Nuclear Medicine Imaging in Epilepsy

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Summary

Nuclear medicine imaging techniques play a relevant role in the investigation of pharmacoresistant epileptic patients, providing in vivo measures of perfusion changes, metabolic changes and neurotransmission abnormalities. This information helps identifying the ictal zone non-invasively in order to accurately plan more invasive procedures and ultimately surgery. In particular, ictal SPECT is the only technique showing the perfusion changes occurring during the epileptic event, while PET imaging in interictal state allows the evaluation of molecular aspects, such as glucose metabolism and various neurotransmission systems, thanks to the binding of different radioligands on specific targets and receptors. Technological developments, in particular the availability of new hybrid tomographs allowing PET and MRI imaging in a single session, will broaden our knowledge of the changes occurring in epilepsy through multiparametric investigations.

This review will update on the state-of-the-art nuclear medicine imaging modalities in the presurgical evaluation of epilepsy and will discuss the potential role played by the newly available hybrid PET/MRI imaging in this field.

Epileptologie 2013; 30: 109 – 121

Key words: Epilepsy, PET, SPECT, PET/MRI, radiotracers, neurotransmission

Imagerie par médicine nucléaire et épilepsie

Les techniques d'imagerie par méthodes de médecine nucléaire jouent un rôle important dans l'investigation des patients avec une épilepsie pharmaco-résistante, grâce à l'évaluation in vivo des modifications de perfusion cérébrale, de métabolisme cérébrale et des anomalies de neurotransmission. Ces informations permettent de guider l'identification non invasive de la zone de début ictal, pour planifier des investigations plus invasives et l'intervention chirurgicale. En particulier, l'imagerie SPECT ictale est la seule méthode d'imagerie qui permet de visualiser les modifications de perfusion qui se produisent au moment de la crise épileptique, alors que l'imagerie PET en phase interictale permet d'évaluer des aspects moléculaires tels que le métabolisme cérébral et différentes voies de neurotransmission. Les progrès technologiques récents, en particulier le développement de tomographes hybrides permettant de réaliser le PET et l'MRI lors d'une seule session d'imagerie, permettra d'approfondir notre connaissance des modifications et mécanismes moléculaires à la base des épilepsies grâce à des investigations multiparamétriques.

Cette revue résume les modalités de médecine nucléaire couramment utilisées dans l'évaluation préchirurgicale des épilepsies et débat du rôle potentiel de la nouvelle technologie hybride PET/MRI dans ce domaine.

Mots clés : Epilepsie, PET, SPECT, PET/MRI, radiotraceurs, neurotransmission

Nuklearmedizinische Bildgebung in der Epilepsie

Nuklearmedizinische Methoden spielen eine wichtige Rolle bei der Untersuchung von Patienten mit pharmakoresistenten Epilepsien. Die Methoden messen Perfusionsveränderungen, metabolische Veränderungen und Anomalien der Neurotransmitter. Die so gewonnenen Informationen erlauben, die iktale Zone nichtinvasiv zu identifizieren, um invasive Prozeduren und chirurgische Therapien zu planen. Das iktale SPECT ist die einzige Technik, die Perfusionsveränderungen während des epileptischen Anfalls messen kann, während PET in der interiktalen Phase die Auswertung der molekularen Aspekte, wie beispielsweise Glukose-Metabolismus und verschiedene Neurotransmitter-Systeme, mithilfe spezifischer Radioliganden ermöglicht. Weitere technologische Entwicklungen, insbesondere die Verfügbarkeit der neuen Hybrid-Bildgebung PET/MRI, die PET- und MRI-Bildgebung in einer einzigen Sitzung liefert, werden unser Wissen über die funktio-

nellen Veränderungen in der Epilepsie vertiefen, insbesondere durch multiparametrische Untersuchungen.

Der vorliegende Überblick fasst State-of-the-art der nuklearmedizinischen Bildgebung in der prächirurgischen Evaluierung der Epilepsie zusammen und diskutiert die mögliche Rolle der neuen PET-MRI-Hybrid-Systeme.

Schlüsselwörter: Epilepsie, PET, SPECT, PET/MRI, Radiotracer, Neurotransmission

Introduction

Two nuclear medicine imaging techniques are currently applied in clinical practice for the investigation of pharmacoresistant epileptic patients: Single Photon Emission Computed Tomography (SPECT) studies of brain perfusion in ictal and interictal state and Positron Emission Tomography (PET) studies of glucose metabolism in interictal state. In addition, molecular imaging by PET may allow measuring various neurotransmission systems, for example the GABAergic, serotonergic, cholinergic and opiate receptor systems, among others: these investigations are still mainly performed in dedicated research centers. Finally, technological developments, in particular the design of hybrid tomographs acquiring both PET and Magnetic Resonance Imaging (MRI) in a single session, called PET/MRI hybrid systems, are currently available and will presumably play a relevant role in the investigation of epileptic patients.

1. SPECT Perfusion Studies in Ictal and Interictal State

The clinical observation that during a seizure there is an increase in cortical blood flow was initially directly observed during brain surgery by Sir Victor Horsley, more than a century ago [1].

SPECT imaging uses perfusion tracers, such as [^{99m}Tc]-HMPAO and [^{99m}Tc]-ECD, which cross the blood brain barrier freely and without significant redistribution. Once injected, the tracer distributes rapidly, over a few minutes, and then this distribution is stable over a long time (up to four or five hours). Thus, the images subsequently acquired reflect the perfusion state at the time of injection, providing a "picture" of ictal perfusion even a few hours after the seizure. The characteristics of these ^{99m}Tc-labelled tracers (low redistribution and 6 hours half-life) give the flexibility to stabilize and transfer the patient to the SPECT unit for imaging conveniently after the injection.

To be able to realize ictal imaging, the patient must be under continuous EEG monitoring and the tracer must be readily available at bedside. The unit must be designed in a way that a trained nurse or technologist is immediately available for performing a bolus injection at the first signs (electrophysiological or clinical) of seizure onset. The availability of automated injection systems represents an additional advantage.

The ictal SPECT imaging, depending on the time delay between seizure onset and tracer administration, reflects the hyperactivity at the ictal onset zone and at the propagation areas [2].

Timing of the injection is thus a crucial issue, critically determining the clinical information that can be obtained with the ictal SPECT imaging. Indeed, the perfusion pattern rapidly evolves after the ictal onset. In temporal lobe epilepsy, the initial ictal hyperperfusion of the seizure onset zone and of the propagation areas is rapidly followed by a hypoperfusion of the same areas, presumably due to autoregulatory mechanisms limiting excitotoxic damage [3]. In extratemporal neocortical epilepsy, different patterns have been observed, including or surrounding the ictal onset zone, depending on the delay of the injection and on the crisis duration [4]. The sensitivity of the ictal SPECT analysis is significantly lower when the injection is performed more than 20 seconds after the onset [5, 6].

Interictal imaging is routinely performed in order to provide a baseline comparison for ictal changes, and indeed increases sensitivity and specificity of SPECT findings. Importantly, the imaging protocols should be identical in both conditions, as well as image display for visual interpretation, in order to ensure comparability [2].

In addition to visual image interpretation, computer-assisted analysis has an important and validated role for detecting changes in brain perfusion, with a proven gain in sensitivity [5, 7, 8]. Ictal and interictal imaging can be compared by normalizing counts in each image to the activity in a given region or to the global activity. Subsequently, the two scans are spatially registered, preferably using also an MRI scan, providing as result a subtraction parametric image of significant deviation between ictal and interictal SPECT. This function is implemented in various software packages: among these, the Subtraction Ictal SPECT CO-registered to MRI (SISCOM) [9] and the HERMES BRASS software suite (www.hermesmedical.com). An example of ictal and interictal images and the result of digital image subtraction is shown in **Figure 1**.

In our institution, ictal SPECT identified correctly the epileptic zone in 75% temporal lobe epilepsy and in 58% of extra-temporal cases [10]. Ictal SPECT is overall most useful in patients with focal epilepsy and normal MRI, or in cases where MRI shows multiple abnormalities: in the latter, ictal SPECT might be able to identify the epileptogenic lesion.

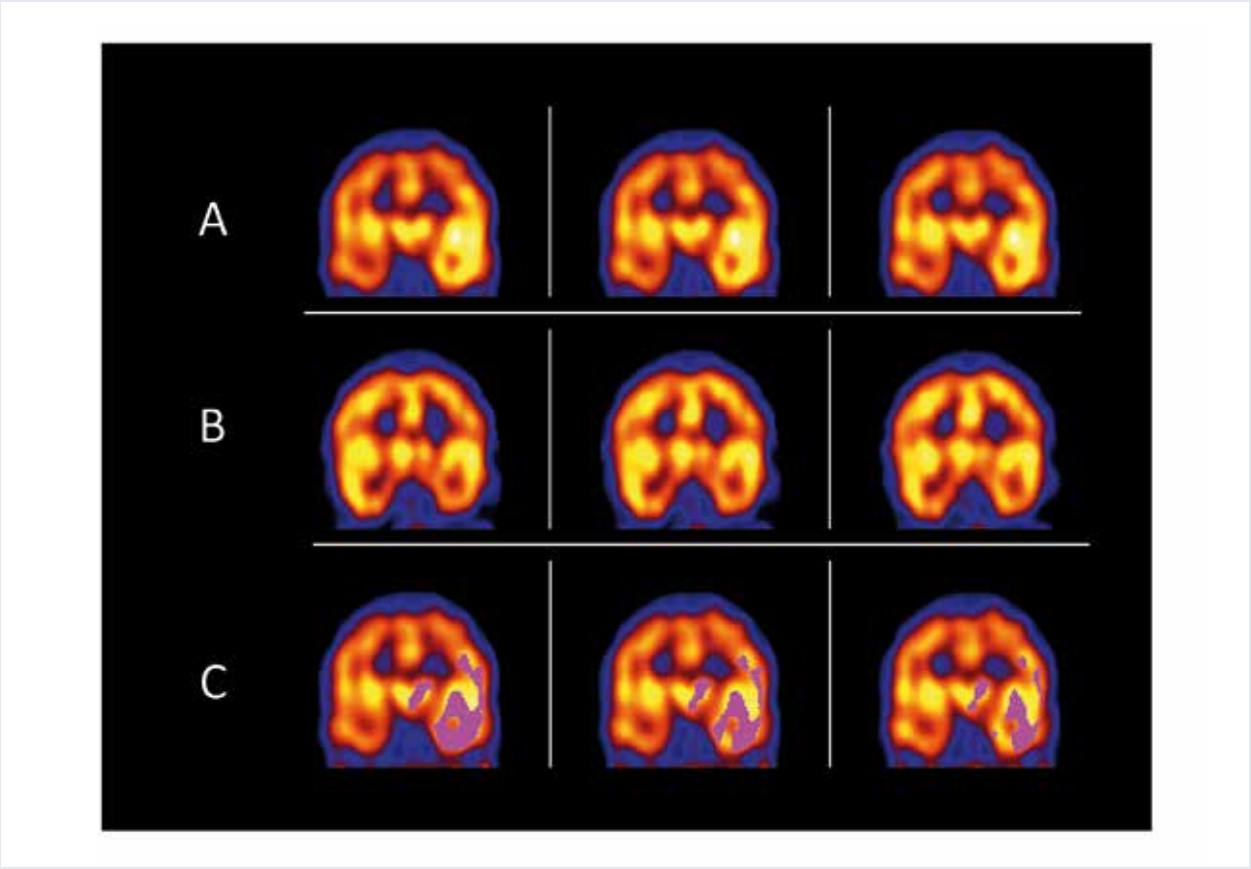

Figure 1: Ictal (A) and interictal (B) perfusion in a patient with left amygdalo-hippocampal dysplasia. In line C the areas significantly hyperperfused in ictal state, obtained by digital subtraction using the HERMES BRASS software suite, are shown (pink overlay on ictal image).

2. FDG PET Imaging in Epilepsy

PET has been the first functional neuroimaging technique applied to presurgical evaluation of pharmacoresistant focal epilepsies, in the late seventies, before MRI was available. It used the [^{18}F]-Fluorodeoxyglucose (FDG) to obtain images of interictal brain glucose metabolism. It was particularly useful in patients with a normal brain CT scan, showing a focal interictal glucose hypometabolism. FDG PET remains today a routinely used examination in the presurgical assessment of drug refractory focal epilepsies [11]. Focal interictal hypometabolism on FDG PET is usually associated with seizure foci, but hypometabolism is typically larger than the epileptogenic cortex, reflecting the altered neuronal function in the ictal focus and possibly extending to the areas of first ictal spread [12]. An example of a large hypometabolic area extending to the whole temporal pole in a patient with amygdalo-hippocampal dysplasia is provided in **Figure 2**. The mechanism explaining the hypometabolism in ictal areas is still mostly unknown: various hypotheses have evoked a protective inhibitory effect induced by repeated seizures on the brain or the underlying dysfunctional cortex (dysplasic areas, tubers, etc) [13]. Hypometabolism is usually less frequent in children with new onset seizures [14]. It is well known that FDG PET distribution reflects mainly synaptic density and activity, therefore hypometabolism presumably reflects mainly synaptic changes rather than cell loss [15].

Given the spatial resolution of PET imaging, ranging between 4 and 8 millimeters depending on the tomograph characteristics and settings, and the fact that FDG PET changes are larger than the actual ictal onset zone, the definition of surgical borders cannot be solely based on PET imaging.

Rather, PET results can help lateralizing and localizing the focus in cases of non-lesional epilepsy, in cases with multiple lesions visible on MRI and can guide intracranial electrode placement [16]. FDG PET has overall an established role in the presurgical evaluation of various types of epilepsy, for diagnostic and prognostic evaluation [17 - 19].

In current clinical practice, FDG PET is usually acquired on PET/CT scanners, although recent developments suggest that the newly available PET/MRI hybrid modality might play a relevant role (see Section 4).

FDG PET images are primarily analyzed visually, with the support of semiquantitative analyses, such as asymmetry indices. Asymmetry is usually rated as significant when a difference above 15% exists between the affected and contralateral sides, given that small

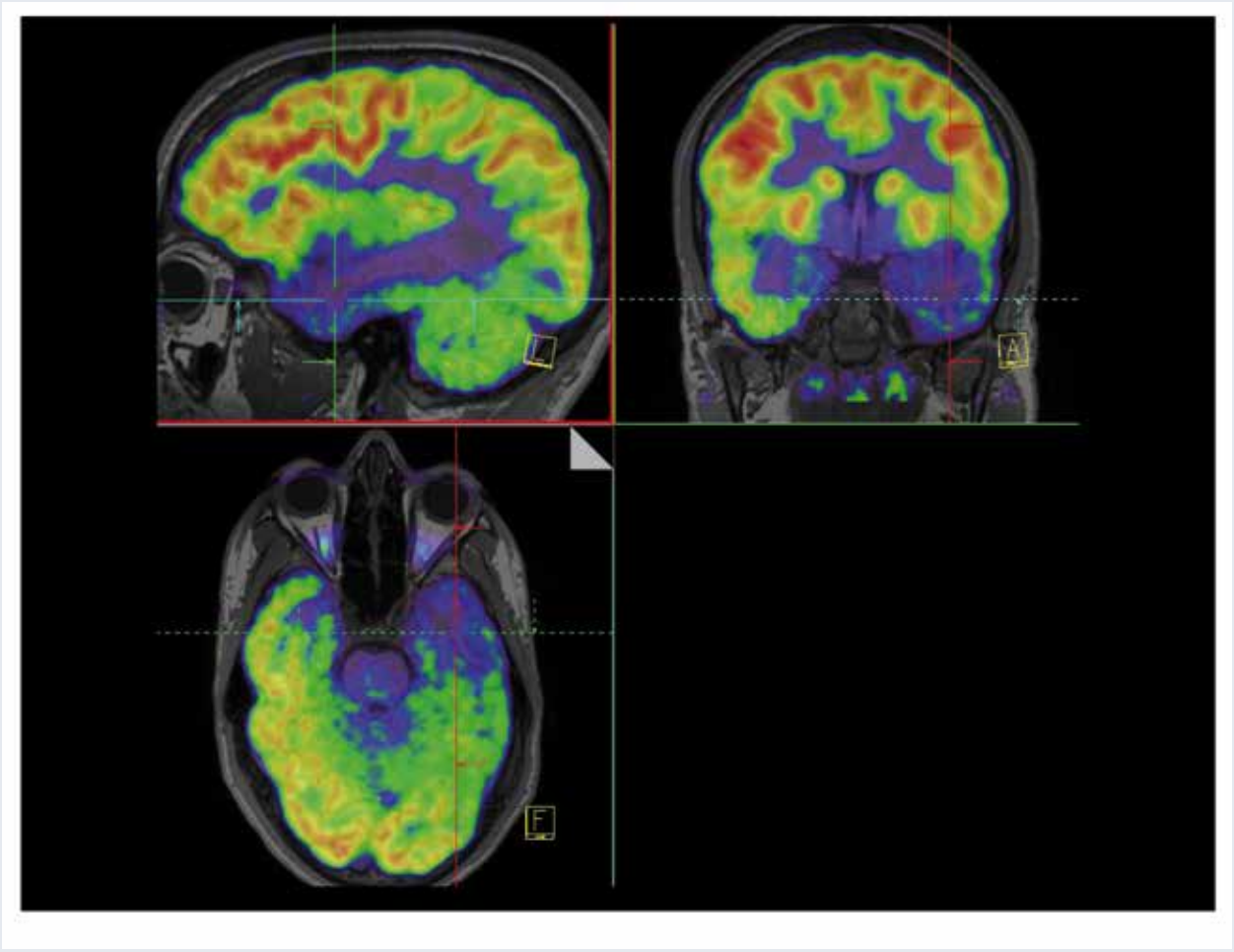

Figure 2: Large left temporopolar hypometabolism in a patient with amygdalo-hippocampal dysplasia (same patient as in Figure 1).

physiological asymmetries can exist [20]. Another tool that is particularly relevant for PET image interpretation is the systematic adoption of software fusion of PET and MRI datasets. There is evidence suggesting that the systematic association of PET and MRI imaging can be recommended for a complete evaluation of epilepsy: previous reports consistently demonstrated the added value of software fusion of PET and MRI data for the pre-surgical evaluation of cortical dysplasia [21, 22]. The image fusion not only allows a more precise localization of hypometabolic areas but also allows identifying small areas of hypometabolic cortex that could be overseen when reading the PET images alone. An additional advantage of a systematic fusion with MRI would be the adoption of strategies for the correction of the partial volume effect on PET images, based on MRI segmentation, that can offer a superior sensitivity for identifying small abnormalities [23].

Overall, in our institution experience FDG PET correctly identified the ictal focus in 69% of patients with temporal lobe epilepsy and in 75% in extratemporal epilepsies [10].

3. Research PET Tracers

PET imaging also allows measuring neurotransmission abnormalities underlying neuronal hyperexcitability. This is of particular importance in the context of presurgical assessment of pharmacoresistant focal epilepsies, or in order to improve our understanding of the pathophysiological mechanisms of epilepsy. This requires radioactively labelled tracers which are either ligands of specific receptors or neurotransmitter precursors or transporters. Thus, one of the most promising applications of PET in the epilepsy study consists in imaging the distribution of these molecular targets in the interictal state.

Various PET tracers are available for neurotransmitter and neuromodulator systems, including the GABA, serotonin, dopamine, glutamate, acetylcholine, adenosine and opioid systems. These tracers are currently used in research centers and are not yet part of the clinical routine investigations.

3.1 GABA system

The selective antagonist of $GABA_A$ receptors, [^{11}C]-flumazenil, has been the first PET receptor ligand which was used in epilepsy. A localized reduction of [^{11}C]-flumazenil binding, closely correlating with the side and site of seizure onset, is usually observed in patients with refractory focal seizures. This reduced binding is thought to largely reflect an underlying neuronal loss, as demonstrated in temporal lobe epilepsy associated with mesial temporal sclerosis (review in [24, 25]). In a study of 20 patients with intractable partial epilepsy of neocortical origin and non-localizing MRI, focal decrease of cortical FMZ binding was detected in the lobe of seizure onset in 85% of the patients [26]. Decreased FMZ binding was also observed in remote cortical areas outside the lobe of seizure onset in 55% of the patients. The authors concluded that these regions are commonly involved in rapid seizure propagation and that although these regions may not always need to be resected to achieve seizure freedom, a careful evaluation of cortex with decreased $GABA_A$ receptor binding prior to resection using intracranial EEG may facilitate optimal surgical outcome in patients with intractable neocortical epilepsy [26].

3.2 Serotonin system

The serotonin system originates from the raphe nuclei, with diffuse projections to the whole central nervous system. According to studies in experimental models of epilepsy, serotonin (5-HT) has an inhibitory role on epileptiform discharges [27, 28]. Specifically, antiepileptic and anticonvulsant properties of 5-HT_{1A} receptor activation has been shown in rodents [29]. This anti-epileptic effect can be blocked by the highly selective 5-HT_{1A} antagonist WAY-100635 [30]. An additional observation supporting the potential role played by serotonergic transmission is that the epileptogenic tissue of patients with cortical dysplasia has enhanced serotonergic innervation [31].

3.2.1 α[^{11}C]*methyl-L-tryptophan (AMT)*

Serotonin is synthesized from the neutral amino acid L-tryptophan. α[^{11}C]methyl-L-tryptophan (AMT) is a tracer for measuring the rate of serotonin synthesis. One of the main advantages of using PET with AMT for imaging in epilepsy is that it shows increased (rather than decreased) uptake in epileptic foci.

AMT PET has a unique ability to successfully identify the epileptogenic tuber(s) in patients with tuberous sclerosis and intractable epilepsy [32 - 35]. It shows locally increased uptake of AMT in and around the epileptogenic tuber, while it shows normal or decreased uptake in non-epileptogenic tubers [34]. The sensitivity of AMT PET in finding the epileptogenic focus is about 70%, but its specificity is almost 100%, indicating that if AMT PET identifies an area of increased uptake, it likely represents the epileptic focus which needs to be resected for better surgical outcome [36]. In a study of 17 children who underwent resective epilepsy surgery following AMT PET, the tuber with the highest uptake was located in an ictal EEG onset region in each patient [36]. Tubers with at least 10% increase of AMT uptake proved to be epileptogenic based on intracranial EEG and outcome criteria. The different studies demonstrated that resection of tubers with increased AMT uptake is essential to achieve seizure-free surgical outcome in these patients.

Increased AMT uptake is also well recognized in cortical developmental malformations. The uptake is higher in patients with histologically proven cortical dysplasia compared to those with nonspecific pathological changes (i.e. gliosis) and may predict type IIB dysplasia (with balloon cells) and good surgical outcome [37]. This correlates with previous human epileptic tissue studies showing serotonergic hyperinnervation in dysplastic tissues [31]. Histopathologic similarities between cortical dysplasia type IIB and epileptogenic cortical tubers may imply a common role of the inflammatory kynurenine pathway of tryptophan metabolism in these lesions [37].

In patients with intractable epilepsy and cortical dysplasia, the increased uptake of AMT was shown to be highly co-localized to the area of neocortical seizure onset defined on electrocorticography. Remote cortex involved in seizure propagation does not appear to show increased uptake on AMT PET images. In contrast, the regions of reduced metabolism on FDG PET are widespread and might be less specific. Increased AMT uptake was also found in a very high proportion of epileptogenic brain tumors, including low-grade gliomas and dysembryoplastic neuroepithelial tumors, but it is not always related to epileptogenicity as it has been observed in some gliomas not associated with seizures [38].

AMT PET has a lower sensitivity for the lateralization and localization of epileptic foci in patients with cryptogenic focal epilepsy. However increased focal uptake of AMT may be observed in a proportion of patients with no detectable lesion on MRI and can be a valuable addition to current methods of investigation [39]. One study showed that AMT PET might be useful for lateralizing the epileptic focus in patients with temporal lobe epilepsy (TLE) and normal hippocampal volumes: an increased AMT uptake was reported in the hippocampus ipsilateral to the seizure focus in a group of seven TLE patients with normal hippocampal volumes [40]. However other larger studies are needed to further substantiate the clinical use of AMT PET in evaluation of patients with suspected TLE and no hippocampal sclerosis. Lastly, AMT PET was shown to be a useful imaging approach for identification of non-resected epileptic

cortex in patients with a previously failed neocortical epilepsy surgery [41]. It is proposed to wait at least 2 months after surgery before scanning the patients.

In conclusion AMT is a useful tracer in the presurgical evaluation of patients with epilepsy and displays a particularly high specificity for the dysplastic lesions of tuberous sclerosis or cortical dysplasia.

3.2.2. Ligands of 5-HT$_{1A}$ receptors

The 5-HT$_{1A}$ receptors constitute the best characterized subtype of currently known 5-HT receptors.

3.2.2.1. [^{11}C]-WAY-100635 and [^{18}F]-FCWAY

[^{11}C]-WAY is an antagonist ligand of 5-HT$_{1A}$ receptors. It is very specific with a much higher affinity than endogenous serotonin for 5-HT$_{1A}$ receptors (Kd in the range of 20 pmol), so [^{11}C]-WAY does not interact with serotonin.

PET using [^{11}C]-WAY-100635 was performed in patients with severe mesial TLE (MTLE) to test the hypothesis that in MTLE there is involvement of serotonin systems outside of mesial structures [42]. Fourteen patients and 14 controls were studied. The 5-HT$_{1A}$ receptor binding potential was calculated for hippocampus, amygdala, orbitofrontal, insular, lateral temporal, anterior cingulate cortex, raphe nuclei, and in two regions presumably uninvolved in the epileptogenic process (parietal, and dorsolateral frontal neocortex). The 5-HT$_{1A}$ binding was significantly reduced in the epileptogenic hippocampus and amygdala ($p = 0.0001$) in all patients, including the six with normal FDG PET and MRI. It was also reduced in the anterior cingulate, insular, and lateral temporal cortex ipsilaterally to the focus, in contralateral hippocampus, and in the raphe nuclei. The authors concluded that there is reduced 5-HT$_{1A}$ receptor binding potential in the EEG focus and its limbic connections and that the affective symptoms in MTLE may result from reductions in 5-HT$_{1A}$ binding in the insular and cingulate cortex. [^{11}C]-WAY-100635 PET was considered to provide additional information to EEG, FDG PET, and MRI when evaluating pharmacoresistant patients.

[^{18}F]-FCWAY presents an affinity for 5-HT$_{1A}$ receptors comparable to that of the original WAY-100635 labeled with ^{11}C. A PET study with [^{18}F]-FCWAY showed decreased temporal 5-HT$_{1A}$ binding ipsilateral to seizure foci in patients with TLE [43]. A complementary study demonstrated that decreased 5-HT$_{1A}$ binding in insula and mesial temporal structures ipsilateral to temporal lobe epileptic foci is not an artifact related to partial volume effect because of the mesial temporal sclerosis and structural atrophy [44]. These studies suggest that the receptor loss may be part of the initial phase of neuronal dysfunction in TLE, followed by hypometabolism and eventual structural atrophy. The decrease in 5-HT$_{1A}$ binding exceeded both FDG hypometabolism and hippocampal atrophy, and could be detected in mesial temporal regions in patients with normal MRI. Thus [^{18}F]-FCWAY PET might be particularly useful for early detection of functional abnormalities in TLE patients. Other recent studies confirmed the additional value of the [^{18}F]-FCWAY PET examination to FDG PET for epileptic focus detection and temporal lobectomy planning, particularly in MRI-negative TLE [45, 46]. One of these studies suggested that reduced left hippocampal receptor 5-HT$_{1A}$ receptor binding may play a role in memory impairment in patients suffering from TLE [47].

PET using [^{11}C]-WAY-100635 was also performed in 12 patients with juvenile myoclonic epilepsy (Savic, personal communication, "The new and very new PET tracers in epilepsy", Satellite symposium to the 26th IEC, Orsay, Paris, 2005). There was a 25% reduction of 5-HT$_{1A}$ binding in the dorsolateral prefrontal cortex. It is worth to note that the same patients were investigated with MR spectroscopy showing reduction in N-acetylaspartate in the dorsolateral prefrontal cortex, concordant at MRI spectroscopy with a reduction in N-acetylaspartate in the same area, and also had impaired working memory. In addition, an unexpected finding was a bilateral reduction of [^{11}C]-WAY-100635 binding in the hippocampus, despite normal hippocampal volumes. The authors suggested that 5-HT$_{1A}$ receptor binding could be a useful approach in future to detect potential hippocampal changes which are not visible on MRI in neocortical epilepsies, generalized epilepsies or in psychiatric disorders.

3.2.2.2. [^{18}F]-MPPF

MPPF is another selective antagonist of 5-HT$_{1A}$ receptors. It has an affinity close to that of endogenous serotonin for 5-HT$_{1A}$ receptors and is thus sensitive to endogenous serotonin variations. Thus a decrease of [^{18}F]-MPPF binding can be interpreted as reflecting either a decrease in receptor density or an increase in endogenous serotonin, resulting in a competition for receptor binding by the radioligand.

PET studies with [^{18}F]-MPPF carried out in a group of TLE patients with hippocampal ictal onset showed significant decreases ipsilateral to the epileptogenic zone in the hippocampus, temporal pole, insula and temporal neocortex [48, 49]. A large study of 42 TLE patients showed that a decreased binding in hippocampus, amygdala and temporal pole (example in **Figure 3**) indicated good candidates for anterior temporal lobectomy, as all these patients became seizure-free after surgery, even when the clinical presentation was not that of a typical mesiotemporal lobe epilepsy or when there was no hippocampal atrophy [50]. The interpretation that the decrease in 5-HT$_{1A}$ receptor binding in epileptic

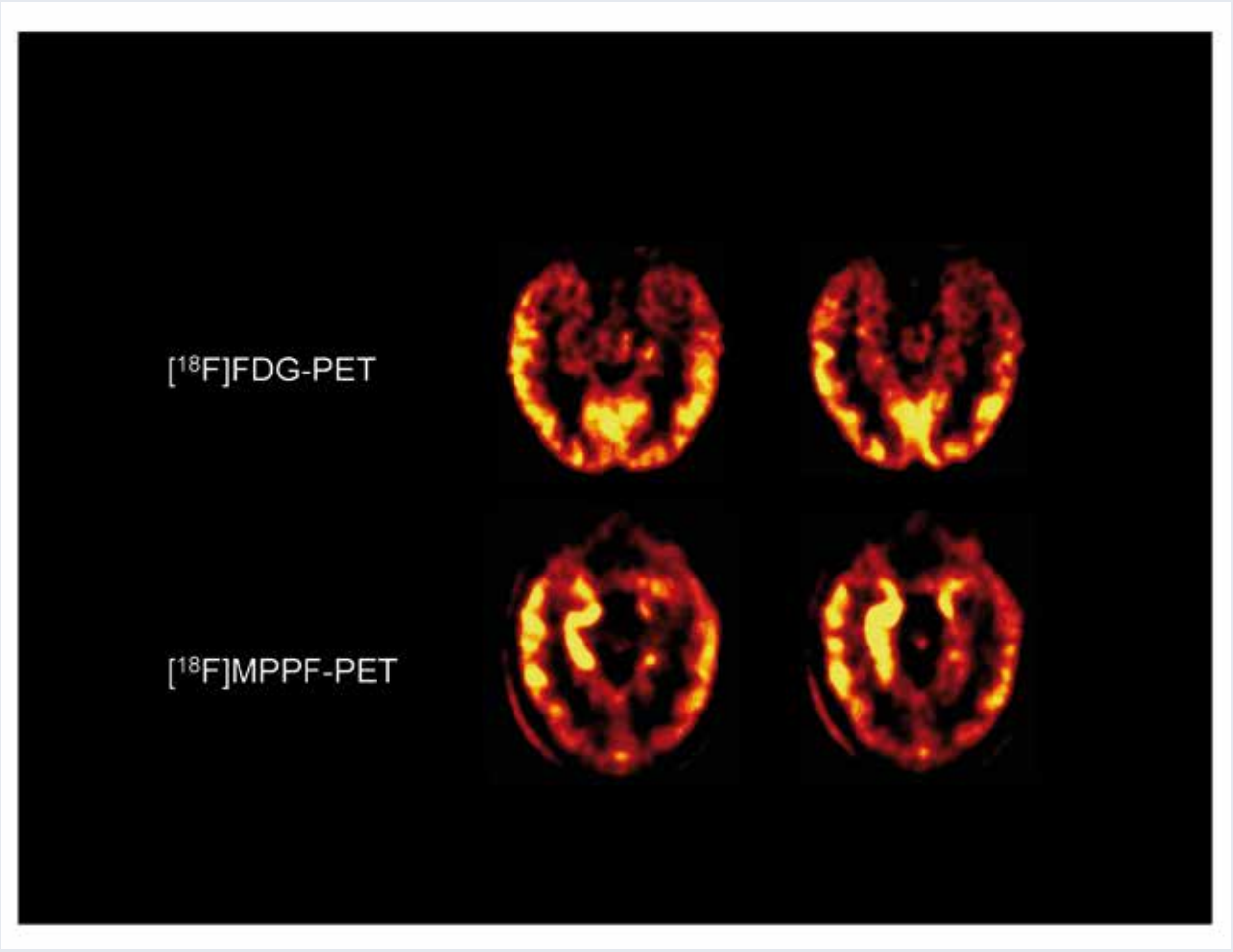

Figure 3: [^{18}F]-FDG PET and [^{18}F]-MPPF PET in a patient with a temporo-limbic epilepsy and normal MRI: the images show a slight decrease in FDG uptake and a clear and severe MPPF binding reduction located within the left temporal region. (Courtesy of Prof. P. Ryvlin)

patients could reflect the loss of neurons in the hippocampus was challenged by the report in epileptic foci of an increase in P-glycoprotein, an ATP-driven transmembrane efflux pump, known to strongly regulate the penetration of [^{18}F]-MPPF in the brain [51]. The binding of [^{18}F]-MPPF might be modified by extracellular serotonin levels, internalization of 5-HT_{1A} receptors and the expression of P-glycoprotein.

3.3 Dopamine system

Studies in animal models and epileptic patients have suggested that circuits of the basal ganglia may control epileptic seizures and that striatal dopaminergic transmission plays a key role in seizure interruption [52]. Moreover there is evidence from clinical experience that antagonizing D2 receptors lower seizure threshold.

3.3.1. [^{18}F]-fluoro-L-DOPA

[^{18}F]-fluoro-L-DOPA is a radiotracer that permits measurements of presynaptic dopaminergic function. A [^{18}F]-fluoro-L-DOPA PET study was performed in patients with a ring chromosome 20 suffering from epilepsy. Their epilepsy is characterized by long-lasting seizures suggesting a dysfunction in the seizure control system. [^{18}F]-fluoro-L-DOPA PET showed a significantly decreased uptake in both putamen and caudate nucleus, suggesting that a dysfunction of the striatal dopamine neurotransmission may impair the mechanisms that interrupt seizures [53].

Patients with generalized seizures and patients with focal seizures related to hippocampal sclerosis were also studied [54]. There was a decreased [^{18}F]-fluoro-L-DOPA uptake, particularly in the substantia nigra bilaterally, in all patients. The uptake was also decreased in the putamen, bilaterally, in patients with generalized seizures and unilaterally, ipsilateral to the hippocampal sclerosis, in patients with focal seizures.

3.3.2. [^{18}F]-Fallypride

[^{18}F]-Fallypride is a highly selective, high-affinity, dopamine D_2/D_3-receptor ligand suitable for measuring D_2/D_3 receptor availability in the extrastriatal regions of the brain. A group of seven patients with TLE and hippocampal sclerosis, was compared with a group of controls [55]. Compared with controls, [^{18}F]-Fallypride binding potential was significantly decreased in the epileptogenic temporal lobe in all patients. On the analysis of regions of interest, this reduction was evident in areas surrounding the seizure onset zone, at the temporal pole (-34%) and the anterior part of the lateral temporal lobe (-33%). Although the hippocampal FDG uptake (-8%) and hippocampal MR volume (-35%) were significantly reduced, no significant decrease of [18F]-Fallypride binding potential was found in the hippocampal area. The area of decreased binding (pole and lateral parts of the epileptogenic temporal lobe) might correspond to "the irritative zone", suggesting that D_2/D_3 receptors might play a specific role in the pathophysiology of MTLE.

3.3.3. [^{11}C]-SCH23390

[^{11}C]-SCH23390 is a dopamine D_1-receptor ligand. A reduced binding in the right putamen (increased extracellular dopamine levels or receptor downregulation) was shown in patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and an identified nicotinic receptor mutation (in the α4 subunit) [56]. The authors suggested that alterations in mesostriatal dopaminergic circuits may contribute to nocturnal paroxysmal motor activity.

3.3.4. [^{11}C]-PE2I

[^{11}C]-PE2I is a radioligand that provides high-contrast delineation of brain regions that are rich in dopamine transporters. Studies have been performed in patients with idiopathic generalized epilepsy. An impaired dopamine uptake was observed in the midbrain in patients with juvenile myoclonic epilepsy [57, 58], and in the putamen in patients with generalized tonic-clonic seizures only [57].

3.4 Glutamate / NMDA system

Glutamate is the principal excitatory neurotransmitter in the human brain. Its receptors are divided into ionotropic and metabotropic receptors. N-methyl-D-aspartate (NMDA) receptors form a subclass of ionotropic glutamate receptors. Enhanced excitatory transmission has long been known to play a central role in the generation of seizures and the development of epilepsy. The NMDA receptors have been studied in human epileptogenic brain with conflicting results. Increased as well as decreased receptor binding has been reported in epileptogenic tissue.

3.4.1. [^{11}C]-CNS 5161

CNS 5161 is an NMDA antagonist that binds with high affinity to NMDA ion channel sites. [^{11}C]-CNS 5161 was developed as a potential PET tracer. Four healthy control subjects and a single pilot case with MTLE were scanned with this tracer (Hammers, "The new and very new PET tracers in epilepsy", Satellite symposium to the 26th IEC, Orsay, Paris, 2005). While hippocampal volume on the affected side was reduced by 27% compared to the contralateral side, [^{11}C]-CNS 5161 volume of distribution was reduced by only 13%. This may indicate an actual increase in open NMDA channels per volume unit of tissue on the epileptogenic side. Larger studies, with partial volume correction, are needed. There are no new reported data since this pilot study in epilepsy, but a study using PET with [^{11}C]-CNS 5161 in patients with Parkinson's disease was published in *Brain* in 2011 [59].

3.4.2. [^{11}C]-ketamine

Ketamine is an anaesthetic which binds specifically and reversibly to the NMDA receptor in a non-competitive manner, with a receptor affinity (Kd) in the µmol range. PET studies in monkeys and humans have shown that the distribution of [^{11}C]-ketamine corresponds to regions with high density of glutamate receptors.

Eight patients with MTLE were evaluated by PET using [^{11}C]-ketamine [60]. A side-to-side comparison revealed a 9-34% reduction of tracer radioactivity in the temporal lobes of ictal onset compared with the contralateral side. The magnitude and distribution of the reduction were similar to the metabolic pattern seen on FDG PET. This reduction may reflect reduced NMDA receptor density, reduced perfusion, focal atrophy, or other factors. Further studies with correction for partial volume effects and perfusion differences are needed.

3.5 Nicotinic cholinergic system

About fifteen years ago, mutations were identified in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), in genes coding for two different subunits of the neuronal nicotinic acetylcholine receptor (nAChR), respectively the α4 and the β2 subunits. To date such mutations have been found in about twenty families. These subunits are known to assemble and form the main brain nicotinic receptor subtype in humans (α4β2 nAChR). The nAChRs are excitatory receptor channels

permeable with cations (Na^+, K^+, $Ca2^+$), and are widely distributed throughout the brain with a particularly high density in the thalamus for the $\alpha4\beta2$ nAChR. Most of these receptors are presynaptic and have a neuromodulatory role consisting of an enhancement of the release of GABA, glutamate, dopamine, norepinephrine, serotonin or acetylcholine.

The [^{18}F]-2-Fluoro-A-85380 (3-[2(S)-2-azetidinylmethoxy]pyridine) (F-A-85380) is a ligand with a high affinity and specificity for the central $\alpha4\beta2$ nAChRs, with brain tracer concentrations reflecting the receptor concentration [61].

A PET using [^{18}F]-F-A-85380 was performed in a group of 8 patients with ADNFLE carrying a mutation in a nAChR subunit, in comparison with a group of healthy volunteers [62]. Patients and volunteers were all non-smokers. Parametric images of volumes of distribution were generated using the ratio between brain tissue concentration and the unchanged plasma concentration. The images showed a clear difference in the pattern of the nAChR density in the brains of the patients compared to the healthy volunteers, with a significant increase (between 12 and 21%, $p < 0.05$) in the ADNFLE patients in the mesencephalon, the pons and the cerebellum. Statistical parametric mapping (SPM) confirmed clear regional differences between patients and controls: patients had a statistically significant increase in nAChR density in the epithalamus, ventral mesencephalon and cerebellum, but decreased nAChR density in the right dorsolateral prefrontal region. In 5 patients who underwent an additional FDG PET experiment, hypometabolism was observed in the neighbouring area of the right orbitofrontal cortex. The demonstration of a regional nAChR density decrease restricted in the prefrontal cortex, despite the known distribution of these receptors throughout the cerebral cortex, is consistent with focal epilepsy involving the frontal lobe. In addition, these results suggest that the nAChR density increase in the mesencephalon is involved in the pathophysiology of ADNFLE through the role of brainstem ascending cholinergic systems in arousal. A PET examination of other forms of epilepsy is currently under way, to confirm the specificity of the above-mentioned results for ADNFLE.

3.6 Adenosine system (A_1 adenosine receptor)

Adenosine is different from regular transmitters: it is not released in a vesicular way, not released in synapses, but is produced in the cell like the "sweat" of the cell. Whenever the cell has to work, adenosine production increases intra- and extra-cellularly, activating the modulatory adenosine receptors. There are four different types of receptors, with different affinities for adenosine. The receptors with the highest affinity are the A_1 and A_{2A} subtypes.

In cases of high energy demand, such as in the early phases of an epileptic seizure, there is a massive increase of adenosine that is transported from the inside to the outside of the cell and thus can activate A_1 receptors. It has been shown in animal models in the last two decades that the activation of A_1 receptors increases activation of inhibitory G proteins and then helps stopping seizure activity. Adenosine is considered to be responsible for seizure arrest and for post-ictal refractoriness and thus appears to be an endogenous antiepileptic regulator. The deficiencies within this system might result in a higher susceptibility for seizures or epileptogenesis. Most studies report reductions of A_1 receptor density in experimental epilepsy models and in human post-mortem brain material of patients with epilepsy.

The radiotracer available for the A_1 adenosine receptor is CPFPX, which stems from the same group as caffeine (caffeine being a non-selective blocker of adenosine receptors). CPFPX is fluorinated ([18F]-CPFPX). It has relatively high affinity of 1.3 nM with rather high selectivity: $A_1/A_{2A} > 700$. In human brain, there is a high uptake within the striatum, the caudate nucleus, the putamen, part of the medial anterior thalamus and neocortical regions. A study performed in a F98 rat model for brain tumors showed that there was an increased density of adenosine A_1 receptors surrounding the tumor as well as surrounding the necrosis which was visible in the tumor [63]. The upregulation of A_1 receptors is primarily on astrocytes. A PET study using [^{18}F]-CPFPX in a patient with a glioma also revealed increases in A_1 adenosine receptor density in the immediate vicinity of the tumor. However, in contrast to the rat findings, there was a decrease of A_1 receptor binding surrounding this zone of increased receptors [63]. This zone of "reduction of inhibitory capacity" could contribute to tumor-associated epilepsy. So the density of A1 receptors is within the normal range in the tumour, increased in the immediate peri-tumoral zone and decreased in the extra-tumoral area, which may result in an increased excitability of the brain. Two patients with TLE have also been studied (Bauer, "The new and very new PET tracers in epilepsy", Satellite symposium to the 26th IEC, Orsay, Paris, 2005). In the first case, including unilateral hippocampal sclerosis, there was a reduction of the hippocampal [^{18}F]-CPFPX signal on the sclerotic side. In a second case of TLE plus with dystrophic changes seen in the neocortex, lateralized decreased signal was observed compared to the contralateral side and compared to control levels. These data were not partial volume corrected. It has to be noted that in autoradiographic studies of surgically resected hippocampi, densities were far lower than in control samples.

3.7 Opioid system

The opioid receptors can be classified into at least three types: μ-, δ- and κ-receptors. Opioid peptide release is calcium-dependent and requires high frequency neuronal firing; opioid peptides act as mediators of use-dependent synaptic activity and as co-transmitters to modulate the actions of the primary transmitter [64]. Opioid receptor availability reflects endogenous opioid concentrations. Animal and limited human data suggest an important anticonvulsant role for opioid peptides and their receptors. Exogenously applied opioids have predominantly inhibitory actions on neuronal activity and transmitter release throughout the brain. There is a large body of animal data showing that endogenous opioid release may occur following induced and spontaneous seizures and that increased opioid neurotransmission has an anticonvulsant role. However, the human relevance of these studies can only, at best, be inferential.

The tracer diprenorphine (DPN) is a non-selective partial agonist, with similar affinity for μ-, δ- and κ-receptors. It is displaced by endogenous opioids [65]. It shows high binding to basal ganglia, amygdala, and layers V and VI of the cerebral cortex. One study aimed to provide direct human in vivo evidence for changes in opioid receptor availability following spontaneous seizures [66]. Nine patients with refractory TLE were scanned by PET using [^{11}C]-DPN within hours of spontaneous temporal lobe seizures (median interval: 8.5 h post-ictally). A second scan was acquired days to weeks later, after as long a seizure-free period was achievable in a given patient, and served as an intra-subject control (corresponding to interictal binding). A regionally specific increase of opioid receptor availability was evident following seizures in the temporal pole and fusiform gyrus ipsilateral to the seizure focus. Thus this study confirmed changes in opioid receptor availability in the hours following seizures, suggesting an important role of the opioid system in seizure control. Previous studies performed during reading-induced seizures and absences demonstrated on the contrary decreased [^{11}C]-DPN binding [67, 68]. Taking together the results of these previous studies and the most recent one, the authors suggest that "synaptic opioid levels increase at the time of seizures, leading to a reduction in [^{11}C]-DPN 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, with a gradual return to normal levels during the interictal phase" [66].

3.8 Markers of inflammation

Translocator protein (TSPO), a marker of neuroinflammation expressed by activated microglial cells, is increased in vitro in surgical samples from patients with TLE. It can be measured in vivo by PET using the novel radioligand [^{11}C]-PBR28. A study of 16 patients with unilateral TLE showed increased uptake of radioactivity ipsilateral to the seizure focus, suggesting increased expression of TSPO [69].

4. Technological developments: PET/MRI

Hybrid tomographs, able to perform in a single imaging session PET and MRI acquisition, called PET/MRI systems, are a new modality with great potential clinical and research applications [70].

PET and MRI are the methods of choice for brain studies, PET providing molecular information (glucose metabolism, receptor imaging) and MRI evaluating a large panel of morphological and functional parameters: for this reason PET/MRI might become the modality of choice in the field of neuroimaging [71]. Indeed, the first prototype tested in humans was a brain-dedicated system [72].

This technological development has needed considerable efforts, to overcome the major challenges of bringing these two image modalities together. The main problem is due to the fact that current PET systems have a detection chain which is based on photomultiplier tubes, which are intrinsically sensitive to magnetic fields. For this reason, the PET/MRI systems replace photomultiplier technology by magnetic field-insensitive avalanche photodiodes or silicon photomultipliers [73, 74]. Alternatively, sequential imaging and proper shielding has been used, in order to minimize magnetic effects on the PET electronics [75, 76]. In addition, the CT component of PET/CT systems is used for correcting the attenuation of photons induced by tissues for PET images. The current PET/MRI systems estimate attenuation using MRI and various segmentation approaches [77, 78].

For hybrid neuroimaging, both brain-dedicated systems as well as whole-body systems have been tested. The first PET/MRI acquisition ever done in humans has been performed on a prototype for simultaneous PET/MRI featuring a PET insert for a standard 3 T MRI scanner (BrainPET; Siemens) [72]. A second dedicated brain system used a shuttle bed-based design, based on separate acquisitions on an ultra-high-field MRI (7 T) and on a PET high-resolution research tomograph (HRRT), on a common bed shifting between the two systems and guaranteeing a common reference system for image coregistration [79]. Both prototypes have been tested in dedicated research environments and no wide clinical application is expected.

Whole-body PET/MRI scanners have recently been introduced on the market for clinical use, about a decade after the commercial introduction of PET/CT. Whole-body systems have a significant advantage over brain dedicated systems, being able to perform both brain and whole-body imaging.

Different designs are adopted by the three commercial solutions available: a non integrated system using a shuttle bed connection by GE Healthcare [80], a sequential system, proposed by Philips Healthcare [81], and a simultaneous system, produced by Siemens Healthcare [82].

MRI, due to its superior soft-tissue contrast, has clear diagnostic advantages over non-contrast-enhanced CT, which is usually coupled to PET in routine brain PET/CT investigations. In addition, avoiding the CT component of PET/CT investigations reduces the total radiation exposure, with relevant advantages in pediatric and young population, representing a relevant proportion of the cases evaluated for refractory epilepsy. As compared with post-hoc fusion, already mentioned (Section 2), hybrid imaging avoids possible misalignements due to different patient positioning and guarantees that both modalities are acquired in the same physiological conditions. Overall, the hybrid design allows obtaining all information in one session, with one sedation/anaesthesia, if required, thus with significant practical advantages for both patients and specialists.

To date, only a few hybrid PET/MRI studies on patients with refractory epilepsy have been reported [81, 83]. One report on six cases studied by sequential PET/MRI hybrid imaging showed that fusion of morphological and functional information allowed the identification of subtle metabolic alterations which could easily have been missed when interpreting the 18F-FDG images alone [81]. The second study demonstrated the feasibility of simultaneous ^{11}C-flumazenil PET and MPRAGE MRI acquisition in one patient with right temporal lobe epilepsy [83].

With the wider diffusion of this new modality, larger investigations are expected, in order to evaluate the advantage of combining the various parameters of MRI (spectroscopy, functional MRI, diffusion studies) with the various molecular targets evaluated by PET. Hybrid PET/MRI, when available, might become the modality of choice for imaging patients in the presurgical evaluation of epilepsy providing multiparametric imaging.

Conclusion

Nuclear medicine imaging techniques have a well established role in the clinical investigation of patients evaluated for presurgical localization of seizure foci. The technological developments, together with the development and wider diffusion of specific molecular tracers, will presumably increase the diagnostic performance of these technologies for a more accurate non-invasive assessment of epileptic patients.

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