncoupled in temporal lobe cortex of patients with complex partial seizures. *Neurology* 1995; 45: 1841-7.

7. Lee DS, Lee JS, Kang KW, Jang MJ, Lee SK, Chung JK, Lee MC. Disparity of perfusion and glucose metabolism of epileptogenic zones in temporal lobe epilepsy demonstrated by SPM/SPAM analysis on 15O water PET, [18F]FDG-PET, and [99mTc]-HMPAO SPECT. *Epilepsia* 2001; 42: 1515-22.

8. Franck G, Sadzot B, Salmon E, *et al.* Regional cerebral blood flow and metabolic rates in human focal epilepsy ans status epilepticus. In: Delgado-Escueta AV, Ward Jr AA, Woodbury DM, Porter RJ (Eds), *Basic Mechanisms of the Epilepsies*. Molecular and Cellular Approaches Advances in Neurology, Volume 44, Raven Press, New-York, 1986, p. 935-48.

9. Theodore WH, Balish M, Leiderman D, Bromfield E, Sato S, Herscovitch P. Effect of seizures on cerebral blood flow measured with 15O-H2O and positron emission tomography. *Epilepsia* 1996; 37: 796-802.

10. Kahane P, Merlet I, Grégoire MC, Munari C, Perret J, Mauguière F. A ^{15}O- H_2O PET study of cerebral blood flow changes during focal epileptic discharges induced by intracerebral electrical stimulation. *Brain* 1999; 122: 1851-65.

11. Delforge J, Syrota A, Mazoyer B. Design optimization: theory and application to estimation of receptor model parameters using dynamic positron emission tomography. *Phys Med Biol* 1989; 34: 419-35.

12. Cunningham VJ, Jones T. Spectral analysis of dynamic PET studies. *J Cereb Blood Flow Metab* 1993; 13: 15-23.

13. Savic I, Ingvar M, Stone Elander S. Comparison of [(11)C]flumazenil and [(18)F]FDG as PET markers of epileptic foci. *J Neurol Neurosurg Psychiatry* 1993; 56: 615-21.

14. Debets RM, Sadzot B, Van Isselt JW, *et al.* Is ^{11}C-Flumazenil PET superior to ^{18}FDG PET and ^{123}I-iomazenil SPECT in presurgical evaluation of temporal lobe epilepsy ? *J Neurol Neurosurg Psychiatr* 1997; 62: 141-50.

15. Ryvlin P, Bouvard S, Le Bars D, *et al.* Clinical utility of flumazenil-PET versus [18F]fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. *Brain* 1998; 121: 2067-81.

16. Henry TR, Frey KA, Sackellares JC, *et al.* In vivo cerebral metabolism and central benzodiazepine receptor binding in temporal lobe epilepsy. *Neurology* 1993; 43: 1998-2006.

17. Koepp MJ, Richardson MP, Brooks DJ, *et al.* Cerebral benzodiazepine receptors in hippocampal sclerosis: An objective in vivo analysis. *Brain* 1996; 119: 1677-87.

18. Koepp MJ, Richardson MP, Labbé C, *et al.* ^{11}C-flumazenil PET, volumetric MRI, and quantitative pathology in mesial temporal lobe epilepsy. *Neurology* 1997; 49: 764-73.

19. Koepp MJ, Labbe C, Richardson MP, *et al.* Regional hippocampal [11C]flumazenil PET in temporal lobe epilepsy with unilateral and bilateral hippocampal sclerosis. *Brain* 1997; 120: 1865-76.

20. Richardson MP, Koepp MJ, Brooks DJ, Fish DR, Duncan JS. Benzodiazepine receptors in focal epilepsy with cortical dysgenesis: An 11C-Flumazenil PET study. *Ann Neurol* 1996; 40: 188-98.

21. Szelies B, Weber-Luxenburger G, Pawlik G, *et al.* MRI-guided flumazenil- and FDG-PET in temporal lobe epilepsy. *Neuroimage* 1996; 3: 109-18.

22. Millet P, Delforge J, Mauguiere F, *et al.* Parameter and index images of benzodiazepine receptor concentration in the brain. *J Nucl Med* 1995; 36: 1462-71.

23. Koepp MJ, Hand KS, Labbe C, *et al.* In vivo [11C]flumazenil-PET correlates with ex vivo [3H]flumazenil autoradiography in hippocampal sclerosis. *Ann Neurol* 1998; 43: 618-26.

24. Savic I, Roland P, Sedvall G, Persson A, Pauli S, Widen L. In-vivo demonstration of reduced benzodiazepine receptor binding in human epileptic foci. *Lancet* 1988; 8616: 863-6.

25. Burdette DE, Sakurai SY, Henry TR, *et al.* Temporal lobe central benzodiazepine binding in unilateral mesial temporal lobe epilepsy. *Neurology* 1995; 45: 934-41.

26. Savic I, Thorell JO, Roland P. [(11)C]flumazenil positron emission tomography visualizes frontal epileptogenic regions. *Epilepsia* 1995; 36: 1225-32.

27. Caldecott-Hazard S, Ackermann RF, Engel Jr J. Opioid involvement in postictal and interictal changes in behavior. In: Fariello RG, Morselli PL, Lloyd K, Quesney LF, Engel Jr J (Eds.), *Neurotransmitters, Seizures and Epilepsy II*. Raven Press, New-York, 1984, p. 305-14.

28. Engel Jr J, Ackermann RF, Caldecott-Hazard S, Chugani HT. Do altered opioid mechanisms play a role in human epilepsy? In: Fariello RG, Morselli PL, Lloyd K, Quesney LF, Engel Jr J (eds.), *Neurotransmitters, Seizures and Epilepsy II*. Raven Press, New-York, 1984, p. 263-74.

29. Bajorek JG, Lee RJ, Lomax P. Neuropeptides: anticonvulsant and convulsant mechanisms in epileptic model systems and in humans. *Adv Neurol* 1986; 44: 489-500.

30. Tortella FC. Endogenous opiod peptides and epilepsy: quieting the seizing brain? *Trends Pharmacol Sci* 1988; 9: 36-72.

31. Ranabadran K, Bansinath M. Endogenous opiod peptides and epilepsy. *Int J Clin Pharmacol Ther Toxicol* 1990; 28: 47-62.

32. Cheng JG, Xie XK.A study of opioid peptides in CSF of patients with epilepsy. *Epilepsy Res* 119; 6, 141-145.

33. Frost JJ, Mayberg HS, Fisher RS, *et al.* Mu-opiate receptors measured by positron emission tomography are increased in temporal lobe epilepsy. *Ann Neurol* 1988; 23: 231-7.

34. Frost JJ, Mayberg HS, Sadzot B, *et al.* Comparison of 11C-diprenorphine and 11C-carfentanil binding to opiate receptors in man by positron emission tomography. *J Cereb Blood Flow Metab* 1990; 10: 484-92.

35. Mayberg HS, Sadzot B, Meltzer CC, *et al.* Quantification of mu and non mu opiate receptors in temporal lobe epilepsy using positron emission tomography. *Ann Neurol* 1991; 30: 3-11.

36. Theodore WH, Carson RE, Andreasen P, *et al.* PET imaging of opiate receptor binding in human epilepsy using [(18)F]cyclofoxy. *Epilepsy Res* 1992; 13: 129-39.

37. Madar I, Lesser RP, Krauss G, *et al.* Imaging of delta- and mu-opiod receptors in temporal lobe epilepsy by positron emission tomography. *Ann Neurol* 1997; 41: 358-67.

38. Koepp MJ, Richardson MP, Brooks DJ, Duncan JS. Focal release of endogenous opiods during reading-induced seizures. *Lancet* 1998; 352: 952-5.

39. Peroutka SJ. 5-HT receptors: past, present and future. *Trends Neurosci* 1995; 18: 68-9.

40. Gerber K, Filakovszky J, Halasz P, Bagdy G. The 5-HT1A agonist 8-OH-DPAT increases the number of spike-wave discharges in a genetic rat model of absence epilepsy. *Brain Res* 1998; 807: 243-5.

41. Filakovszky J, Gerber K, Bagdy G. A serotonin-1A receptor agonist and an N-methyl-D-aspartate receptor antagonist oppose each others effects in a genetic rat epilepsy model. *Neurosci Lett* 1999; 261: 89-92.

42. Lerner-Natoli M. Serotonin and kindling development. *Int J Neurosci* 1987; 36: 139-51.

43. Wada Y, Nakamura M, Hasegawa H, Yamaguchi N. Role of serotonin receptor subtype in seizures kindled from the feline hippocampus. *Neurosci Lett* 1992; 141: 21-4.

44. Wada Y, Shiraishi J, Nakamura M, Koshino Y. Role of serotonin receptor subtypes in the development of amygdaloid kindling in rats. *Brain Res* 1997; 747: 338-42.

45. Gariboldi M, Tutka P, Samanin R, Vezzani A. Stimulation of 5-HT1A receptors in the dorsal hippocampus and inhibition of limbic seizures induced by kainic acid in rats. *Br J Pharmacol* 1996; 119: 813-8.

46. Salgado-Commissariat D, Alkadhi KA. Serotonin inhibits epileptiform discharge by activation of 5-HT1A receptors in CA1 pyramidal neurons. *Neuropharmacology* 1997; 36: 1705-12.

47. Tokarski K, Zahorodna A, Bobula B, Hess G. Comparison of the effects of 5-HT1A and 5-HT4 receptor activation on field potentials and epileptiform activity in rat hippocampus. *Exp Brain Res* 2002; 147: 505-10.

48. Trottier S, Evrard B, Vignal JP, Scarabin JM, Chauvel P. The serotonergic innervation of the cerebral cortex in man and its changes in focal cortical dysplasia. *Epilepsy Res* 1996; 25: 79-106.

49. Favale E, Rubino V, Mainardi P, Lunardi G, Albano C. Anticonvulsant effect of fluoxetine in humans. *Neurology* 1995; 45: 1926-7.

50. Gunn RN, Sargent PA, Bench CJ, *et al.* Tracer kinetic modeling of the 5-HT1A receptor ligand [carbonyl-11C]WAY-100635 for PET. *Neuroimage* 1998; 8: 426-40.

51. Lang L, Jagoda E, Schmall B, *et al.* Development of fluorine-18-labeled 5-HT1A antagonists. *J Med Chem* 1999; 42: 1576-86.

52. Le Bars D, Lemaire C, Ginovart N, *et al.* High-yield radiosynthesis and preliminary in vivo evaluation of p- [18F]MPPF, a fluoro analog of WAY-100635. *Nucl Med Biol* 1998; 25: 343-50.

53. Zimmer L, Mauger G, Le Bars D, Bonmarchand G, Luxen A, Pujol JF. Effect of endogenous serotonin on the binding of the 5-hT1A PET ligand 18F-MPPF in the rat hippocampus: kinetic beta measurements combined with microdialysis. *J Neurochem* 2002; 80: 278-86.

54. Costes N, Merlet I, Zimmer L, Lavenne F, *et al.* Modeling [18 F]MPPF positron emission tomography kinetics for the determination of 5-hydroxytryptamine(1A) receptor concentration with multiinjection. *J Cereb Blood Flow Metab* 2002; 22: 753-65.

55. Toczek MT, Carson RE, Lang L, *et al.* PET imaging of 5-HT1A receptor binding in patients with temporal lobe epilepsy. *Neurology* 2003; 60: 749-56.

56. Merlet I, Ryvlin P, Costes N, *et al.* Statistical parametric mapping of 5HT1A receptor binding in temporal lobe epilepsy with hippocampal ictal onset on intracranial EEG. *Neuroimage* 2004; 22: 886-96.

57. Merlet I, Ostrowsky K, Costes N, *et al.* 5-HT1A receptor binding and intracerebral activity in temporal lobe epilepsy: A [18F]MPPF-PET study. *Brain* 2004; 127: 900-13.

58. Chugani DC, Chugani HT, Muzik O, *et al.* Imaging epileptogenic tubers in children with tuberous sclerosis complex using alpha-[11C]methyl-L-tryptophan positron emission tomography. *Ann Neurol* 1998; 44: 858-66.

59. Fedi M, Reutens DC, Andermann F, *et al.* Alpha-[11C]-Methyl-L-tryptophan PET identifies the epileptogenic tuber and correlates with interictal spike frequency. *Epilepsy Res* 2003; 52: 203-13.

60. Fedi M, Reutens D, Okazawa H, *et al.* Localizing value of alpha-methyl-L-tryptophan PET in intractable epilepsy of neocortical origin. *Neurology* 2001; 57: 1629-36.

61. Juhasz C, Chugani DC, Muzik O, *et al.* Alpha-methyl-L-tryptophan PET detects epileptogenic cortex in chidren with intractable epilepsy. *Neurology* 2003; 60: 960-8.

62. Natsume J, Kumakura Y, Bernasconi N, *et al.* Alpha-[11C] methyl-L-tryptophan and glucose metabolism in patients with temporal lobe epilepsy. *Neurology* 2003; 60: 756-61.

63. Lapin IP, Prakhie IB, Kiselva IP. Excitatory effects of kynurenine and its metabolites, amino acids and convulsants administered into brain ventricles:differences between rats and mice. *J Neural Transm* 1982; 54: 229-38.

64. Perkins MN, Stone TW. An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. *Brain Res* 1982; 247: 184-7.

65. Rosenow F, Lüders H. Presurgical evaluation of epilepsy. *Brain* 2001; 124: 1683-700.

66. Kuhl D, Engel Jr J, Phelps ME, Selin C. Epileptic patterns of local cerebral metabolism and perfusion in humans, determined by emission computed tomography of 18FDG and 13NH3. *Ann Neurol* 1980: 348-60.

67. Barrington SF, Koutroumanidis M, Agathonikou A, *et al.* Clinical value of 18F fluorodeoxyglucose positron emission tomography and the routine use of simultaneous scalp EEG studies in patients with intractable partial epilepsies. *Epilepsia* 1998; 39: 753-66.

68. Engel Jr J, Kuhl DE, Phelps ME, Mazziotta JC. Interictal cerebral glucose metabolism in partial epilepsy and its relation to E.E.G changes. *Ann Neurol* 1982; 12: 510-7.

69. Kessler RM, Margolin R, Manning R, Channing M, Porter RJ. 18F fluorodeoxyglucose positron emission tomography in refractory complex partial seizures. *Ann Neurol* 1983; 14: 429-37.

70. Engel Jr J, Henry TR, Risinger MW, *et al.* Presurgical evaluation for partial epilepsy: relative contributions of chronic depth electrode recordings versus FDG PET and scalp sphenoidal ictal EEG. *Neurology* 1990; 40: 1670-7.

71. Theodore WH, Katz D, Kufta C, Sato S, Patronas N, Smothers P, Bromfield E. Pathology of temporal lobe foci: correlation with CT, MRI, and PET. *Neurology* 1990; 40: 797-803.

72. Stefan H, Pawlik G, Bocher Schwarz HG, *et al.* Functional and morphological abnormalities in temporal lobe epilepsy: a comparison of interictal and ictal EEG, CT, MRI, SPECT and PET. *J Neurol* 1987; 234: 377-84.

73. Ryvlin P, Philippon B, Cinotti L, Froment JC, Le Bars D, Mauguiere F. Functional neuroimaging strategy in temporal lobe epilepsy: a comparative study of 18FDG-PET and 99mTc-HMPAO-SPECT. *Ann Neurol* 1992; 31: 650-6.

74. Andersen AR, Rogvi-Hansen B, Dam M. Utility of interictal SPECT of rCBF for focal diagnosis of the epileptogenic zone(s). *Acta Neurol Scand* 1994; 89(Suppl. 152) : 129-34.

75. Fink GR, Pawlik G, Stefan H, Pietrzyk U, Wienhard K, Heiss WD. Temporal lobe epilepsy: evidence for interictal uncoupling of blood flow and glucose metabolism in temporomesial structures. *J Neurol Sci* 1996; 137: 28-34.

76. Theodore WH, Brooks RD, Patronas N, *et al.* The effect of phenobarbital and phenytoin on cerebral glucose metabolism measured by positron emission tomography. *Neurology* 1984; 34: S118.

77. Theodore WH, Dorwart R, Holmes M, Porter RJ, Di Chiro G. Neuroimaging in refractory partial seizures: Comparison of PET, CT, and MRI. *Neurology* 1986; 36: 750-9.

78. Theodore WH, Sato S, Kufta C, Balish MB, Bromfield EB, Leiderman DB. Temporal lobectomy for uncontrolled seizures: The role of positron emission tomography. *Ann Neurol* 1992; 32: 789-94.

79. Theodore WH, Fishbein D, Dubinsky R. Patterns of cerebral glucose metabolism in patients with partial seizures. *Neurology* 1988; 38: 1201-6.

80. Ryvlin Ph, Cinotti L, Froment JC, *et al.* Metabolic patterns associated with non-specific resonance imaging abnormalities in temporal lobe epilepsy. *Brain* 1991; 114: 2363-83.

81. Ryvlin P, Mauguière F, Sindou M, Froment JC, Cinotti L. Interictal cerebral metabolism and epilepsy in cavernous angiomas. *Brain* 1995; 118: 677-87.

82. Henry TR, Mazziotta JC, Engel Jr J. Interictal metabolic anatomy of mesial temporal lobe epilepsy. *Arch Neurol* 1993; 50: 582-9.

83. Henry TR, Sutherling WW, Engel Jr J, *et al.* Interictal cerebral metabolism in partial epilepsies of neocortical origin. *Epilepsy Res* 1991; 10: 174-82.

84. Henry TR, Mazziotta JC, Engel Jr J. The functional anatomy of frontal lobe epilepsy studied with PET. In: Chauvel P, Delgado-Escueta AV, Halgren E, Bancaud J (eds.), *Advances in Neurology*. Vol 57 ,Frontal lobe seizures and epilepsies, Raven Press, New-York, 1992, p. 487-97.

85. Sperling MR, Wilson G, Engel Jr J, Babb TL, Phelps M, Bradley W. Magnetic resonance imaging in intractable partial epilepsy: correlative studies. *Ann Neurol* 1986; 20: 57-62.

86. Hajek M, Antonini A, Leenders KL, Wieser HG. Mesiobasal versus lateral temporal lobe epilepsy: Metabolic differences in the temporal lobe shown by interictal (18)F FDG positron emission tomography. *Neurology* 1993; 43: 79-86.

87. Sadzot B, Debets RMC, Maquet P, *et al.* Regional brain glucose metabolism in patients with complex partial seizures investigated by intracranial EEG. *Epilepsy Res* 1992; 12: 121-9.

88. Swartz BE, Halgren E, Delgado-Escueta AV, *et al.* Neuroimaging in patients with seizures of probable frontal lobe origin. *Epilepsia* 1989; 30: 547-58.

89. Swartz BE, Theodore WH, Sanabria E, Fischer RS. Positron emission and single photon computed tomographic studies in the frontal lobe with emphasis on the relationship to seizure foci. In: Chauvel P, Delgado-Escueta A, Halgren E, Bancaud J (eds), *Advances in Neurology*, Vol 57, Frontal lobe seizures and epilepsies, Raven Press, New-York, 1992, p. 487-97.

90. Swartz BE, Khonsari A, Brown C, Mandelkern M, Simpkins F, Krisdakumtorn T. Improved sensitivity of 18FDG-positron emission tomography scans in frontal and "frontal plus" epilepsy. *Epilepsia* 1995; 36: 388-95.

91. Franck G, Maquet P, Sadzot B, *et al.* Contribution of Positron Emission Tomography to the investigation of epilepsies of frontal lobe origin. In: Chauvel P, Delgado-Escueta AV, Halgren E, Bancaud J (eds.), *Advances in Neurology*, Vol 57, Frontal lobe seizures and epilepsies, Raven Press, New-York, 1992 p. 471-85.

92.. Da Silva EA, Chugani D, Muzik O, Chugani HT. Identfication of frontal lobe epileptic foci in children using positron emission tomography. *Epilepsia* 1997; 38: 1198-208.

93. Drzezga A, Arnold S, Minoshima S, *et al.* 18-FDG PET in patients with extratemporal and temporal epilepsy: evaluation of an observer-independent analysis. *J Nucl Med* 1999; 40: 737-46.

94. Kim YK, Lee DS, Chung CK, Chung JK, Lee MC. 18F-FDG PET in localization of frontal lobe epilepsy: comparison of visual and SPM analysis. *J Nucl Med* 2002; 43: 1167-74.

95. Franceschi M, Lucignani G, De Sole A, *et al.* Increased interictal cerebral glucose metabolism in a cortical-subcortical netwok in drug naive patients with cryptogenic temporal lobe epilepsy. *J Neuro Neurosurg Psychiatry* 1995; 59: 427-31.

96. Van Bogaert P, Massager N, Tugendhaft P, *et al.* statistical parametric mapping of regional glucose metabolism in mesial temporal lobe epilepsy. *Neuroimage* 2002; 12: 129-38.

97. Gaillard WD, Kopylev L, Weinstein S, *et al.* Low incidence of abnormal (18)FDG PET in children with new-onset partial epilepsy: a propective study. *Neurolgy* 2002; 58: 717-22.

98. Matheja P, Kuvert T, Ludemann P, *et al.* Temporal hypometabolism at the onset of cryptogenic temporal lobe epilepsy. *Eur J Nucl Med* 2001; 28: 625-32.

99. Gaillard WD, White S, Malow B, *et al.* FDG-PET in children and adolescents with partial seizures: role in epilepsy surgery evaluation. *Epilepsy Res* 1995; 20: 77-84.

100. Markand ON, Salanova V, Worth R, Park HM, Wellman HN. Comparative study of interictal PET and ictal SPECT in complex partial seizures. *Acta Neurol Scand* 1997; 95: 129-36.

101. Coubes P, Awad IA, Antar M, Magdinec M, Sufka B. Comparison and spatial correlation of interictal HMPAO-SPECT and FDG-PET in intractable temporal lobe epilepsy. *Neurol Res* 1993; 15: 160-8.

102. Nagata T, Tanaka F, Yonrkura Y, *et al.* Limited value of interictal brain perfusion SPECT for detection of epileptic foci: high resolution SPECT studies in comparison with FDG-PET. *Ann Nucl Med* 1995; 9: 59-63.

103. Lamusuo S, Ruottinen HM, Knuuti J, *et al.* Comparison of (18F)FDG-PET, (99mTC)-HMPAO-SPECT, and (123I)-iomazenil-SPECT in localizing the epileptogenic cortex. *J Neurol Neurosurg Psychiatry* 1997; 63: 743-8.

104. Abou-Khalil BW, Siegel GJ, Sackellares JC, Gilman S, Hichwa R, Marshall R. Positron emission tomography studies of cerebral glucose metabolism in chronic partial epilepsy. *Ann Neurol* 1987; 22: 480-6.

105. Engel Jr J, Kuhl DE, Phelps ME, Crandall PH. Comparative localization of epileptic foci in partial epilepsy by PCT and EEG. *Ann Neurol* 1982; 12: 529-37.

106. Kim YK, Lee DS, Kim SK, *et al.* Differential features of metabolic abnormalities between medial and lateral temporal lobe epilepsy: Qauntitative analysis of (18)F-FDG PET using SPM. *J Nucl Med* 2003; 44: 1006-12.

107. Koutroumanidis M, Hennessy MJ, Seed PT, *et al.* Significance of interictal bilateral temporal hypometabolism in temporal lobe epilepsy. *Neurology* 2000; 54: 1811-21.

108. Lucignani G, Tassi L, Fazio F, *et al.* Double-blind stereo-EEG and FDG PET study in severe partial epilepsies: are the electric and metabolic findings related? *Eur J Nucl Med* 1996; 23: 1498-507.

109. Juhasz C, Chugani DC, Muzik O, *et al.* Electroclinical correlates of flumazenil and fluorodeoxyglucose PET abnormalities in lesional epilepsy. *Neurology* 2000: 825-35.

110. Lee SK, Yun CH, Oh JB, *et al.* Intracranial ictal onset zone in nonlesional lateral temporal lobe epilepsy on scalp ictal EEG. *Neurology* 2003; 61: 757-64.

111. Hong KS, Lee SK, Kim JY, Lee DS, Chung CK. Pre-surgical evaluation and surgical outcome of 41 patients with non-lesional neocortical epilepsy. *Seizure* 2002; 11: 184-92.

112. Duncan JS, Koepp MJ. PET: central benzodiazepine neuroreceptor mapping in localization-related epilepsies. *Adv Neurol* 2000; 83: 131-6.

113. Theodore WH. When is positron emission tomography really necessary in epilepsy diagnosis? *Curr Opin Neurol* 2002; 15: 191-5.

114. Choi JY, Kim SJ, Hong SB, Seo DW, Hong SC, Kim BT, Kim SE. Extratemporal hypometabolism on FDG PET in temporal lobe epilepsy as a predictor of seizure outcome after temporal lobectomy. *Eur J Nucl Med Mol Imaging* 2003; 30: 581-7.

115. Lee SK, Lee DS, Yeo JS, *et al.* FDG-PET images quantified by probabilistic atlas of brain and surgical prognosis of temporal lobe epilepsy. *Epilepsia* 2002; 43: 1032-8.

116. Swartz BE, Tomiyasu U, Delgado Escueta AV, Mandelkern M, Khonsari A. Neuroimaging in temporal lobe epilepsy: Test sensitivity and relationships to pathology and postoperative outcome. *Epilepsia* 1992; 33: 624-34.

117. Chee MWL, Morris III HH, Antar MA, *et al.* Presurgical evaluation of temporal lobe epilepsy using interictal temporal spikes and positron emission tomography. *Arch Neurol* 1993; 50: 45-8.

118. Knowlton RC, Laxer KD, Ende G, *et al.* Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy. *Ann Neurol* 1997; 42: 829-37.

119. Won HJ, Chang KH, Cheon JE, *et al.* Comparison of MR imaging with PET and ictal SPECT in 118 patients with intractable epilepsy. *Am J Neuroradiol* 1999; 20: 593-9.

120. Nagarajan L, Schaul N, Eidelberg D, Dhawan V, Frase R, Labar DR. Contralateral temporal hypometabolism on positron emission tomography in temporal lobe epilepsy. *Acta Neurol Scand* 1996; 93: 81-4.

121. Rubin E, Dhawan V, Moeller JR, *et al.* Cerabral metabolic topography in unilateral temporal lobe epilepsy. *Neurology* 1995; 45: 2212-23.

122. Holmes MD, Kelly K, Theodore WH. Complex partial seizures. Correlation of clinical and metabolic features. *Arch Neurol* 1988; 45: 1191-3.

123. Yamamoto YL, Ochs R, Gloor P, *et al.* Pattern of rCBF and focal energy metabolism changes in relation to electroencephalographic abnormality in the inter-ictal phase of partial epilepsy. In: Badly-Moulinier M, Ingvar DH, Meldrum BS (eds.), *Cerebral blood flow, metabolism and epilepsy*. John Libbey Eurotext, London, 1984, p. 51-62.

124. Valk PE, Laxer KD, Barbaro NM, Knezevic S, Dillon WP, Budinger TF. High resolution (2.6 mm) PET in partial complex epilepsy associated with mesial temporal sclerosis. *Radiology* 1993; 186: 55-8.

125. Bouilleret V, Dupont S, Spelle L, Baulac M, Samson Y, Semah F. Insular cortex involvement in mesiotemporal lobe epilepsy: a positron emission tomography study. *Ann Neurol* 2002; 51: 202-8.

126. Dupont S, Bouilleret V, Hasboun D, Semah F, Baulac M. Functional anatomy of the insula: new insights from imaging. *Surg Radiol Anat* 2003; 25: 113-9.

127. Juhasz C, Nagy F, Watson C, *et al.* Glucose and 11C-flumazenil positron emission tomography abnormalities of thalamic nuclei in temporal lobe epilepsy. *Neurology* 1999; 53: 2037-45.

128. Sackellares JC, Siegel GJ, Abou-Khalil BW, *et al.* Differences between lateral and mesial temporal metabolism interictally in epilepsy of mesial temporal origin. *Neurology* 1990; 40: 1420-6.

129. Kim SK, Lee DS, Lee SK, Kim YK, Chung CK, Chung JK, Lee MC. Diagnostic performance of (18)F-FDG-PET and ictal (99mTc)-HMPAO SPECT in occipital lobe epilepsy. *Epilepsia* 2001; 42: 1531-40.

130. Merlet I, Garcia-Larrea L, Grégoire MC, Lavenne F, Mauguière F. Source propagation of interictal spikes in temporal lobe epilepsy. Correlations between spike dipole modelling and [18F]fluorodeoxyglucose PET data. *Brain* 1996: 377-92.

131. Pozo M, Pascau J, Rojo P, *et al.* Correlation between FDG PET data and EEG dipole modeling. *Clin Positron Imaging* 2002; 3: 173.

132. Hong SB, Han HJ, Roh SY, Seo DW, Kim SE, Kim MH. Hypometabolism and interictal spikes during positron emission tomography scanning in temporal lobe epilepsy. *Eur Neurol* 2002; 48: 65-70 (2002b).

133. Snead 3rd OC, Chen LS, Mitchell WG, *et al.* Usefulness of 18F-fluorodeoxyglucose positron emission tomography in pediatric epilepsy surgery. *Pediatr Neurol* 1996; 14: 98-107.

134. Theodore WH, Sato S, Kufta CV, Gaillard WD, Kelley K. FDG-positron emission tomography and invasive EEG: seizure focus detection and surgical outcome. *Epilepsia* 1997; 38: 81-6.

135. Koutroumanidis M, Binnie CD, Elwes RD, *et al.* Interictal regional slow activity in temporal lobe epilepsy correlates with lateral temporal hypometabolism as imaged with 18FDG PET: neurophysiological and metabolic implications. *J Neurol Neurosurg Psychiatry* 1998; 65: 170-6.

136. Dupont S, Semah F, Baulac M, Samson Y. The underlying pathophysiology of ictal dystonia in temporal lobe epilepsy: an FDG-PET study. *Neurology* 1998; 51: 1289-92.

137. Wunderlich G, Schuller MF, Ebner A, *et al.* Temporal lobe epilepsy with sensory aura: interictal glucose hypometabolism. *Epilepsy Res* 2000; 38: 139-49.

138. Muzik O, da Silva EA, Juhasz C, *et al.* Intracranial EEG versus flumazenil and glucose PET in children with extratemporal lobe epilepsy. *Neurology* 2000; 54: 171-9.

139. Radtke RA, Hanson MW, Hoffman JM, *et al.* Temporal lobe hypometabolism on PET: Predictor of seizure control after temporal lobectomy. *Neurology* 1993; 43: 1088-92.

140. Manno EM, Sperling MR, Ding X, *et al.* Predictors of outcome after anterior temporal lobectomy: positron emission tomography. *Neurology* 1994; 44: 2331-6.

141. Salanova V, Markand O, Worth R, *et al.* FDG-PET and MRI in temporal lobe epilepsy: relationship to febrile seizures, hippocampal atrophy and outcome. *Acta Neurol Scand* 1998; 97: 146-53.

142. Lamusuo S, Forss N, Ruottinen HM, *et al.* [18F]FDG-PET and whole-scalp MEG localization of epileptogenic cortex. *Epilepsia* 1999; 40: 921-30.

143. Newberg AB, Alavi A, Berlin J, Mozley PD, O'Connor M, Sperling M. Ipsilateral and contralateral thalamic hypometabolism as a predictor of outcome after temporal lobectomy for seizures. *J Nucl Med* 2000; 41: 1964-8.

144. Juhasz C, Chugani DC, Muzik O, *et al.* relationship of flumazenil and glucose PET abnormalities to neocortical epilepsy surgery outcome. *Neurology* 2001; 56: 1650-8.

145. Isnard J, Guénot M, Ostrowsky K, Sindou M, Mauguière F. The role of the insular cortex in temporal lobe epilepsy. *Ann Neurol* 2000; 48: 614-23.

146. Engel Jr J, Kuhl DE, Phelps ME, Rausch R, Nuwer M. Local cerebral metabolism during partial seizures. *Neurology* 1983; 33: 400-13.

147. Peyron R, Le Bars D, Cinotti L, *et al.* Effects of GABA-A receptors activation on brain glucose metabolism in normal subjects and Temporal Lobe Epilepsy (TLE) patients. A Positron Emission Tomography (PET) study. Part I: Brain glucose metabolism is increased after GABA-A receptors activation. *Epilepsy Res* 1994; 19: 45-54.

148. Peyron R, Le Bars D, Cinotti L, *et al.* Effects of GABA-A receptors activation on brain glucose metabolism in normal subjects and Temporal Lobe Epilepsy (TLE) patients. A Positron Emission Tomography (PET) study. Part II: The focal hypometabolism is reactive to GABA-A agonist administration in TLE. *Epilepsy Res* 1994; 19: 55-62.

149. Griffith HR, Perlman SB, Woodard AR, *et al.* Preoperative FDG-PET temporal lobe hypometabolism and verbal memory after temporal lobectomy. *Neurology* 2000; 54: 1161-5.

150. Hong SB, Roh SY, Kim SE, Seo DW. Correlation of temporal lobe glucose hypometabolism with the Wada memory test. *Epilepsia* 2000; 41: 1554-9.

151. Salanova V, Markand O, Worth R. Focal functional deficits in temporal lobe epilepsy on PET scans and the intracarotid amobarbital procedure: comparison of patients with unitemporal epilepsy with those requiring intracranial recordings. *Epilepsia* 2001; 42: 198-203.

152. Cornford EM, Gee MN, Swartz BE, *et al.* Dynamic18F-fluorodeoxyglucose positron emission tomography and hypometabolic zones in seizures; reduced capillary influx. *Ann Neurol* 1998; 43: 801-8.

153. Pfund Z, Chugani DC, Juhasz C, *et al.* Evidence for coupling between glucose metabolism and glutamate cycling usin FDG PET and 1H magnetic resonance spectroscopy in patients with epilepsy. *J Cereb Blood Flow Metab* 2000; 20: 871-8.

154. Henry TR, Babb TL, Engel Jr J, Mazziotta JC, Phelps ME, Crandall PH. Hippocampal neuronal loss and regional hypometabolism in temporal lobe epilepsy. *Ann Neurol* 1994; 36: 925-7.

155. Semah F, Baulac M, Hasboun D, *et al.* Is interictal temporal hypometabolism related to mesial temporal sclerosis ? A positron emission tomography/magnetic resonance imaging confrontation. *Epilepsia* 1995; 36: 447-56.

156. O'Brien TJ, Newton MR, Cook MJ, *et al.* Hippocampal atrophy is not a major determinant of regional hypometabolism in temporal lobe epilepsy. *Epilepsia* 1997; 38: 74-80.

157. Dlugos DJ, Jaggi J, O'Connor WM, *et al.* Hippocampal cell density and subcortical metabolism in temporal lobe epilepsy. *Epilepsia* 1999; 40: 408-13.

158. Foldvary N, Lee N, Hanson MW, *et al.* Correlation of hippocampal neuronal density and FDG-PET in mesial temporal lobe epilepsy. *Epilepsia* 1999; 40: 26-9.

159. Choi D, Na DG, Byun HS, *et al.* White-matter change in mesial temporal sclerosis: correlation of MRI with PET, pathology and clinical features. *Epilepsia* 1999; 40: 1634-41.

160. Lamuosuo S, Jutila L, Ylinen A, *et al.* 18F-FDG-PET reveals temporal hymetabolism in patients with temporal lobe epilepsy even when quantitative MRI and histopathological analysis show only mild hippocampal damage. *Arch Neurol* 2001; 58: 933-9.

161. Theodore WH, Gaillard WD, De Carli C, Bhatia S, Hatta J. Hippocampal volume and glucose metabolism in temporal lobe epileptic foci. *Epilepsia* 2001; 42: 130-2.

162. Knowlton RC, Laxer KD, Klein G, *et al.* In vivo hippocampal glucose metabolism in me sial temporal lobe epilepsy. *Neurology* 2001; 57: 1184-90.

163. Latack JT, Abou-Khalil BW, Siegel GJ, Sackellares JC, Gabrielsen TO, Aisen AM. Patients with partial seizures: evaluation by MR, CT, and PET Imaging. *Radiology* 1986; 159: 159-63.

164. Diehl B, LaPresto E, Najm I, *et al.* Neocortical temporal FDG-PET hypometabolism correlates with temporal lobe atrophy in hippocampal sclerosis associated with microscopic cortical dysplasia. *Epilepsia* 2003; 44: 559-64.

165. Chassoux F, Semah F, Bouilleret V, *et al.* Metabolic changes and electro-clinical patterns in mesio-temporal lobe epilepsy: a correlative study. *Brain* 2004; 127: 164-74.

166. Rausch R, Henry TR, Ary CM, Engel Jr J, Mazziotta J. Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. *Arch Neurol* 1994; 51: 139-44.

167. Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW, Ebner A. Prefrontal asymmetric interictal glucose metabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain* 1997; 120: 2283-94.

168. Salanova V, Morris 3rd HH, Rehm P, *et al.* Comparison of the intracarotid amobarbital procedure and interictal cerebral 18-fluorodeoxyglucose positron emission tomography scans in refractory temporal lobe epilepsy. *Epilepsia* 1992; 33: 635-8.

169. Hajek M, Wieser HG, Khan N, *et al.* Preoperative and postoperative glucose consumption in mesiobasal and lateral temporal lobe epilepsy. *Neurology* 1994; 44: 2125-32.

170. Régis et al. à compléter ????

171. Spanaki MV, Kopylev L, DeCarli C, *et al.* Postoperative changes in cerebral metabolism in temporal lobe epilepsy. *Arch Neurol* 2000; 57: 1447-52.

172. Ryvlin P, Garcia-Larrea L, Philippon B, *et al.* High signal intensity on T2-weighted MRI correlates with hypoperfusion in temporal lobe epilepsy. *Epilepsia* 1992; 33: 28-35.

173. Ryvlin P, Coste S, Hermier M, Mauguiere F. Temporal pole MRI abnormalities in temporal lobe epilepsy. *Epileptic Disord* 2002; 4: S33-39.

174. Meiners LC, Witkamp TD, de Kort GA, *et al.* Relevance of temporal lobe white matter changes in hippocampal sclerosis. Magnetic resonance imaging and histology. *Invest Radiol* 1999; 34: 38-45.

175. Mitchell LA, Jackson GD, Kalnins RM, *et al.* Anterior temporal abnormality in temporal lobe epilepsy: a quantitative MRI and histopathologic study. *Neurology* 1999; 52: 327-36.

176. Colombo N, Tassi L, Galli C, *et al.* Focal cortical dysplasias: MR imaging, histopathologic, and clinical correlations in surgically treated patients with epilepsy. *Am J Neuroradiol* 2003; 24: 724-33.

177. Savic I, Swanborg E, Thorell JO. Cortical benzodiazepine receptor changes are relayed to frequency of partial seizures: a positron emission tomography study. *Epilepsia* 1996; 37: 236-44.

178. Koepp MJ, Hammers A, Labbé C, Wörmann FG, Brooks DJ, Duncan JS. ^{11}C-flumazenil PET in patients with refractory temporal lobe epilepsy and normal MRI. *Neurology* 2000; 54: 332-9.

179. Hammers A, Koepp MJ, Richardson MP, *et al.* Central benzodiazepine receptors in malformations of cortical development: A quantitative study. *Brain* 2001; 124: 1555-65.

180. Ryvlin P, Bouvard S, Le Bars D, Mauguière F. Transient and falsely lateralizing flumazenil-PET asymmetries in temporal lobe epilepsy. *Neurology* 1999; 53: 1882-5.

181. Hammers A, Koepp MJ, Labbe C, *et al.* Neocortical abnormalities of [11C]-flumazenil PET in mesial temporal lobe epilepsy. *Neurology* 2001; 56: 897-906.

182. Szelies B, Sobesky J, Pawlik G, *et al.* Impaired benzodiazepine receptor binding in peri-lesional cortex of patients with symptomatic epilepsies studied by [(11)C]-flumazenil PET. *Eur J Neurol* 2002; 9: 137-42.

183. Lamusuo S, Pitkanen A, Jutila L, *et al.* [11 C]Flumazenil binding in the medial temporal lobe in patients with temporal lobe epilepsy: correlation with hippocampal MR volumetry, T2 relaxometry, and neuropathology. *Neurology* 2000; 54: 2252-60.

184. Szelies B, Weber-Luxenburger G, Mielke R, *et al.* Interictal hippocampal benzodiazepine receptors in temporal lobe epilepsy: comparison with coregistered hippocampal metabolism and volumetry. *Eur J Neurol* 2000; 7: 393-400.

185. Hammers A, Koepp MJ, Hurlemann R, *et al.* Abnormalities of grey and white matter [11C]flumazenil binding in temporal lobe epilepsy with normal MRI. *Brain* 2002; 125: 2257-71.

186. Hammers A, Koepp MJ, Richardson MP, Hurlemann R, Brooks DJ, Duncan JS. Grey and white matter flumazenil binding in neocortical epilepsy with normal MRI. A PET study of 44 patients. *Brain* 2003; 126: 1300-18.

187. Arnold S, Berthele A, Drzezga A, *et al.* Reduction of benzodiazepine receptor binding is related to the seizure onset zone in extratemporal focal cortical dysplasia. *Epilepsia* 2000; 41: 818-24.

188. Richardson MP, Friston KJ, Sisodiya SM, *et al.* Cortical grey matter and benzodiazepine receptors in malformations of cortical development. A voxel-based comparison of structural and functional imaging data. *Brain* 1997; 120: 1961-73.

189. Richardson MP, Koepp MJ, Brooks DJ, Duncan JS. 11C-flumazenil PET in neocortical epilepsy. *Neurology* 1998; 51: 485-92.

190. Francione S, Kahane P, Tassi L, Hoffmann D, Durisotti C, Pasquier B, Munari C. Stero-EEG of interictal and ictal electrical activity of a histologically proven heterotopic gray matter associated with partial epilepsy. *Electroencephalogr Clin Neurophysiol* 1994; 90: 284-90.

191. Mattia D, Olivier A, Avoli M. Seizure-like discharges recorded in human dysplastic neocortex maintained in vitro. *Neurology* 1995; 45: 1391-5.

192. Palmini A, Gambardella A, Andermann F, *et al.* Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol* 1995; 37: 476-87.

193. Sisodiya SM, Free SL, Thom M, Everitt AE, Fish DR, Shorvon SD. Evidence for nodular epileptogenicity and gender differences in periventricular heterotopia. *Neurology* 1999; 52: 336-41.