PET and ictal SPECT can be helpful for localizing epileptic foci

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Purpose of review
Functional neuroimaging with PET and SPECT is a commonly used tool in presurgical evaluation. The following article reviews the literature of PET and SPECT in presurgical assessment of epilepsies published in the last year.

Recent findings
FDG-PET adds concomitant information in temporal and extratemporal lobe epilepsy in adults and children. The pattern of hypometabolism in FDG-PET is a good additional predictor or seizure outcome in TLE with mesial temporal sclerosis or negative MRI. There is growing evidence that diagnostic value of FDG-PET increases with postprocessing. Although several methods were applied in the reviewed literature, all of them seem to outperform the visual analysis. Imaging of the epileptic focus with ictal SPECT is depending on short injection latencies. It is particularly useful in patients with nonlesional MRI and mostly of extratemporal localization. Areas of hyperperfusion remote of SOZ are reflecting the epileptic network. Combining more concordant investigations including PET and SPECT in MRI-negative evaluation adds to better presurgical stratification and therefore, better postsurgical outcome. FET-PET shows increased uptake in status epilepticus.

Summary
PET and SPECT are important investigations to localize the epileptic focus in temporal lobe and nonlesional extratemporal epilepsies. Postprocessing for both modalities is important to increase diagnostic value.

Keywords
epilepsy, functional neuroimaging, computer assisted image processing, positron-emission tomography, single photon emission computed tomography

INTRODUCTION

Localizing epileptogenic foci is of interest in presurgical evaluation of drug refractory epilepsy. Functional neuroimaging with nuclear medicine tracers using positron emission tomography (PET) or single photon emission computed tomography (SPECT) are well established techniques and are recommended in presurgical evaluation by the neuroimaging subcommission of the International League Against Epilepsy (ILAE) [1].

PET is primarily used to image the glucose metabolism by using ^{18}F-fluorodeoxyglucose (FDG) tracer. Particularly in temporal lobe epilepsy (TLE), ipsilateral metabolic activity for glucose might be reduced [2,3]. However, the area of temporal hypometabolism might extend beyond the seizure onset zone (SOZ) indicating rather a lateralizing than localizing value [4]. Unilateral hypometabolism in FDG-PET is predictive of good outcome particularly in TLE with nonlesional MRI or equivocal ictal EEG recording [5]. Bilateral hypometabolism may predict less favorable surgical outcome [6]. Localizing the epileptogenic zone in neocortical epilepsies with FDG-PET has also been reported [7,8]. Postprocessing of FDG-PET was shown to increase sensitivity detecting the epileptogenic area [8,9].

Functional imaging of regional cerebral blood flow (rCBF) is shown by SPECT using either ^{99m}Tc-hexamethyl-propylene-amine-oxime (HMPAO) or

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Curr Opin Neurol 2018, 31:184–191

DOI:10.1097/WCO.0000000000000527

KEY POINTS

- FDG-PET in temporal lobe epilepsy with hippocampal sclerosis predicts outcome according to hypometabolic distribution pattern.
- Ipsilateral localizing FDG-PET hypometabolism in temporal lobe epilepsy and negative MRI indicates good surgical outcome.
- Computer-assisted postprocessing increases the diagnostic value of FDG-PET.
- Ictal hyperperfusion in SPECT remote from seizure onset zone correlate with nodes in the epileptic network.
- Combination of two or more concordant investigations in MRI-negative patients predict good surgical outcome.

^{99m}Tc-ethylene-cysteine-diethylester (ECD) [10]. Detection of rCBF is seen as secondary marker of neuronal activity. Sensitivity and specificity for the epileptogenic focus is low with interictal SPECT but significantly increased with ictal application and comparison with interictal perfusion patterns [11–13]. Subtraction interictal from ictal SPECT and coregistration to MRI (SISCOM) further increased sensitivity and specificity [14]. Ictal SPECT requires video– Electroencephalography (EEG) monitoring for early injection within a seizure. Hence, it is applied in cases with discordant or negative MRI results mostly extratemporal epilepsies and has shown to be helpful in planning of intracranial electrode placement or identification of SOZ [15–17]. Complex partial seizures and early injection time have been prognostic markers for a highly localizing SPECT [16,18,19]. Different patterns of hyperperfusion have been described in correlation to temporal seizure semiology and propagation as well as injection latency in patients with focal cortical dysplasia (FCD) [20,21].

The aim of this review is to give an overview of the publications on PET and SPECT in focus localization of epilepsy published between November 2016 and November 2017.

PET IN TEMPORAL LOBE EPILEPSY WITH MESIAL TEMPORAL SCLEROSIS

Mesial temporal sclerosis is the most common histopathological finding in epilepsy surgery [22]. There are four studies focusing on mTLE with MTS only. Two studies showed that restricted rather than widespread hypometabolism in FDG-PET is correlated with Engel class Ia outcome [23▪▪,24]. The larger study assessed outcome of 97 patients with histologically proven mesial temporal sclerosis (MTS) and long postsurgical follow-up (mean >6 years) in relation to postprocessed FDG-PET and voxel-based morphometry (VBM) of MRI [23▪▪]. Eighty-five percentage of patients were classified with outcome Engel I (45% Engel IA). IA outcome showed ipsilateral anterior mesial temporal hypometabolism only. Non-IA outcome showed different pattern for left and right MTS whereas right MTS non-IA outcome was associated with ipsilateral mesial frontal and perisylvian hypometabolism, correlated left MTS non-IA outcome with contralateral frontoinsular hypometabolism and posterior white matter hypermetabolism. Furthermore, outcome Engel I and II without IA showed similar temporal patterns as IA outcome but with more extratemporal and in left sided MTS contralateral involvement. Failures (outcomes III and IV) showed less temporal hypometabolism sparing the hippocampus and more extratemporal hypometabolism bilaterally. These findings were concordant with electroclinical features but independent of atrophy in VBM. A smaller study of 18 patients with histologically proven MTS and 2-year surgical follow-up showed similar results [24]. Predictors for non-IA outcome were lateralizing rather than localizing EEG, lateralizing rather than localizing hypometabolism in FDG-PET and history of status epilepticus.

The extend of ipsilateral hypometabolism in TLE with MTS is correlated to early onset of disease in hippocampal area and longer disease duration in amygdala area indicating premature insult affecting more hippocampal areas whereas disease duration seems to have a progressive effect on decreased metabolic activity of amygdala [25].

PET IN TEMPORAL LOBE EPILEPSY OTHER THAN MESIAL TEMPORAL SCLEROSIS-RELATED

Localizing hypometabolism of FDG-PET in lesional TLE without MTS was shown in approximately 40% of patients only in a small sub-cohort [26]. High-density electric source imaging (hd-ESI) showed a higher localizing value of 72% in another sub-cohort. As not all patients had all investigations performed, direct comparison of modalities remains limited.

LOCALIZING VALUE OF PET IN MRI-NEGATIVE EPILEPSIES

A large single centre study on 142 MRI-negative neocortical epilepsies compared two clinical protocols within this cohort. The first protocol considered surgical resection with one concordant investigation (interictal EEG, ictal EEG, FDG-PET or ictal SPECT)

in line with the seizure semiology [27▪▪]. The second protocol applied from a specific date required concordant results of two or more investigations, that is, interictal/ictal EEG and functional neuroimaging were localizing to the same epileptogenic lobe. Seizure-free outcome improved significantly (47.2 versus 75.5%). Concordance between two or more investigations and localizing PET were predictive for seizure-free outcome in a multivariate analysis. The outcome in the second group is remarkable for MRI-negative neocortical epilepsy surgery. PET was visually reported and postprocessed with SPM. A large cohort of 109 patients with MRI-negative neocortical epilepsy showed correlation to concordant functional neuroimaging with the highest odds ratio of 0.3 for FDG-PET (other results are discussed in SPECT section) [28▪▪]. In a smaller study of 36 patients with MRI-negative epilepsy, hypometabolism in FDG-PET was correlated to favorable outcome in temporal as well as extratemporal lobe epilepsy [29]. Interestingly, favorable (Engel I and II) outcome was achieved in histopathology of FCD type I in 10 pediatric patients of which 5 had no abnormality in PET but were all seizure free. This is an unusual good outcome for this histopathology. Similar results were shown in a study of 26 patients (10 temporal) with nonlesional 3T MRI, in which all underwent invasive presurgical evaluation. Concordance of FDG-PET hypometabolism with ECoG SOZ in TLE correlated with seizure-free outcome (Engel IA) whereas TLE patients without PET lateralization had outcome Engel IIA–IV [30]. No predictive value was found for visually assessed PET localization in extratemporal lobe epilepsy. A comprehensive review of outcome in MRI-negative temporal lobe epilepsy with concordant FGD-PET hypometabolism indicates outcome rates similar to TLE with MTS [31▪▪].

PET IN OTHER PRESURGICAL EVALUATION

Fronto-orbital SOZ is a rare localization. A recent Canadian multicenter study described 16 patients with this entity and reviewed the literature [32]. In their patient cohort, only one patient had localizing PET hypometabolism, another four more extensive areas of decreased metabolic activity (nine in total). This is in line with other investigations, for example, interictal scalp EEG, which often extends over the ipsilateral fronto-temporal area.

Patients who failed to become seizure-free after epilepsy surgery were reevaluated with FDG-PET with co-registration to MRI, MRI and EEG monitoring. Out of 16 patients, all showed concordant results for extension of the previous surgery with 4 showing evidence of tumor recurrence [33]. One patient with acute seizures had 18F-Dopa-PET, MRI and routine EEG concordant to site of previous surgery and was operated without further video-EEG monitoring.

A large pediatric cohort with 166 patients showed highest localizing value for FDG-PET [34]. Interestingly, most patients had only interictal video–EEG monitoring. Concordance of MRI, PET and EEG abnormality showed the best predictive value for favorable postsurgical outcome.

An interesting study compared histopathological classification of FCDs to patterns of MRI+/PET+, MRI-/PET+ and MRI-/PET- but could not show any correlations [35▪]. As in other studies, FDG-PET hypometabolism correlated with younger age of onset.

LOCALIZATION OF ^{18}F-FLUORODEOXYGLUCOSE-PET WITH DIFFERENT METHODS OF REVIEWING/POSTPROCESSING

Several studies focused on the difference of PET image postprocessing or reviewing. Co-registration of PET or SPECT or both to MRI showed reduction in need for invasive monitoring in a cohort of 166 pediatric epilepsy patients and significantly higher rates of seizure-free outcome after 1 and 2 years postsurgery [36▪▪]. Co-registration of PET to gray matter-segmented MRI increased concordance to ictal EEG localization compared with visual non-segmented PET analysis [37▪]. Semiquantitative analysis of FDG-PET in 39 patients with possible FCD on MRI compared with visual analysis showed comparable pick-up rate in TLE but much higher pick-up rate in frontal lobe epilepsy [38▪]. Whereas visual analysis in FLE failed to detect any PET abnormality in 50% of patients and was only concordant with EEG SOZ in 22%, semiquantitative analysis showed hypometabolism concordant to EEG SOZ in 72% (Fig. 1). Interestingly, four patients with FLE who initially had negative MRI result were re-reviewed positively after semiquantitative PET showed an area with hypometabolism. Semiquantitative analysis was done with an integrated software on the PET scanner, which added only a few minutes to the PET reviewing time.

A combined surface analysis of MRI and FDG-PET by a machine-learning approach was developed to detect FCDs in 28 patients with histologically proven FCDs [39▪▪]. The classifier outperformed both, conventional postprocessing and visual analysis (93 versus 82 versus 68%). Different patterns of lesion distribution allowed to differentiate between FCD I–IIa and IIb. Surgical outcome was as expected,

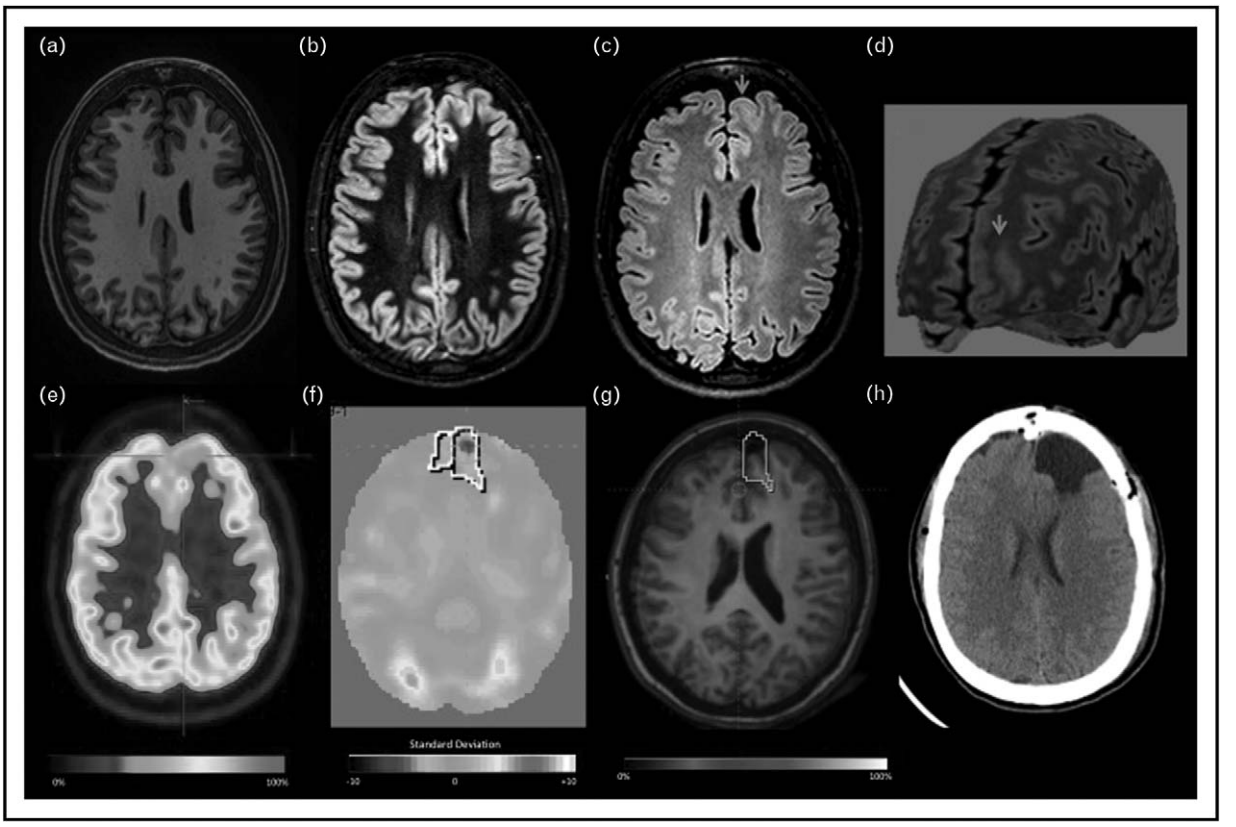

FIGURE 1. Focal cortical dysplasia II-B left frontal lobe. (a–d) T1, double inversion recovery, FLAIR axial MRI, and curvilinear reconstruction, showing abnormal cortical thickening, focal increased signal, white and gray matter junction blurred (arrow). (e) Visual PET initially was considered normal. (f) Quantitative-PET showed −3.6 SD in the left frontal lobe. (g) Coregistration MRI and PET. (h) Axial CT after surgery resection (for color coding please refer to online version). Reproduced with permission from from Coelho *et al.* [38▪].

better in the FCD IIb group (91% positive outcome) compared with the other FCDs (71%).

COMPARISON OF PET/COMPUTED TOMOGRAPHY AND PET/MAGNETIC RESONANCE

Two studies focused on FDG-PET images acquired on PET/MR. Attenuation correction and results on PET/MR are not inferior to PET/CT in a prospective comparative study in 35 patients with focal epilepsy [40]. Another prospective study reported 54 patients undergoing presurgical assessment with so far 9 patients operated [41]. PET/MR showed concordant abnormality in both modalities in five patients, in one modality in three and no abnormality in one patient.

CAUSE OF ^{18}F-FLUORODEOXYGLUCOSE-PET HYPOMETABOLISM

The reason for the more widespread hypometabolism remains unclear. No correlation of hippocampal metabolic activity was found in comparison with temporal hypometabolism whereas hypometabolism in focal cortical dysplasias showed a correlation to reduced mitochondrial complex IV function [42,43]. A new study showed now in four TLE patients that propagation of interictal epileptic activity recorded by magnetoencephalography (MEG) calculated by a statistical voxel by voxel analysis corresponds to the area of reduced hypometabolism in FDG-PET [44▪▪]. These findings are supported by a study investigating ictal high frequency oscillations (HFOs) and hypometabolism showing a correlation in temporal lobe epilepsy [45]. Interestingly, there was no correlation for extratemporal lobe epilepsies and for lower frequency bands. In contrast is another recent study comparing FDG-PET hypometabolism and hypermetabolism to intracranial ECoG SOZ and interictal discharges [46▪▪]. Hypometabolic areas showed a good correlation to SOZ on the lobar level but were up to 3 cm distant from SOZ in detailed analysis with a sensitivity of up to 0.39 and a specificity of 0.9.

A study on remote areas with reduced metabolic activity in PET in 28 patients with hypothalamic hamartoma correlated with the

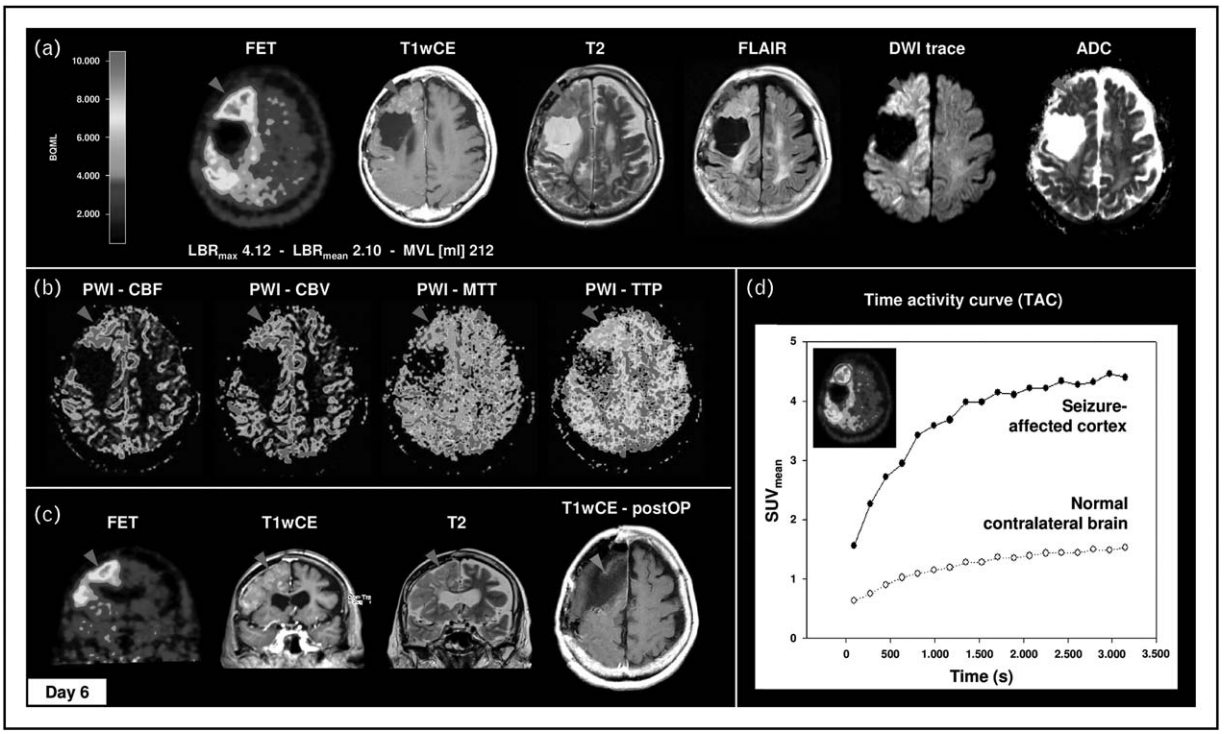

FIGURE 2. Widespread ^{18}F-FET uptake, vasogenic and cytotoxic edema, contrast enhancement, and hyperperfusion with strict gyral pattern during nonconvulsive SE. Case 3 demonstrates a 66-year-old woman with clinically stable right frontal oligodendroglioma WHO II without residual tumor. In 2014, the patient presented with repeated CPS followed by treatment-resistant nonconvulsive SE. ^{18}F-FET PET revealed distinct elevated cortical ^{18}F-FET uptake of right hemisphere with frontal and parietal accentuation (LBR$_{max}$ 4.42; LBR$_{mean}$ 2.45), corresponding to cortical contrast enhancement in T1wCE, marked gyral vasogenic (T2/FLAIR, cortical swelling), and cytotoxic (DWI/ADC) edema (a) and cortical hyperperfusion in DSC-PWI (b). (c) Clinical deterioration in combination with MRI and ^{18}F-FET PET imaging was interpreted as tumor recurrence. Therefore, patient underwent subtotal frontal lobe resection without any histologic evidence of tumor progression. (d) Additional ^{18}F-FET kinetic analysis of right frontal lesion and normal contralateral brain demonstrated SUV$_{mean}$ time–activity course curve pattern with continuously increasing ^{18}F-FET uptake without washout. CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; TTP, time to peak (for color coding please refer to online version). Reproduced with permission from Hutterer *et al.* [48▪▪].

impairment in cognitive function indicating remote network nodes involved [47]. It is not reported if these areas are also impaired by interictal epileptic activity.

OTHER PET TRACERS AND LOCALIZATION

One very interesting study on ^{18}F-fluoroethyl- L-tyrosine amino acid (FET)-PET in patients with brain tumors and status epilepticus revealed increased FET uptake with status activity (Fig. 2) [48▪▪]. Histopathological studies showed no sign of tumor progression, therefore, increased cerebral amino acid transport was most likely related to status. This is an interesting finding and deserves further studies identifying if amino acid transport activity is increased in SOZ or related to seizure activity as well.

ICTAL SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY AND INJECTION LATENCY

In a cohort of 95 pediatric epilepsy patients, 60 had localizing SISCOM with 85% indicating focal hyperperfusion concordant to lobe of EEG SOZ [49]. Short injection time (mean 18 s) was seen with concordant results whereas longer injection latency was apparent in discordant (mean 27 s) and nonlocalizing (mean 35 s) SISCOMs being statistically significant differences. No significant differences were seen for MRI findings, epilepsy cause or seizure duration. Concordance of SISCOM, SOZ and resected area was correlated with 6-month postoperative seizure freedom. The authors conclude that injection delay should be shorter then 25 s. A more systematical approach to injection time and SISCOM threshold to avoid detection related to seizure propagation

showed a recommendation of injection latency below 35 s [50].

LOCALIZING VALUE OF SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IN MRI-NEGATIVE EPILEPSY

A large cohort of 109 MRI-negative patients showed Engel IA outcome after 1 year of 54.1% and almost 60% seizure-free at last follow-up [28▪▪]. Localizing patterns of neuroimaging showed odd ratio of 0.37 for ictal SPECT. Concordant results in presurgical assessment, presence of aura and complete resection of SOZ including interictal frequent spikes in ECoG were further positive predictors for favorable surgical outcome. In another study on MRI-negative epilepsy patients, intracranial electrodes were implanted guided by VBM of MRI (11 patients) or ictal SPECT results (3 patients) [51]. Thirteen of 14 patients underwent resective surgery and 57% were seizure-free postsurgically. Less successful were the SPECT results reported in a study investigating high-density scalp EEG in FLE [52]. Although 12/14 patients had localizing hd-EEG results, only 3/12 had localizing SISCOM.

STRONG CONNECTIVITY BETWEEN HYPERPERFUSED AREAS

SISCOM hyperperfused and hypoperfused areas were correlated to corticocortical-evoked responses from cortical electrostimulation in sEEG in 31 patients with epilepsy [53▪]. Hyperperfused areas in SISCOM remote from SOZ showed strong correlation to evoked potentials indicating network connectivity.

NEW METHODS

A new approach of joint ictal/interictal reconstruction method was developed and tested on phantom studies as well as on 35 patients [54]. The new method showed better performance than standard subtraction method. Another study investigated arterial spin labelling (ASL) MRI to identify postictal hypoperfusion as marker of SOZ [55]. Twenty patients were investigated but only two underwent surgical resection. Interestingly, comparison to FDG-PET and SISCOM showed higher rate of concordance of postictal hypoperfusion in ASL MRI to SOZ in EEG.

REVIEWS

Several reviews on PET and SPECT in presurgical evaluation were published during this period [31▪▪,56▪▪–59▪▪,60▪].

CONCLUSION

Functional Imaging with PET and SPECT adds concomitant imaging information on localizing the epileptic focus. A recent review on surgical treatment of TLE suggested to use FDG-PET only in MRI-negative patients [61]. The literature of the past year, strongly supports the use of FDG-PET in TLE, even in patients with MTS. These finding support an earlier publication on added value of PET from an economical view [62]. There is growing evidence that diagnostic value of FDG-PET is increasing with postprocessing. Several methods were applied in the reviewed literature and all of them seem to outperform the visual analysis. In SPECT, machine-learning approaches may further increase the specificity of results. Hyperperfused areas in SISCOM remote from SOZ indicate nodes of the epileptic network.

SPECT literature further supports the indication in nonlesional MRI and mostly of extra-temporal localization and short injection latencies. Combining more concordant investigations in MRI-negative evaluation adds to better presurgical stratification and therefore, postsurgical outcome. Re-reviewing of negative MRI with PET and SPECT results may help to find subtle lesions, keeping in mind that negative MRI is highly dependent on imaging technique and reviewers experience [63]. Only sparse recommendations exist for use of PET and SPECT in presurgical evaluation and application in clinical practice shows broad variation [1,64]. Future research should focus on a structured approach gathering evidence for functional imaging in presurgical evaluation and a standardized computer-assisted processing. FET-PET, indicating that increased amino acid transport is caused by status, warrants further investigation if it is as another biomarker for the SOZ.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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