The use of SPECT and PET in routine clinical practice in epilepsy
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Purpose of review
The aim of this article is to give a subjective review of the usefulness of single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging in clinical practice in epilepsy for 2007.

Recent findings
Both ictal perfusion SPECT and interictal fluorodeoxyglucose PET can provide new information in the presurgical evaluation of intractable partial epilepsy. These functional imaging modalities reflect dynamic seizure-related changes in cerebral cellular functions. Although asymmetry of fluorodeoxyglucose PET metabolism has been useful to localize the epileptic temporal lobe, which tends to be more hypometabolic than the contralateral one, both frontal lobes are more hypometabolic than the epileptic temporal lobe, and may represent a region of ‘surround inhibition’. Due to its low temporal resolution, ictal perfusion SPECT hyperperfusion patterns often contain both the ictal onset zone and propagation pathways. These patterns often have a multilobulated ‘hourglass’ appearance. The largest and most intense hyperperfusion cluster often represents ictal propagation, and does not always need to be resected in order to render a patient seizure free.

Summary
Optimized interictal FDG-PET and ictal perfusion SPECT as part of a multimodality imaging platform will be important tools to better understand the neurobiology of epilepsy and to better define the epileptogenic, ictal onset, functional deficit and surround inhibition zones in refractory partial epilepsy.

Keywords
epilepsy, PET, SPECT

Introduction
Ictal perfusion single photon emission computed tomography (SPECT) and interictal fluorodeoxyglucose (FDG) positron emission tomography (PET) remain important imaging tools in the presurgical evaluation of patients with refractory partial epilepsy. It has usually been assumed that the largest and most intense ictal hyperperfusion cluster represents the ictal onset zone, and that the region of predominant hypometabolism contains the epileptogenic zone. We will first review recent studies that have used these assumptions. We will then discuss recent evidence that these assumptions may not always be correct. Finally, we will make suggestions as to how ictal perfusion SPECT and interictal FDG-PET could be used in a multimodality imaging platform to improve our understanding of the neurobiology of seizures, and to better define the ictal onset zone, ictal propagation pathways, functional deficit and the surround inhibition zones.

Usefulness of ictal perfusion SPECT and PET in the presurgical evaluation of partial epilepsy
Several recent studies have stressed that both ictal perfusion SPECT and FDG-PET can give additional information in the presurgical evaluation of patients with refractory partial epilepsy, that is independent of results of other investigations. Two studies reported surgical outcome in patients with refractory partial epilepsy and normal MRI of the brain, in whom it is a major challenge to correctly pinpoint the epileptogenic zone. In these studies, results of ictal perfusion SPECT and interictal FDG-PET were considered as localizing when the region of predominant hyperperfusion and hypometabolism was...
confined to the resected lobe. Lee and colleagues [1\textsuperscript{st}] reported their experience with ictal perfusion SPECT and FDG-PET in the largest series to date of surgical outcome in 89 patients with refractory partial epilepsy and normal MRI. Thirty-five had frontal lobe epilepsy (FLE), 31 neocortical temporal lobe epilepsy (TLE), 11 occipital lobe epilepsy, 11 parietal lobe epilepsy and one multifocal epilepsy. Forty-seven percent of patients remained seizure free for more than 2 years after surgery and 80\% had a seizure reduction of at least 90\%. Diagnostic sensitivity of FDG-PET as analyzed by statistical parametric mapping (SPM) was 44\% and subtraction ictal perfusion SPECT as analyzed by independent visual review was 41\%. FDG-PET localization was greatest in neocortical TLE and significantly related to seizure-free outcome. Ictal perfusion SPECT localization, on the other hand, was not related to surgical outcome. This study confirmed the usefulness of lateralized hypometabolism in magnetic resonance-negative TLE [2], and suggests that the area of predominant ictal SPECT hyperperfusion may give misleading information in cryptogenic epilepsy: it may represent propagated ictal activity and not the ictal onset zone. Chapman and colleagues [3\textsuperscript{st}] reported a seizure reduction of at least 90\% after epilepsy surgery in 18 of 24 patients (75\%) with normal MRI of the brain. Twelve patients had strong evidence from both scalp electroencephalography (EEG) and PET of a single epileptogenic zone within the resected region. Three of these 12 were seizure free and eight had a seizure reduction of more than 90\%. Among 13 patients whose ictal SPECT showed a single focal zone of hyperperfusion maximal in the resected region, seven were seizure-free and 10 had more than 90\% seizure reduction. In this study, no single test or combination of tests predicted postoperative seizure outcome.

Ollenberger and colleagues [4\textsuperscript{st}] assessed the role of FDG-PET in the diagnosis and management of children with refractory epilepsy. FDG-PET provided information additional to that obtained with other investigations regarding the epileptogenic zone in 88 of 113 patients (77\%), and changed management in half of the patients. In surgical candidates, FDG-PET scan was most useful in excluding potential candidates from surgery. The authors concluded that FDG-PET should be part of a routine work-up in pediatric patients with refractory epilepsy who are being considered for surgery.

Wetjen and colleagues [5\textsuperscript{st}] reported SISCOM findings in the re-evaluation after failed epilepsy surgery. SISCOM hyperperfusion was localized at the site of the previous focal cortical resection in around 70\% of cases. Although SISCOM hyperperfusion was concordant with the epileptogenic zone in 20 of 23 patients (87\%), only five of 26 reoperated patients (19\%) became seizure free. Kim and colleagues [6\textsuperscript{st}] studied bilateral temporal lobe hypometabolism and EEG findings in mesial TLE (mTLE) using SPM. SPM was better than visual assessment in the detection of bitemporal hypometabolism. Bilateral temporal hypometabolism correlated with bitemporal interictal epileptic discharges. Bilateral independent seizure onset was observed only in the group with bitemporal hypometabolism.

**Poor time resolution of ictal perfusion SPECT: the problem of differentiation of ictal onset zone and seizure propagation**

Ictal perfusion SPECT has a poor time resolution. After injection of the radioligand in an arm vein, it takes around 30\,s to reach the brain, and only around 70\% of the radioligand is taken up during first-pass. An ictal perfusion SPECT image, therefore, usually displays both the ictal onset zone and seizure propagation pathways. In all current studies using ictal perfusion SPECT, it is common practice to consider the region with the largest and most intense hyperperfusion as the ictal onset zone. We showed that these regions may also represent ictal propagation [7\textsuperscript{st}]. In our study of ictal perfusion patterns associated with single MRI-visible focal dysplastic lesions (FDLs), we described three patterns of hyperperfusion. In pattern 1, hyperperfusion was most intense at the FDL. Pattern 2 showed an hourglass pattern with the least intense lobule overlapping with the FDL, and the most intense at a distance, representing propagation (Fig. 1). Pattern 3 was a variant of pattern 2, showing a complicated multilobulated propagation pattern at a subtraction threshold of z = +1, but separate clusters at the usual threshold of z = +2 (Fig. 2). Propagation patterns were most often found in frontal lobe seizures. Fukuda and colleagues [8\textsuperscript{st}] reported results of very early ictal perfusion SPECT (i.e. injections within 5\,s after seizure onset) in 18 patients with FLE. Ictal perfusion SPECT was analyzed by 3D-stereotactic surface projection. In 11 of 18 patients, ictal perfusion SPECT findings were concordant with other investigations, such as invasive EEG studies. In three of these 11 (27\%), the hyperperfusion was localized within the epileptic focus, but in eight (73\%), areas of hyperperfusion extended to other regions. In a large and comprehensive study of factors affecting the pattern of hyperperfusion of ictal perfusion SPECT in neocortical epilepsies, Lee and colleagues [9\textsuperscript{st}] found that an injection delay of less than 20\,s after seizure onset was significantly correlated with correct localization. These observations imply that the earlier the injection is given during a seizure, the more likely the largest and most intense ictal perfusion SPECT cluster represents the ictal onset zone, and not seizure propagation. Contralateral spread of ictal activity is often restricted to a region homotopic to the ictal onset zone, resulting in a ‘mirror’ image [10].
Interictal fluorodeoxyglucose-PET hypometabolism and ictal SPECT perfusion changes represent dynamic seizure-related phenomena

Although the underlying neurobiology of FDG-PET hypometabolism is not well understood, and has been ascribed to factors such as neuronal loss, diaschisis, inhibitory processes or reduction in synaptic density, recent studies have provided new insights into its pathophysiology. Benedek and colleagues [11**] reported longitudinal changes in cortical glucose hypometabolism in children with intractable epilepsy. They compared two sequential FDG-PET scans performed 7–44 months apart in 15 children with intractable nonlesional partial epilepsy. The change in seizure frequency between the two PET scans correlated positively with the change in

Figure 1 Ictal perfusion SPECT propagation pattern 2

(a) A FLAIR image showed an increased signal in the left superior frontal gyrus (white circle). (b) On a T1-weighted image there was blurring of the grey–white matter transition, consistent with a focal dysplastic lesion (FDL). (c) The FDL was manually outlined in green. The ictal perfusion SPECT injection was given during a complex partial seizure that lasted 70 s, with initiation of the injection 18 s after seizure onset. (d) On a SISCOM, thresholded at $z = +2$, the cluster with the largest size had the configuration of an hourglass. (e) Co-registration of the manual outline of the FDL and SISCOM showed that the voxel with the lower local maximal $z$-score fell within the FDL, and that the highest $z$-score was at a distance of 28 mm from the FDL, measured from the margin of the manual outline of the FDL. (f) Taking all the information of the presurgical evaluation into consideration, which was concordant, we considered the region containing the FDL and the part of the SPECT cluster with the lower local maximal $z$-score, up to the ‘bottleneck of the hourglass’ as the epileptogenic zone (yellow circle), and decided to operate on the patient on the basis of these data. The patient has remained seizure free since the operation with a follow-up of more than 1 year.

Figure 2 Ictal perfusion SPECT propagation pattern 3

(a) This small focal dysplastic lesion (FDL) was picked up by its increased FLAIR signal and transmantle sign in the left middle frontal gyrus (white circle). The ictal perfusion SPECT injection was given during a complex partial seizure that lasted 46 s, with initiation of the injection 10 s after seizure onset. SISCOM thresholded at $z = +2$ showed a small cluster of hyperperfusion overlapping with the FDL (b and d; white arrow). The cluster with the highest $z$-score, that had also the largest size, was a separate cluster at 53 mm from the FDL (c and d; yellow circle). (e) At a threshold of $z = +1$ the four cluster in the left hemisphere, that were separate at a threshold of $z = +2$ (d), formed one large cluster, and were connected by more or less fine trails of hyperperfusion, giving it the appearance of a complicated hourglass. The surgical strategy consisted of removal of the magnetic resonance-visible FDL and the part of the SPECT cluster with the lower local maximal $z$-score overlapping with the FDL, up to the ‘bottleneck of the hourglass’. The patient has remained seizure free since the operation with a follow-up of more than 1 year.
the extent of cortical glucose hypometabolism. Most patients with persistent or increased seizure frequency showed enlargement in the area of hypometabolism on the second PET scan. In patients with improved seizure control a decrease in the size of the hypometabolic cortex was observed (Fig. 3). These results support the notion that the extent of cortical glucose hypometabolism on PET scan represents a dynamic process related to the frequency of seizures. Bouvard and colleagues [12] reported a 1-week test–retest flumazenil PET study in 10 patients with refractory partial epilepsy, including six with mTLE, and 10 control subjects. Five patients demonstrated clinically significant test–retest flumazenil-PET variations in the mesial temporal region. In three patients with mTLE without hippocampal sclerosis, only the PET with the shortest interval after the last seizure correctly identified the epileptogenic zone. In the group of patients with TLE, a significant seizure-related effect was found, with greater mesial temporal asymmetries in PET studies with the shortest interictal period. These observations provide evidence that also flumazenil-PET abnormalities are functional, transient and seizure-related. The authors stressed the importance of obtaining flumazenil-PET scans as soon as possible after a seizure in order to optimize the sensitivity and specificity of the scans in the presurgical evaluation. Joo and colleagues [13**] compared preoperative and postoperative FDG-PET scans in patients with mTLE-hippocampal sclerosis who were rendered seizure free after surgery. Increases in FDG metabolism after surgery were seen in the propagation pathways of ictal and interictal epileptic discharges, such as temporal stem white matter, inferior precentral gyrus and anterior cingulate gyrus in the ipsilateral hemisphere, suggesting that hypometabolism in these regions was functional, seizure-related and reversible. On the other hand, decreases were seen in brain structures with afferents from resected anterior mesial temporal structures. We [14**] correlated interictal FDG-PET metabolism and ictal SPECT perfusion changes in mTLE-hippocampal sclerosis. Intercital hypometabolism was greatest in the ipsilateral frontal lobe and represented a seizure-related dynamic process in view of further ictal decreases (Fig. 4). Crossed cerebellar diaschisis suggested that there is a strong ipsilateral frontal lobe inhibition during complex partial seizures. We formulated the hypothesis of surround inhibition, which is a dynamic (i.e. seizure-related) process, present in seizure propagation pathways, and which is a defense mechanism against seizure propagation. It is characterized by interictal hypometabolism and ictal hypoperfusion, and may be responsible for interictal and ictal functional deficits that may be reversible upon cessation of seizure activity. In the light of the observation that the frontal lobes are the most hypometabolic in mTLE-hippocampal sclerosis [14**] and that reversible changes occur in areas of the functional deficit zone, a ‘PETectomy’, that is, tailoring resection margins based on the extent and severity of temporal lobe hypometabolism in patients with refractory TLE, as suggested by Vinton and colleagues [15], does not seem a good surgical strategy.

Pathophysiological metabolic patterns have also been related to neuropsychological functioning in epilepsy. McDonald and colleagues [16] correlated interictal FDG-PET with frontal lobe executive function, and found that resting frontal lobe metabolic values were strong predictors of executive functioning in patients with epilepsy.

### Multimodality imaging

Several imaging modalities with different spatial and temporal resolutions are available to study the brains of patients with epilepsy in vivo. Combinations of these imaging modalities that integrate the strengths of modalities, and at the same time eliminate one or more weaknesses of an individual modality, may provide new information that is superior to the information provided by
each individual imaging modality [17]. Although SISCOM is routinely performed, co-registration of ictal perfusion SPECT, PET, structural MRI, fMRI, diffusion-tensor imaging (DTI), EEG and magneto-encephalography (MEG) in one multimodality imaging platform could provide a very powerful tool to systematically study the relationships between the epileptic lesion (MRI), irritative zone (MEG and interictal EEG), ictal onset zone (ictal perfusion SPECT and ictal EEG), functional deficit zone (FDG-PET), eloquent cortex (functional MRI), and the connectivity between the different cortical regions (Fig. 5) [18]. Knowlton [19] summarized the mounting evidence that multimodality imaging combining FDG-PET, ictal perfusion SPECT, and MEG in combination with MRI is increasing the number of patients being considered for epilepsy surgery without the need for invasive EEG studies. Lee and colleagues [11C]-methionine PET can reliably detect primary or recurrent glioma with high sensitivity and high negative diffusion coefficient. Altay et al. [21*] reported a correlation between severity of FDG-PET hypometabolism and interictal regional delta slowing in TLE, which suggested related underlying pathophysiological mechanisms for metabolic and electrical dysfunction in TLE.

**Developments in analysis methods of ictal perfusion SPECT**

Analysis of ictal SPECT is usually done in comparison with an interictal SPECT image, and has evolved from side-by-side visual assessment to more sophisticated techniques, such as subtraction ictal SPECT and statistical comparison with a control database. Each method has advantages and disadvantages, and the combination of several methods may give complementary information (Table 1) [7**,9*,22,23,24**,25,26].

**PET ligands other than fluorodeoxyglucose in epilepsy**

Although not routinely performed, imaging of receptors and other central nervous system processes reflecting metabolic or proliferative pathways by means of PET allows extraction of additional diagnostic and prognostic information in selected series of epilepsy patients.

[11C]-methionine PET can reliably detect primary or recurrent glioma with high sensitivity and high negative
Figure 5 Multimodal image registration

Information obtained from different imaging modalities such as MRI, SISCOM and PET have been combined into comprehensive multimodal images. The patient was a 44-year-old woman with refractory left OLE. (a) A T2-weighted-FLAIR dataset showed a focal dysplastic lesion (FDL) in the left occipital lobe (blue cross). (b) A T1-weighted high resolution 1 mm isotropic dataset. (c) Manual delineation of the FDL overlaid in pseudocolor onto the T1-weighted dataset. (d) Functional MRI statistical parametric maps of the vertical (green) and horizontal (yellow) meridian representation of the visual field overlaid onto the T1-weighted dataset. (e) Optic radiation and occiptotemporal fiber bundles obtained through deterministic fiber tractography diffusion tensor MRI overlaid onto the T1-weighted dataset. (f) SISCOM. Notice the partial overlap of ictal hyperperfusion cluster and the FDL, and the cloverleaf configuration of the ictal SPECT hyperperfusion cluster, indicating seizure propagation in several directions. The ictal SPECT injection was given during a complex partial seizure that lasted 68 s, with initiation of injection 38 s after seizure onset. (g) FDG-PET showing hypometabolism co-localized with the FDL. Combined transversal (h), coronal (i) and sagittal (j) views of the information from a to g. From these comprehensive multimodal images, we formulated the surgical strategy to remove the FDL and immediately surrounding SISCOM hyperperfusion (white circles in h, i, j), but not the ‘petals of the cloverleaf’. The functional MRI with depiction of retinotopically organized visual areas showed that the FDL was situated outside the primary visual areas V1, V2 and V3 (VP). Therefore, a resection would spare most (low-order) visual functions; for deficits of higher order visual functions such as color vision, object/face recognition and 3D-depth bilateral lesions are necessary.
predictive value. Dysembryoplastic neuroepithelial tumors (DNETs) can cause refractory partial epilepsy, and have a much more benign course than gliomas. Differentiation of DNETs from gliomas on the basis of MRI characteristics may not be reliable. Rosenberg and colleagues [27] reported that normal methionine PET findings in patients with an epileptogenic and nonrapidly progressing brain tumor are suggestive of DNET, whereas a markedly increased tumor methionine uptake makes this diagnosis unlikely.

High uptake of α-[11C]methyl-L-tryptophan (AMT) on PET occurs in a subset of epileptogenic tubers consistent with the location of seizure focus. Kagawa and colleagues [28] analyzed the surgical outcome of children with tuberous sclerosis complex in relation to AMT PET results. Their findings suggested that resection of tubers with increased AMT uptake is highly desirable to achieve seizure-free surgical outcome in children with tuberous sclerosis complex and intractable epilepsy.

Fedi and colleagues [29] reported an association of the GABRG2(R43Q) mutation with reduced benzodiazepine receptor binding in patients who had a history of childhood absence epilepsy, and febrile seizures. Hammers and colleagues [30] performed a retrospective flumazenil-PET study in 15 patients with refractory mTLE-HS and 13 control subjects. Periventricular increased flumazenil binding, implying heterotopic neurons, was observed in three of 13 controls (23%), three of eight patients (38%) with Engel class IA outcome (i.e. completely seizure free) and four of seven patients (57%) who were not completely seizure free. Although these periventricular increases correlated with poorer outcome, individual predictions of postoperative outcome were difficult in view of the poor sensitivity and specificity of the method.

Picard and colleagues [31] studied the nicotinic receptor density using [18F]-F-A-85380, a high affinity agonist of α4β2 nicotinic acetylcholine receptors, in patients with

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
<th>Individual data</th>
<th>Group data</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side-by-side visual assessment</td>
<td>Visual comparison of interictal and ictal SPECT</td>
<td>✔</td>
<td></td>
<td>Ictal SPECT may be localizing in cases when subtraction ictal SPECT was nonlocalizing due to interictal injection during subclinical seizure activity. Complementary with SISCOM [9]</td>
<td>Less sensitive than SISCOM</td>
</tr>
<tr>
<td>SISCOM [22,23]</td>
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<td></td>
<td>Interictal study necessary</td>
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<td>SPM <a href="http://www.fil.ion">http://www.fil.ion</a>. ucl.ac.uk/spm/</td>
<td>Statistical comparison of individual ictal SPECT scan with normal database ictal–interictal SPECT difference image analyzed by SPM (ISAS) [24]</td>
<td>✔</td>
<td></td>
<td>Objective, no a priori hypotheses, voxel-based</td>
<td>Normal age-matched datasets needed. Not applicable with major structural brain abnormalities. Most significant hyperperfusion cluster may represent propagated seizure activity.</td>
</tr>
<tr>
<td>Composite SISCOM [26]</td>
<td>Statistical comparison of ictal SPECTs of seizures of several patients fulfilling certain criteria [25]</td>
<td>✔</td>
<td></td>
<td>Objective assessment of systematic changes during specified seizure types</td>
<td>Selection criteria to group SPECT studies make this type of studies relatively small</td>
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SPECT, single photon emission computed tomography; SPM, statistical parametric mapping.

Table 1 Methods to analyze ictal perfusion SPECT images
autosomal dominant nocturnal LLE. Patients had increased densities in the epithalamus, ventral mesencephalon and cerebellum, and decreased densities in the right dorsolateral prefrontal region, implicating these changes in the pathophysiology of autosomal dominant FLE. Serotonin 1A receptors (5-HT_1A) have been shown to be reduced in TLE using \(^{18}\)F-trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-N(2-pyridyl)cyclohexanecarboxamide (\(^{18}\)F-FCWAY), a 5-HT_1A receptor antagonist. Theodore and colleagues [32] showed that reductions of 5-HT_1A receptor binding in mesial temporal structures and insula remained significantly reduced after partial volume correction.

**Conclusion**

Ictal perfusion SPECT and FDG-PET are useful imaging techniques in routine clinical practice in epilepsy, and are first-line noninvasive investigations in patients with refractory partial epilepsy undergoing presurgical evaluation. A better understanding of the biological processes causing perfusion and metabolic changes in epilepsy will improve the diagnostic sensitivity of these functional imaging tools.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 225–226).


This large study of surgical outcome and prognostic factors of cryptogenic partial epilepsy highlighted contributions of FDG-PET and ictal SPECT, and reported encouraging results in these invariably difficult cases.


This study showed that no single test, including ictal SPECT and FDG-PET, could predict seizure-free outcome in patients with refractory partial epilepsy and normal MRI.


The results of this study indicate that FDG-PET should be part of the routine presurgical work-up of patients with refractory partial epilepsy.


This was the first study to describe ictal SPECT ‘hour-glass’ propagation patterns and a noninvasive presurgical strategy based on SISCOM for patients with refractory partial epilepsy due to single magnetic resonance-visible FDLS.


This study stressed that ictal SPECT propagation is common in frontal lobe seizures even with ictal SPECT injections within 5 s after seizure onset.


This study stressed that analysis of ictal SPECT using side-by-side visual assessment and subtraction ictal SPECT are complementary, and that injection delay of less than 20 s after seizure onset was significantly correlated with correct localization.


This longitudinal FDG-PET study showed that the extent of cortical FDG hypometabolism undergoes dynamic changes related to seizure frequency.


This describes a test–retest flumazenil-SPECT study showing the lowest flumazenil binding in the epileptic hippocampus in the study with the shortest interictal period, and stressing the importance of obtaining a flumazenil-PET soon after a seizure in patients with mTLE and normal MRI.


In patients with mTLE-hippocampal sclerosis, FDG-PET metabolism increased in seizure propagation pathways and decreased in de-afferented regions after successful epilepsy surgery. Correlating these postoperative metabolic changes with neuropsychological and quality-of-life changes may be important to understand functional changes in the brain after epilepsy surgery.


This was the first study to show that the frontal lobes are the most hypometabolic regions in the brain in patients with mTLE-hippocampal sclerosis. Ictal frontal lobe hyperperfusion and crossed cerebellar diaschisis suggests a seizure-related ‘surround’ inhibitory process in the frontal lobes.


This was the first study to correlate FDG-PET hypometabolism in the frontal lobes with executive functions, supporting the concept of functional deficit zone.


This was a multimodality imaging study showing that the combination of FDG-PET and DTI reliably identifies the epileptic tuber in patients with tuberous sclerosis complex.


This interesting study showed that the severity of temporal lobe hypometabolism correlated significantly with the amount of delta activity in the interictal EEG. A combination of these two imaging modalities would make longitudinal correlation studies of hypometabolism/delta slowing and the occurrence of seizures possible.


This is a validated and readily available method to determine statistically significant ictal SPECT perfusion changes.

This study described the flumazenil-PET phenotype in patients with mutation in gene coding for the GABA(A) receptor.

This study described in-vivo nicotinic receptor density in patients with autosomal dominant nocturnal frontal lobe epilepsy, highlighting the importance of imaging-phenotype and genetic correlations to better understand idiopathic partial epilepsies.

This study described the flumazenil-PET phenotype in patients with mutation in gene coding for the GABA(A) receptor.