PET and SPECT in epilepsy: A critical review

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1. Introduction

Epilepsy is a chronic disorder characterized by repeated seizures caused by the excessive electrical firing of a number of neurons. Antiepileptic drugs are useful in controlling the seizures, but 20 to 30% of patients with epilepsy continue to have seizures despite treatment [1]. Surgical intervention is an important option and has become an accepted treatment method in properly selected patients with intractable focal epilepsy, but accurate resection of epileptogenic areas is imperative for successful seizure control. For the selection of patients eligible for surgery, as well as for best treatment response, precise localization of the epileptogenic region in the brain is necessary to identify the epileptogenic area and minimize the side effects of the operation. This localization should be done ideally using several methods based on different pathophysiological principles. To plan the optimal surgical approach for the achievement of complete seizure control, an additional important objective of presurgical investigation is definition of the boundaries of the epileptogenic region.

Although long-term intracranial EEG evaluation remains the gold standard here, the invasiveness of this approach requires careful patient preselection. Structural imaging with magnetic resonance imaging (MRI) is necessary for presurgical investigation to identify morphological abnormalities such as hippocampal sclerosis and malformations of cortical development. In addition, MRI can provide anatomical information for functional imaging modalities like single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

Functional neuroimaging by PET and SPECT has a role in the presurgical evaluation of epilepsies, as these methods are able to detect epileptogenic foci in morphologically inconspicuous areas and because they are, in contrast to EEG-based methods, not primarily dependent on the electrical activity of the brain. State-of-the-art imaging with PET and SPECT should be an integral part of a multimodality imaging platform and can, if properly used, substantially reduce the number of invasive EEG recordings. In addition, these are important research tools to gain a better understanding of the neurobiology of epilepsy.
2. SPECT

Although brain perfusion SPECT allows only quantitative estimations through tracer uptake ratios, it is widely used to measure regional cerebral blood flow (rCBF) and is an accepted adjunctive technique in the presurgical evaluation of patients with refractory partial epilepsy [2]. In epilepsy, its application is based on the assumption that the increased ictal neuronal activity occurring during epileptic seizures is associated with increased metabolism and regional cerebral blood flow. For brain perfusion SPECT investigations, iodine-123- and technetium-99m-labeled radiopharmaceuticals are commercially available that differ in pharmacokinetic behavior and physical characteristics [3]. However, these radiopharmaceuticals have in common the ability to cross the intact blood–brain barrier rapidly, because of their small molecular size and their lipophilicity, to be distributed proportionally to the blood flow in the cerebral tissue and to be retained in the brain for a sufficient time to permit image acquisition (>30 min) [4].

Initially 123I-labeled amines were used for this purpose, but these tracers reach peak brain activity as late as 20 min after injection and, additionally, show redistribution over time, resulting in reuptake into the cerebral cortex that is not proportional to rCBF [5]. Because of this, 99mTc-hexamethylpropyleneamine-oxime (99mTc-HMPAO) and 99mTc-ethyl cysteinate dimer (99mTc-ECD), which have several advantages over 123I-labeled amines, are currently the most frequently used tracers for investigating rCBF. These tracers have a quicker initial uptake in brain and reach the peak within 2 min of injection, without redistribution. Thus, the initial tracer uptake and distribution correspond to rCBF of tracer variations occurring after the fixation time. Consequently, the radiotracer can be injected into the patient outside the nuclear medicine facility, for example, during an epileptic seizure in the epilepsy ward; rCBF images reflecting the distribution at the moment of seizure can be acquired later with a SPECT camera after recovery from the seizure. The appropriate half-time (6 h) of technetium, as well as the stability of the tracer (particularly ECD), renders this technique useful and affordable for clinical routine.

The superiority of ictal SPECT compared with interictal SPECT for identification of the location or the lateralization of epileptic seizures has been demonstrated by several studies of patients with temporal lobe epilepsy (TLE), indicating sensitivities between 73 and 97% for ictal SPECT and only 50% for interictal SPECT [6–9]. Although there are fewer studies dealing with the role of SPECT in extra-TLE, data suggest lower sensitivity (66%) for ictal SPECT compared with the results found in TLE [8,10].

Cortical and subcortical rCBF changes during seizures may begin with hyperperfusion in the epileptic zone followed by rapid extension to other regions through seizure spread and generalization. However, because of its low temporal resolution, ictal SPECT hyperperfusion patterns often contain both the ictal onset zone and the propagation pathways; however, the latter region does not need to be resected to render a patient seizure free [11].

Ictal SPECT has been shown to be more accurate for localization of temporal lobe seizures when the radiotracer is injected immediately after the seizure [12], but usually, tracer injection is performed briefly after the seizure starts, and moreover, a delay must be overcome before the radiotracer gets to the brain. Therefore, ictal SPECT shows an increase in rCBF that is related to the seizure, but that also might indicate propagation from the area of ictal onset. Moreover, the so-called “postictal switch” phenomenon, which results in false localization or lateralization of the ictal seizure, can be observed when the delay between seizure onset and tracer application is too long [13].

The marksmanship of SPECT has been shown to be improved by digital analysis of ictal and interictal examinations, that is, by subtraction of ictal and interictal scans, as shown in Fig. 1, which should preferentially be co-registered to MRI (SISCOM) [14–19]. This multimodality imaging, which combines the structural and functional imaging information, improves the ability to detect and define the extent of epileptogenic lesions and to regionalize potentially epileptogenic regions in patients who have normal MRI scans. In addition, the remarkable predictive value of SISCOM with respect to surgical outcome has been described, and could be of help in the decision making for epilepsy surgery: among patients whose SISCOM findings fell within the margins of the resected tissue or in the disconnected hemisphere, 75% were rendered seizure free; among those whose SISCOM findings fell outside the margins of the surgery, 100% continued to have seizures [19].

3. Glucose metabolism with 18F-FDG

Positron emission tomography with fluorine-18 fluorodeoxyglucose ([18F]FDG), as well as other receptor ligands, is an important tool to define the ictal onset zone and to better understand the neurobiology and functional alterations induced by various forms of epilepsy.

The glucose analog [18F]FDG is an indirect marker of neuronal activity and allows absolute quantification of cerebral glucose metabolism when additional arterial (ideally) or venous blood samples are taken. Interictal [18F]FDG-PET has an established role in the noninvasive localization of epileptogenic foci and also re-

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Fig. 1. Patient with focal epilepsy in the left frontal lobe left. Ictal 99mTc-ECD SPECT scan (A) shows a discrete hyperperfusion in the left frontal lobe (red arrow), but the interictal 99mTc-ECD SPECT scan (B) reveals no significant asymmetry. The result of subtraction of the ictal and interictal scans (blue area), which is superimposed on the interictal scan (B), delineates ictal activation. In the corresponding interictal [18F]FDG-PET investigation (C), a discrete hypometabolism was observed in this area (red arrow).
flects dynamic seizure-related changes in cerebral cellular functions.

The epileptogenic focus in the interictal phase usually appears as a hypometabolic area on $^{18}$F-FDG-PET. In TLE, comparison with the contralateral side has been shown to be useful for localization of the epileptic zone. However, $^{18}$F-FDG uptake frequently extends beyond the seizure onset zone, which makes precise focus localization difficult. For example, many patients with TLE present with an additional pronounced hypometabolism of the frontal lobe, which may represent inhibitory phenomena induced by the epileptogenic focus.

Numerous studies, some of which consisted of large numbers of patients, have reported a sensitivity of 70–85% for $^{18}$F-FDG-PET in patients with TLE. In patients with extra-TLE, however, the populations investigated were smaller, and the values for diagnostic sensitivity and accuracy reported for interictal studies were significantly lower: 30–60% depending on the localization of the focus [20–25]. The highest clinical benefit of $^{18}$F-FDG-PET can be achieved in patients with suspected TLE and normal MRI findings. In this situation, PET correctly lateralizes the lesion in 80% of the cases [25].

Ictal $^{18}$F-FDG-PET cannot be routinely performed because of logistic difficulties due mainly to the short half-life of the $^{18}$F label (110 min). In addition, interpretation is difficult because of the prolonged cerebral $^{18}$F-FDG uptake, which may lead to contamination of the signal by seizure propagation [26].

4. Neuroreceptor PET

Neurotransmitters are directly responsible for modulating synaptic activity and PET also allows quantification of specific ligand–receptor relationships that seem to be important for epileptogenesis and spread of epileptic activity. Several PET receptor ligands have been used to investigate the neurochemical basis of the epilepsies and have partially entered clinical routine.

4.1. $\text{GABA}_A$ receptors: $[^{11}\text{C}]$Flumazenil

$[^{11}\text{C}]$Flumazenil binds to the central benzodiazepine receptor (cBZR)-$\gamma$-aminobutyric acid ($\text{GABA}_A$) receptor complex. Measurements of $\text{GABA}_A$ receptor density with PET and $[^{11}\text{C}]$Flumazenil have been demonstrated to be promising methods of identifying and localizing epileptogenic regions. In this context, $\text{GABA}_A$ receptor binding was significantly lower in the epileptic focus than in the contralateral homotopic reference region and the remaining neocortex [27]. Reduced binding can be seen at the epileptogenic focus and the seizure onset region, however, in a more restricted distribution than the corresponding area of $^{18}$F-FDG hypometabolism, and sometimes also in projection areas [28]. In addition, the degree of $\text{GABA}_A$ receptor reduction showed a positive correlation with seizure frequency.

Furthermore, $[^{11}\text{C}]$Flumazenil PET has been shown to distinguish patients with frequent seizures. Therefore, the method may not only be suitable for noninvasive localization of the seizure focus, but may also provide a biochemical marker of epileptogenicity, strengthening the hypothesis that inhibitory mechanisms are disturbed in the epileptic focus [29]. Moreover, $[^{11}\text{C}]$Flumazenil PET was shown to be more accurate than $^{18}$F-FDG-PET for the detection of cortical regions of seizure onset and frequent spiking in patients with extra-TLE, whereas both $^{18}$F-FDG and $[^{11}\text{C}]$Flumazenil PET showed low sensitivity in the detection of cortical areas of rapid seizure spread [30]. Even if $[^{11}\text{C}]$Flumazenil PET did not prove superior to $^{18}$F-FDG-PET in assessing the extent of the ictal onset zone, as defined by intracranial EEG recordings, some authors stated that it may provide useful data complementary to those of MRI and $^{18}$F-FDG PET [24], as shown in Fig. 2. However, the use of

![Fig. 2. $^{[18]F}$FDG (A: coronal, B: transversal) and $^{[18]F}$ethylflumazenil (C: coronal, D: transversal) PET scans of a patient with right TLE showing relatively decreased glucose metabolism and reduced binding to the cBZR-$\text{GABA}_A$ receptor complex in the mesial temporal lobe (red arrows).](image-url)
interictal \([11C]\)flumazenil PET in patients with idiopathic generalized epilepsy has yielded nonuniform results: thus, a slight reduction in the neocortex of patients with idiopathic generalized epilepsy has been reported in comparison with patients with partial seizures [31]; in another study, the authors reported a widespread increase in benzodiazepine receptors in cerebral neocortex, thalamus, and cerebellar cortex [32]. Also observed was increased benzodiazepine receptor density in the cerebellar nuclei and decreased density in the thalamus [33].

In unilateral hippocampal sclerosis, reduction of binding of \([11C]\)flumazenil has been shown to be confined to the hippocampus and to be over and above that caused by neuron loss and hippocampal atrophy [34]. In malformations of cortical development, abnormalities of benzodiazepine receptors, as demonstrated with \([11C]\)flumazenil PET, were more extensive than the structural abnormality revealed with MRI [35]. There often were areas of increased benzodiazepine receptors, a pattern that may reflect both functional and structural anomalies [36].

Currently, the clinical role of \([11C]\)flumazenil and its SPECT derivative \([123I]\)iomazenil for the detection of temporal and extra-temporal foci is viewed controversially in the literature [37,38]. Even though \([11C]\)flumazenil binding has revealed focal abnormalities in 80% of patients with refractory TLE and normal high-quality MRI [38], this method has not been considered consistently helpful in localizing epileptic foci. In addition, the short half-time of \([11C]\)flumazenil (20 min) hampers the wide use of \([11C]\)flumazenil for clinical routine. The possible implementation of \([18F]\)flumazenil in clinical routine will most probably provide a more definite answer about the clinical benefit of benzodiazepine receptor imaging [39]. This radiopharmaceutical has ideal properties for PET imaging and will allow with state-of-the-art equipment to image benzodiazepine-GABA\(_{A}\) receptor binding with a spatial resolution of approximately 3 mm [40].

4.2. Serotonin receptors (5-HT\(_{1A}\)) \([18F]\)MPPF

Experimental data in animals indicate that 5-HT\(_{1A}\) receptors are located predominantly in limbic areas and that serotonin, via these receptors, mediates an antiepileptic and anticonvulsant effect. \([18F]\)MPPF (2-methoxyphenyl-(N-2-pyridinyl)-p-[18F]fluoro-benzamidoethylpiperazine), an antagonist of the 5-HT\(_{1A}\) receptors, was used to assess the extent of 5-HT\(_{1A}\) receptor binding changes in patients with TLE and hippocampal ictal onset. A significantly decreased binding potential (BP\(_{\text{ND}}\)) was detected ipsilateral to the epileptogenic zone in the hippocampus, temporal pole, insula, and temporal neocortex. In patients with normal hippocampus volume, the BP decrease was restricted to the temporal pole [41]. The decrease was more pronounced in the seizure onset zone and in regions where the discharge propagated than in regions where only interictal paroxysms or no epileptic activity was recorded [42]. Therefore, these results indicate that \([18F]\)MPPF binding not only reflects structural changes or neuronal loss, but can also be considered a marker of the epileptogenic zone.

The reduction in 5-HT\(_{1A}\), BP\(_{\text{ND}}\) in patients with mesial TLE may be explained, on the one hand, by a decrease in receptor density due to depletion of serotonin, which leads to downregulation and hyperexcitability, or, on the other hand, by an increase in endogenous serotonin as a reational process to modulate hyperexcitability.

A recent study showed that, in individual patients with TLE, visual analysis of \([18F]\)MPPF PET data, blinded to clinical information and data from other presurgical investigations, permits identification of the epileptogenic lobe with a sensitivity of 90% (38 of 42 patients), even in those without hippocampal sclerosis, and proved usable in clinical practice for preoperative evaluation of patients with TLE [43]. Comparison between \([18F]\)FDG and \([18F]\)MPPF PET data showed the clear-cut superiority of the latter for localizing visually the epileptogenic area in patients with mesial TLE. The specificity of \([18F]\)FDG PET was lower than that of \([18F]\)MPPF PET, with only 23% of patients showing hypometabolism restricted to hippocampus, amygdala, and temporal pole, versus 38% demonstrating such abnormalities with \([18F]\)MPPF PET [43].

4.3. Opioid receptors

PET studies using opioid receptor ligands with different selectivity support findings from animal experiments suggesting a predominantly anticonvulsant effect of opioid peptides (for review see Henriksen et al. [44]). The earliest human PET study indicating selective modulation of the opioid system in partial epilepsy was that of Frost et al. [45], who demonstrated, with the \(\mu\)-selective ligand \([11C]\)carfentanil, increased \(\mu\)-opioid receptor availability in the areas of the epileptogenic temporal lobe exhibiting interictal hypometabolism. In contrast to this finding no comparable asymmetry was detectable with the nonspecific opioid receptor ligand \([11C]\)diprenorphine and the \(\mu\) - and \(\kappa\)-selective ligand \([18F]\)cyclofenil [46–48]. A study with the \(\delta\)-selective opioid receptor ligand \([18F]\)methylatirindole also showed increased receptor availability in the epileptogenic temporal lobe, but with a different regional pattern [49]. The in vivo demonstration in humans of selective regional alterations of \(\mu\) - and \(\kappa\)-receptor binding in TLE supports the hypothesis derived from animal studies that endogenous ligand binding to these receptor subtypes plays a role in the tonic anticonvulsive mechanism that limits the spread of seizure activity from the epileptogenic focus [44].

The in vivo demonstration of a generalized displacement of opioid receptor ligands during absence seizures [50] and a focal displacement during seizures of reading epilepsy [51] provides strong support for the prevailing opinion that endogenous opioids are released following generalized and partial seizures [52]. Results of a study with \([13C]\)diprenorphine by Hammers et al. [53] suggest a role for the opioid system in the postictal rise in seizure threshold. This study demonstrated a postictal increase in \([11C]\)diprenorphine binding. The authors of the study suggested that synaptic opioid levels increase at the time of seizures, leading to a reduction in \([11C]\)diprenorphine binding, and that this is followed by a gradual recovery of available surface receptors with an overshoot over basal levels, which is detected by PET about 8 h after seizures, and a gradual return to normal or low-normal levels during the interictal phase.

4.4. Dopamine receptors: \([18F]\)Fallypride

The role of dopamine in the pathophysiology of focal epilepsy is a matter of controversy. The dopaminergic influence on epileptic seizures arising from mesial temporal structures [54] might be inhibitory (i.e., via dopaminergic hippocampal projections enhancing Ca\(^{2+}\)-dependent K conductance) [55]. Data obtained in animals suggest that activation of the dopaminergic D1- and D2-receptors has diverging effects on the regulation of seizure threshold, D2 being anticonvulsant and D1 activation more proconvulsant [54,56]. Further studies in animals suggest a neuroprotective role of dopamine through the inhibitory control of glutamate neurotransmission and excitotoxicity in epilepsy [57].

The high-affinity dopamine D2/D3-receptor antagonist \([18F]\)Fallypride can be used to characterize striatal as well as extrastriatal D2/D3-receptor binding. In patients with mesial TLE and hippocampal sclerosis, D2/D3-receptor binding was reduced at the pole and the lateral aspects of the epileptogenic temporal lobe, but there was no change in hippocampal binding although all patients had hippocampal atrophy. This selective decrease in \(D_2/D_3\) receptor binding in the pole and lateral temporal lobe, which show hypometabolism on
[18F]FDG-PET, is an indication of a modulation of the dopaminergic system in “the irritative zone,” indicating that the dopaminergic system might also be part of the endogenous anticonvulsant mechanism that prevents seizure generalization [58].

In conclusion, SPECT and PET are useful and reliable tools for imaging epilepsies in clinical routine as well as for research purposes. Their unique ability to image in vivo changes in brain biochemistry has provided valuable insights into the mechanisms of epileptogenesis, seizure propagation, and termination. Progress in the sensitivity and spatial resolution achieved by modern instrumentation will probably further increase the clinical role of functional imaging in the preoperative assessment of patients with epilepsy.

References


