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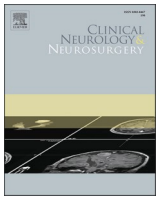

Positron Emission Tomography (PET) in presurgical planning of anterior temporal lobectomy: A systematic review of efficacy and limitations

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ABSTRACT

Introduction: Temporal lobe epilepsy (TLE), a debilitating neurological disorder, necessitates refined diagnostic and treatment strategies. This comprehensive review appraises the potential of positron emission tomography (PET) in enhancing the presurgical planning of Anterior Temporal Lobectomy (ATL) for patients afflicted with TLE.

Methods: A comprehensive literature search was conducted using the PubMed, SCOPUS, and ScienceDirect databases from 1985 to 2022, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for studies investigating PET and ATL. This review studied a range of radiotracers, including FDG, H_2O, FMZ, MPPF, and FCWAY, analyzing their efficacy in detecting epileptogenic foci, establishing resection boundaries, and predicting postoperative outcomes. The study paid special attention to cases where MRI findings were inconclusive.

Results: A total of 52 studies were included in the final analysis. Our analysis revealed that FDG-PET imaging was instrumental in identifying seizure foci and predicting postoperative results. It exhibited significant value in situations where structural abnormalities were absent on MRI scans. Furthermore, newer radiotracers such as 5-HT_{1A} antagonists, FCWAY and MPPF, presented promising potential for localizing seizure foci, particularly in MRI-negative TLE, despite their comparatively limited current usage.

Conclusion: PET imaging, although challenged by issues such as radiation exposure, limited accessibility, and high costs, offers considerable promise. Integration with other imaging modalities, such as EEG and MRI, has contributed to improved localization of epileptogenic foci and subsequently, enhanced surgical outcomes. Further research must focus on establishing the relative efficacy and optimal combinations of these radiotracers in the orchestration of ATL surgical planning and prognostication of postoperative outcomes for TLE patients. Encouragingly, these advancements hold the potential to revolutionize the management of TLE, delivering a better quality of life for patients.

1. Introduction

Temporal lobe epilepsy (TLE) represents a predominant subtype of epilepsy, affecting over 400,000 individuals within the United States and approximately 50 million people worldwide [1]. The etiological underpinnings of TLE, while not fully elucidated, are closely associated with aberrant electrophysiological processes within the cerebral cortex. These anomalies often result from scarring or traumatic insults to the temporal lobe. Common causes of TLE include head injury, infection, brain tumors, and genetic factors. A typical seizure sequence is characterized by an initial phase known as an epileptic aura, which is marked by cognitive or affective alterations. This initial phase is customarily succeeded by limitations in motor activity, a vacant gaze, modifications in linguistic capabilities, and automatisms [2,3]. The

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process of diagnosing TLE is complex, necessitating a comprehensive approach that combines patient's medical history, neurological examinations, and appropriate laboratory analyses. In the clinical evaluation of TLE, physicians also employ neuroimaging techniques such as electroencephalograms (EEGs), video EEG monitoring, magnetic resonance imaging (MRI), and computerized tomography (CT). These modalities assist in the assessment of the electrophysiological characteristics of the brain and in the detection of structural anomalies or lesions [4,5]. TLE can be further classified as either mesial temporal lobe epilepsy (mTLE), the more common form, or neocortical temporal lobe epilepsy (nTLE), with average onset ages of 10.9 years and 23.2 years, respectively [2].

Anterior temporal lobectomy (ATL) is a neurosurgical procedure recommended for TLE patients unresponsive to medications or other modalities of treatment [6,7]. ATL entails resecting the lateral and mesial temporal structures, either en bloc or separately [8]. Surgical resection of the anterior temporal lobe has proven to be an effective TLE treatment option, controlling seizures in up to 80 % of patients [9,10]. Post-surgical seizure outcomes are primarily assessed using the Engel Epilepsy Surgery Outcome Scale, a stratification system that categorizes seizure incidence into six distinctive classes [11]. Although seizure outcomes are generally favorable following an ATL procedure, less desirable cognitive outcomes, such as declines in verbal memory, episodic memory, and naming can occur [12–14].

Surgical damage to the temporal lobe can result in changes to cognition, behavior, memory, language, and personality [10]. To minimize the extent of temporal lobe damage and reduce the incidence of adverse effects, determining the seizure focus is one of the most crucial steps in the strategic planning of an ATL. Precise localization of the seizure focus further reduces the risk of post-surgical seizures. The primary techniques employed for the accurate delineation of the seizure focus include magnetic resonance imaging (MRI) and electroencephalograms (EEGs) [5]. While MRIs can identify structural lesions contributing to epileptic seizures, they exhibit limited capacity in localizing seizure foci in the absence of structural anomalies [4]. EEGs, while adept at detecting surface brain electrical activity, encounter difficulties in pinpointing deep-seated seizure foci within the temporal lobe. To detect such foci, more invasive methods, such as intracranial EEG monitoring (which places electrodes directly on the brain's surface), are required to accurately localize the seizure focus [15]. Furthermore, the data procured from EEGs is limited to the duration of the recording session, and therefore they may not adequately capture all seizure events.

An additional critical aspect in ATL planning involves predicting post-surgical outcomes, with a focus on declines in episodic memory, verbal memory, and, most importantly, seizure recurrence [13,14]. Understanding post-surgical outcomes enables physicians to make informed decisions regarding ATL surgery and proactively develop targeted post-surgery treatment plans. Several multivariate models have been developed to predict the impact of ATL on episodic, verbal, and seizure outcomes [16–19]. These models consider factors such as the hemisphere of resection, hemisphere dominance as measured by the Wada test, the baseline frequency/severity of seizures, and baseline memory assessed through tests like the Intracarotid Amobarbital Test (IAT) [20]. A commonality across these multivariate models is the incorporation of neuroimaging techniques, with MRI, functional MRI (fMRI), and EEGs being the most frequently utilized. These imaging techniques are employed to analyze structural elements, identify patterns in interictal epileptiform discharges, and quantify memory test results.

Positron emission tomography (PET) has emerged as a valuable tool in the evaluation of ATL in cases of TLE, augmenting traditional neuroimaging modalities such as MRIs and EEGs. Despite promising evidence supporting the application of PET in the management of TLE with ATL, its use is not as widespread as traditional imaging techniques. PET's distinguishing feature is its high sensitivity relative to other imaging methods, coupled with its capacity to detect nonstructural abnormalities in a relatively non-invasive manner [5,21]. The existing literature on PET's application in ATL primarily focuses on the [^{18}F] fluorodeoxyglucose (FDG) radiotracer, which enables detection of metabolic abnormalities, such as hypometabolism, within seizure foci. In recent years, PET has been increasingly utilized in the preoperative evaluation of patients undergoing ATL resection for TLE. PET's applications in the context of ATL include the identification of the seizure focus, the determination of the extent of the resection, and the prediction of postoperative outcomes. Several studies have examined the utility of PET in the context of ATL resection for TLE, yielding promising results. One of the earliest reported studies involving the use of PET with an ATL was described by Bairamian et al., wherein FDG-PET imaging was used to guide an ATL, resulting in improved control over the patient's epilepsy [22]. Subsequent studies have compared PET to other neuroimaging methods, such as MRI and EEGs, examining the potential benefits that may arise from integrating PET into the ATL surgery planning protocol [23,24]. Studies have also investigated PET's effectiveness in localizing the seizure focus, quantifying the extent of TLE, facilitating ATL surgery decision-making, predicting postoperative outcomes in terms of seizure recurrence and memory alterations, and utilizing radiotracers other than FDG. In conclusion, PET demonstrates significant potential to enhance the efficiency and quality of ATL procedures, thereby improving prognosis for TLE patients who exhibit resistance to antiepileptic medications.

2. Methods

2.1. Literature search and study selection

A comprehensive literature search was conducted using the PubMed, SCOPUS, and ScienceDirect databases from 1985 to 2022 to identify relevant articles following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. These references were reviewed by two independent reviewers, and a third reviewer was consulted in cases of discrepancies. The search criteria included the following terms:

1. PubMed: ("positron emission tomography" OR "PET") AND "temporal lobe epilepsy" AND ("anterior temporal lobectomy" OR ATL): 169 results.
2. After removal of duplicates, 153 results remained for screening.
3. Post-screening, 101 articles were excluded based on the set inclusion and exclusion criteria, leaving 52 articles eligible for review. The PRISMA flow diagram of this process is shown in Fig. 4.

We limited our search to articles available in English. Article quality, study type, and patient outcomes were evaluated. Inclusion criteria specified studies that assessed the use of PET imaging for localizing seizure foci and predicting post-surgical outcomes in patients with temporal lobe epilepsy undergoing anterior temporal lobectomy. Studies included in the analysis were those that provided detailed comparisons of PET imaging with other diagnostic tools used in presurgical evaluation, including clinical evaluation, scalp EEG (both ictal and interictal), and invasive techniques like subdural strip or FO electrodes. Exclusion criteria involved studies involving pediatric patients, animals, case reports, letters, conference abstracts, meta-analyses, and non-clinical studies. The selection criteria prioritized studies that offered quantitative data on the influence of these modalities on surgical decision-making, such as the choice between amygdalohippocampectomy, tailored resection, or classical anterior lobectomy, and their subsequent impact on surgical outcomes. To ensure robust comparisons, we emphasized studies that provided data on sensitivity, specificity, and accuracy of PET in relation to other modalities

2.2. Data extraction and quality assessment

From the 52 eligible articles, data extraction was performed by two

independent reviewers. Any discrepancies were resolved through discussion or consultation with a third reviewer. The following information was extracted from each included study: study title, author, year of publication, sample size, treatment modality, histology, PET radiotracer used and reported outcomes such as seizure control and changes in memory. The quality of each article was assessed using the Newcastle-Ottawa Scale by two independent reviewers.

2.3. Data analysis

A descriptive analysis was performed to summarize the characteristics and findings of the included studies. The reported outcomes, such as seizure control and changes in memory, were synthesized and presented. The findings of the included studies were synthesized and discussed in the context of the research questions and objectives of this review. Limitations and potential sources of bias within the included studies were also considered during data analysis and interpretation.

3. Results

The systematic literature search yielded 169 potential articles across PubMed, SCOPUS, and ScienceDirect databases. After the elimination of duplicates and further screening, a total of 52 studies met the inclusion criteria and were subsequently analyzed. The publication years of these studies ranged from 1985 to 2022.

The selected studies employed a variety of treatment strategies and highlighted different histological findings. These investigations were mainly observational, with a few randomized controlled trials (RCTs) and sample sizes ranging from tens to hundreds of patients. The most frequently used PET radiotracer across studies was FDG.

3.1. Seizure foci localization

The ability of PET imaging, specifically FDG-PET, to localize seizure foci demonstrated a sensitivity range between 75 % and 93 % across different studies. Notably, Carvalho et al. demonstrated that depending on the resolution of the PET/CT scanner, the sensitivity of interictal FDG PET/CT to detect hypometabolism varied according to the location of the epileptogenic zone (EZ): approximately 80 % in temporal lobe epilepsy, 52 % in frontal lobe epilepsy, and 53 % overall. The accuracy of this localization improved considerably when PET was combined with other neuroimaging techniques such as MRI and EEGs, with some studies showing that PET enabled the detection of seizure foci in 75–100 % of cases where MRI findings were inconclusive or negative [26]. Valk et al. found that in cases where MRI findings were normal, FDG-PET detected hypometabolism in 75 % of patients, highlighting the utility of PET in identifying seizure foci in MRI-negative cases [29].

3.2. Comparison with other techniques

When compared to perfusion MRI, PET showed similar or slightly superior sensitivity in identifying seizure foci, particularly in MRI-negative patients. Perfusion MRI relies on detecting changes in cerebral blood flow, which may not always correlate with metabolic abnormalities detected by PET. While MRI is effective in identifying structural lesions, its ability to detect non-structural abnormalities like those seen in PET is limited.

Magnetic Resonance Spectroscopy (MRS) and functional MRI (fMRI) are additional techniques used in pre-surgical planning. MRS has shown utility in detecting metabolic changes similar to PET, particularly in patients with temporal lobe epilepsy, but its sensitivity varies depending on the metabolites targeted and the specific brain regions assessed. MRS, like MRI, may miss non-structural abnormalities that PET can detect. fMRI is valuable for mapping functional areas of the brain, especially in the context of language and motor functions, but it is less effective in localizing seizure foci compared to PET.

Electrophysiological methods such as ECoG and SEEG offer high spatial and temporal resolution for identifying seizure foci. However, these methods are invasive, involving intracranial electrode placement, which carries risks. PET, being non-invasive, provides a valuable alternative or complementary tool. Studies have shown that the combination of PET with EEG, including invasive monitoring techniques, often results in higher localization accuracy and improved post-surgical outcomes. For example, a combination of FDG-PET with ECoG or SEEG has been shown to enhance the detection of epileptogenic zones, particularly in cases where surface EEG alone is insufficient.

3.3. Predicting Post-ATL outcomes

Numerous studies demonstrated PET imaging's capability to forecast potential cognitive changes and control of seizures post-surgery. For predicting cognitive outcomes, verbal memory, episodic memory, and naming abilities were often identified as the cognitive functions most affected post-ATL. Specifically, FDG-PET demonstrated an association between greater relative hypometabolism in specific brain regions and improved postoperative seizure outcomes. A substantial correlation was found in most studies between pre-surgical PET findings and post-surgical seizure control, as measured using the Engel Epilepsy Surgery Outcome Scale. Sensitivity and specificity values varied depending on the radiotracer and brain region analyzed, with ranges of 70–89 % reported for seizure outcome predictions.

Comparatively, studies using perfusion MRI, MRS, and fMRI have reported variable predictive capabilities, with some showing a correlation between imaging findings and postoperative cognitive outcomes. However, the sensitivity and specificity of these modalities generally fall short when compared to PET, especially in cases where MRI findings are negative or inconclusive. ECoG and SEEG, while providing precise localization of epileptogenic foci, primarily contribute to predicting seizure outcomes rather than cognitive ones.

3.4. Methodological quality and limitations

The methodological quality of the studies, as assessed via the Newcastle-Ottawa Scale, varied. Some studies demonstrated high quality, while others revealed potential biases and methodological shortcomings. Common limitations across the studies were identified as sample size, heterogeneity of treatment modalities, and histological findings. Additionally, the availability and accessibility of PET imaging technology and the associated financial costs were noted as significant limitations in some studies.

In conclusion, the literature analysis highlighted the significant potential of PET imaging, especially FDG-PET, for improving the surgical management of TLE patients undergoing ATL. Despite some methodological limitations, the findings underscore the necessity for further research, including larger, multi-center RCTs, to confirm and extend these results.

4. Discussion

4.1. Seizure Foci Localization

4.1.1. [18F]fluorodeoxyglucose (FDG)

FDG is the most commonly utilized radiotracer in the preoperative evaluation of patients with temporal lobe epilepsy (TLE). In approximately 80 % of cases, FDG-PET discerns the epileptogenic temporal lobe, often in combination with conventional imaging methods such as CT and MRI [25]. FDG-PET provides insight into cerebral metabolism, thereby facilitating the detection of abnormalities such as hypermetabolism or hypometabolism, which can assist in the localization of seizure foci. Specifically, Caravalho et al. demonstrates that depending on the resolution of the PET/CT scanner, the sensitivity of interictal FDG PET/CT to detect hypometabolism varies according to the location of the

EZ: in temporal lobe epilepsy, it is nearly 80 %, whereas it is only 52 % in frontal lobe epilepsy and only approximately 53 % overall. However, notably, FDG-PET did not differ significantly with EEG monitoring in determining the epileptogenic zones (P =0.85), signifying non-inferiority [26,27]. Interictal FDG-PET typically reveals hypometabolism in one temporal lobe or bilateral temporal hypometabolism with a more dominant side. Unilateral frontal, parietal, thalamic, or basal ganglia hypometabolism is generally found ipsilateral to the temporal hypometabolism [28].

The initial recognition of FDG-PET in presurgical planning arose from its ability to detect abnormalities in eleven TLE cases where MRI imaging yielded inconclusive results due to the absence of structural abnormalities. Valk et al. showed that in this cohort of 11 patients with partial complex epilepsy, FDG-PET detected hypometabolism in 75 % of cases (3 out of 4 patients) where MRI findings were normal. Furthermore, in the 7 patients where MRI showed structural abnormalities, FDG-PET detected corresponding hypometabolism in 100 % of cases. These findings underscore FDG-PET's crucial role in localizing seizure foci, especially when MRI fails to reveal structural abnormalities [29]. Additionally, the ictal and interictal SPECT procedure, which involves subtraction between the two scans, is resource-intensive and time-consuming, unlike FDG-PET. Despite these challenges, comparative analyses show that the sensitivity of FDG-PET is on par with ictal 99mTc-HMPAO SPECT, suggesting that FDG-PET could offer a more efficient alternative in certain clinical contexts. The sensitivity of ictal SPECT and interictal PET was 34/36 and 32/36, respectively, the difference was not statistically significant (X^2,=0.18, DF=1, P = 0.67) [30]. FDG-PET exhibited a significantly superior concurrence (0.93) with successful temporal lobectomy outcomes, in comparison to MRI (0.60) or Magnetic Resonance Spectroscopy (MRS) (0.75) [31]. Presurgical evaluation employing solely FDG-PET for patients without lesions (PET+/MRI-) demonstrated similar surgical outcomes to those patients with MRI-identified temporal lesions (MRI+). Furthermore, PET+/MRI- patients who underwent intracranial monitoring achieved surgical outcomes comparable to patients who underwent ATL without intracranial monitoring. Class I surgical outcomes at 2 and 5 years were 76 % and 75 % for PET+/MRI− patients and 71 % and 78 % for MRI+ patients (P = 0.68 for 2 years, 0.78 at 5 years using Fisher's exact test). The Kaplan-Meier survival curves using time to any seizure recurrence as a first event were not statistically different between PET+/MRI− patients and MRI+ patients at 5 years (P =0.44) [32]. A combination of FDG-PET with other non-invasive imaging modalities, such as scalp EEG, SPECT, MRI, and neuropsychological testing, yielded superior post-surgical outcomes (85 % seizure-free) compared to invasive subdural EEG focus localization (40 % seizure-free) [33].

A retrospective study revealed that patients with favorable surgical outcomes post-ATL had a larger proportion of total FDG-PET hypometabolism volume resected in comparison to those with less favorable outcomes (24.1 % versus 11.8 %, P = 0.02) [34]. Extratemporal hypometabolism has also emerged as a significant factor in the localization of seizure foci. Evidence suggests that ipsilateral thalamic hypometabolism identified by FDG-PET can aid in the lateralization of epileptic foci in most cases [35]. Furthermore, the presence of remote hypometabolism beyond the temporal lobe is associated with less optimal surgical outcomes (P <0.005), particularly in instances where hypometabolism is observed in the hemisphere contralateral of the epileptic lobe [36].

4.1.2. [15O]H_2O

$H_2^{15}O$-PET offers a sensitive approach for detecting alterations and irregularities in cerebral blood flow. When FDG and H_2O-PET were used to compare measurements of brain metabolism and blood flow in the preoperative evaluation of temporal lobe epilepsy patients before an anterior lobe lobectomy, a significant positive correlation was found between hypoperfusion and hypometabolism measured by H_2O and FDG, respectively (r=0.74, p <0.000). However, a negative correlation was observed in two out of 35 cases with no definitive cause determined. The hyperperfusion observed in these two cases could be explained by transient subclinical ictal activity in an epileptic focus unrecognized by surface EEG, uncoupling of blood flow, and glucose metabolism during interictal spike activity. If the subclinical ictal state is the true cause of the negative correlation, then the specificity of H_2O-PET can be calculated as 100 %. Additionally, the sensitivity and specificity of qualitative MRI was 60 % and 97 %. Out of 14 patients with normal MRI, FDG-PET and blood flow PET was abnormal in 11 patients (78 %), and 9 patients (64 %), respectively. O-15 water PET was superior to MRI for the detection of abnormal temporal lobes [37]. In summary, initial findings suggest that H_2O-PET may serve as a viable alternative to FDG-PET for seizure foci localization in patients with TLE. An advantage of H_2O- over FDG includes its potential use during an ictal event, or while a seizure episode occurs during the scanning process, although achieving this in practice may pose challenges. In particular, the relatively lower radiation dose associated with H_2O-PET, attributed to its short half-life of 2 min, offers a distinct advantage, making it especially suitable for use in populations such as children and young adults where minimizing radiation exposure is critical, even during challenging circumstances such as ictal events.

4.1.3. [11C]flumazenil FMZ-PET

[^{11}C]-flumazenil (FMZ), a radiotracer that binds to the benzodiazepine site of the γ-Aminobutyric acid (GABA(A)) receptor complex, has been found to be a valuable asset in assessing patients with neuronal damage. FMZ possesses several desirable properties, including polar metabolites that do not cross the blood-brain barrier, minimal nonspecific binding, and suitable kinetics. In patients with TLE, the seizure focus is associated with cortical decreases in FMZ binding, with an average reduction of 30 % in the seizure focus region [38].

FMZ-PET is particularly useful in MRI-negative TLE cases, where it has demonstrated greater sensitivity than FDG-PET in epileptogenic focus localization. In one study, abnormalities in FMZ binding were identified in 16 out of 18 MRI-negative refractory epilepsy cases, highlighting the potential utility of FMZ-PET in such situations [39]. FMZ-PET has also been shown to be more sensitive and accurate than FDG-PET in focus delineation, as confirmed by extracranial and intracranial EEG recordings across a study containing eight patients [40]. Furthermore, another study reported increased FMZ binding around the posterior horn of the ventricles, both ipsilaterally (z=2.53) and contralaterally (z=4.44) to the seizure [41].

4.1.4. 5-HT_{1A} receptor antagonists [18F]MPPF/[18F]FCWAY)

Research into the use of antagonistic radioligands for 5-HT_{1A} receptors such as [^{18}F]-4-(2′-methoxyphenyl)-1-[2′-(N-2-pirydynyl)-p-fluorobenzamido]-ethyl-piperazine (MPPF) and [^{18}F]-trans-4-fluoro-N-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexane carboxamide (FCWAY) for seizure focus localization in TLE is relatively scarce. Preliminary findings suggest a connection between decreased 5-HT_{1A} receptor binding and temporal lobe epileptic foci [42].

In one study, MPPF parametric binding potential (BP) decreases were identified in 90.5 % of patients diagnosed with TLE. Among these patients, BP coincided with the epileptogenic zone in 40 % of patients with mesial-TLE and 33 % in other TLE subtypes. Nevertheless, in all cases, decreases in BP aligned with correct identification of the epileptogenic temporal lobe, with no false positives in control subjects [43].

Comparatively, FCWAY BP was significantly reduced in MRI-negative TLE patients within the fusiform gyrus, hippocampus, and parahippocampus ipsilateral to the epileptic foci, as compared to normal controls. Of the 12 patients analyzed in this study, 11 patients had clearly lateralized epileptogenic zones. The evidence suggests that FCWAY may offer comparable or even superior seizure-focus localization potential to that of FDG. During pre-surgical planning for ATL, Theodore et al. reports that the probability of being seizure-free was explained by both FDG and FCWAY PET, but not MRI, with a significant additional FCWAY effect (χ^2_2=9.8796; P = 0.0072) after the probability

of being seizure-free was explained by FDG. Although MRI alone was not predictive, any combination of 2 lateralizing imaging studies was highly predictive of seizure freedom [44,45].

In summary, existing literature indicates that 5-HT_{1A} antagonist radiotracers, such as MPPF and FCWAY, are promising agents for focus localization, particularly in cases of MRI-negative TLE. The predictive capacities of post-surgical outcomes for each radiotracer will be discussed separately in the following sections. It should be noted that this review of radiotracers and their applications in localizing seizure foci in TLE is not exhaustive. Future studies are required to further assess the comparative efficacy and potential combinations of these and emerging radiotracers.

4.2. Predicting Post-ATL outcomes

The utilization of PET technology in predicting post-ATL surgical outcomes has seen considerable growth since the introduction of PET in the ATL planning process. The majority of the existing literature focuses on the impact of hypometabolism in specific brain regions, as measured by FDG-PET, on seizure outcomes. A smaller body of literature examines PET's predictive capabilities regarding non-seizure outcomes, as well as the potential of non-FDG radiotracers in predicting surgical outcomes.

4.2.1. Non-seizure-related post-surgical outcomes

PET has proven to be a useful tool for identifying clinical markers relevant to memory outcomes. Verbal memory is processed in the left medial temporal lobe. With particular reference to verbal memory, which is processed primarily in the left medial temporal lobe, it has been observed that patients undergoing left anterior temporal lobectomy (ATL) who exhibit significantly greater verbal memory decline post-surgery compared to those with moderate to severe hypometabolism [46].

PET has proven to be a useful tool for identifying clinical markers relevant to non-seizure-related cognitive outcomes after temporal lobectomy. A study by Kamm et al. in 2017 compared FDG-PET uptake asymmetry in regions of the temporal lobe to neuropsychological assessment scores in 47 patients with unilateral temporal lobe epilepsy who underwent surgical resection. Verbal memory, language and naming, executive function, visual search, and motor speed were assessed. In patients where the dominant temporal lobe was resected, FDG-PET uptake asymmetry in the medial anterior temporal lobe significantly predicted outcomes in verbal memory ($P = 0.02$) and naming ($P = 0.02$). In patients where the non-dominant temporal lobe was resected, no regional uptake asymmetry could predict verbal memory and naming outcomes. These results are consistent with verbal memory and naming being primarily processed in the dominant medial anterior temporal lobe. Additionally, FDG-PET uptake asymmetry in all regions of the temporal lobe, across all patients and irrespective of dominance, significantly predicted outcome scores in executive functioning, visual scores, and motor speed. In all cases, a greater degree of relative hypometabolism on FDG-PET study was correlated with improved post-surgical outcomes [47].

4.2.2. Seizure outcome prediction

4.2.2.1. General hypometabolism. A major study utilized FDG-PET to delineate temporal and extratemporal hypometabolism (EH) in patients with mTLE and evaluate EH's predictive ability for seizure outcomes post-ATL. Through the use of statistical parametric mapping (SPM), the study identified and classified statistically significant hypometabolic brain regions into one of three categories: temporal lobe hypometabolism, contiguous hypometabolism (hypometabolism in brain regions adjacent to the temporal lobe), or remote hypometabolism (hypometabolism not contiguous with the temporal lobe) [48].

Remote hypometabolism was found to be an independent predictor of seizure outcomes ($P < 0.005$), with the extent of remote hypometabolism correlating with the occurrence of secondarily generalized tonic–clonic seizures. Among the remote hypometabolism cohort, 62 % of patients achieved seizure-free outcomes if hypometabolism was confined to the hemisphere ipsilateral to the side of surgery, compared to only 30 % of patients with hypometabolism also present in the contralateral hemisphere [36]. Patients with remote hypometabolism and poor outcomes presented with more extensive hypometabolism in the regions listed in Table 1. Notably, a separate study combining FDG-PET with 3D-SSP (three-dimensional stereotactic surface projection) did not find the frontal lobe to be a significant predictor of post-surgical outcome (Fig. 5) [49].

Patients with remote hypometabolism also exhibited hypometabolism in the ipsilateral insula, ipsilateral occipital lobe, contralateral temporal, parietal, and occipital lobe, and thalami. However, this was not significantly different between groups with positive or negative outcomes [36]. The aforementioned study that combined PET with 3D-SSP did not find the parietal lobe, occipital lobe, or thalamus to be significant predictors [49]. However, a recent study using a machine learning framework found that FDG-PET identified hypometabolism and fMRI variations in the contralateral hippocampal network were associated with unfavorable surgical outcomes [50].

4.2.2.2. Extratemporal insular hypometabolism. In one study, the focus was placed on the potential predictive power of insular hypometabolism regarding surgical outcomes in pediatric patients undergoing ATL [51]. Possibly due to the limited sample size, the study did not establish a significant correlation between insular hypometabolism and post-surgical outcomes ($P = 0.266$), a conclusion in line with previous research [25]. Nevertheless, a non-significant trend suggested a tendency towards improved surgical outcomes in patients without insular hypometabolism, suggesting that an examination involving a larger patient cohort could potentially yield different results.

4.2.2.3. Extratemporal cortical hypometabolism. A separate study examined the correlation between extratemporal hypometabolism, as evidenced by FDG-PET, and seizure outcome post-ATL in patients with medically intractable TLE. All patients exhibited hypometabolism ipsilateral to the temporal lobe. Patients were evaluated according to three specific cortical metabolic patterns: hypometabolism confined to the ipsilateral temporal cortex (Type 1), extratemporal cortical hypometabolism limited to the ipsilateral cerebral hemisphere (Type 2), and hypometabolism in the contralateral cerebral cortex (Type 3). 78 % of Type 1 patients achieved complete seizure-free outcomes (Engel class Ia), while only 44 % and 22 % of Type II and III patients, respectively, achieved seizure-free outcomes (Fig. 1). Multivariate analysis revealed that cortical metabolic patterns were an independent factor in predicting postoperative seizure outcomes ($P<0.05$) [25].

4.2.2.4. Extratemporal thalamic hypometabolism. The prevailing

Table 1
Regions of Hypometabolism Seen in Patients with Poor Seizure Outcomes. Remote hypometabolism independently predicts the occurrence of poor seizure outcomes ($P < 0.005$), with statistically significant regions seen in the ipsilateral and contralateral frontal lobe, as well as the ipsilateral and contralateral cingulate cortex. Results adapted from Wong et al. 2010 [64-86].

Ipsilateral Frontal Lobe	$P < 0.005$
Contralateral Frontal Lobe	$P < 0.005$
Ipsilateral Central Cortex	$P = 0.006$
Contralateral Central Cortex	$P = 0.07$
Ipsilateral Cingulate Cortex	$P < 0.005$
Contralateral Cingulate Cortex	$P < 0.005$
Ipsilateral Parietal Lobe	$P = 0.03$
Ipsilateral Basal Ganglia	$P = 0.01$

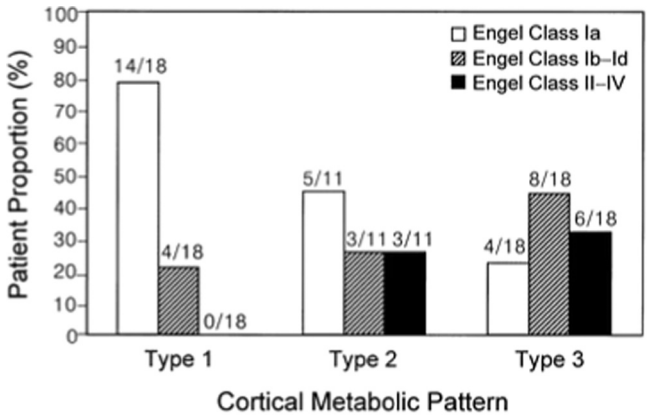

Fig. 1. Relationship between Cortical Metabolic Patterns and Postoperative Seizure Outcomes. Engel Class Ia = seizure-free outcomes; Engel Class Ib-Id = almost seizure free; Engel Class II-IV = rare seizures or patients with a non Class I outcome. Type 1 = hypometabolism confined to the ipsilateral temporal cortex; Type 2 = extratemporal cortical hypometabolism limited to the ipsilateral cerebral hemisphere; Type 3 = hypometabolism in the contralateral cerebral cortex. The completely seizure-free (Engel class Ia) rates were significantly different across the three groups of patients with different types of cortical metabolic pattern ($P<0.005$). Figure reproduced with permission from Choi et al., 2003.

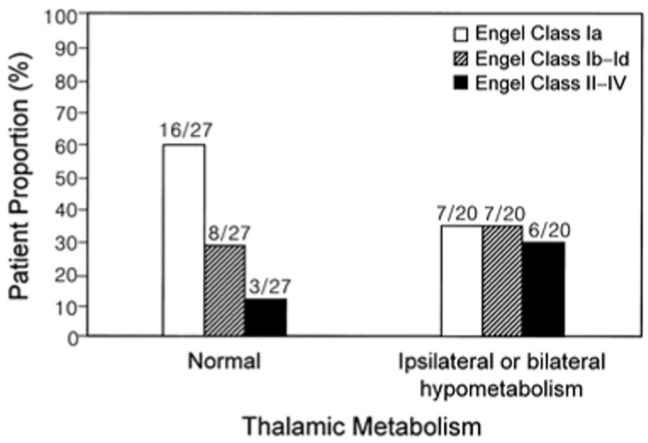

Fig. 2. Relationship between Thalamic Metabolism and Postoperative Seizure Outcomes. Engel Class Ia = seizure-free outcomes; Engel Class Ib-Id = almost seizure free; Engel Class II-IV = rare seizures or patients with a non Class I outcome. The completely seizure-free (Engel class Ia) rates were significantly different between patients with and patients without thalamic hypometabolism ($P<0.05$). However, thalamic hypometabolism was associated with, but not an independent predictor of, postoperative seizures. Figure reproduced with permission from Choi et al., 2003.

consensus in the existing literature regarding the capacity of thalamic hypometabolism in the prediction of post-surgical seizure outcomes suggests an association with poor seizure outcomes. However, it is yet to be definitively established as an independent prognostic marker. One of the earliest studies to establish this association observed differences between thalamic hypometabolism ipsilateral (thalamic asymmetry) and contralateral (reverse thalamic asymmetry) to the hypometabolic temporal lobe. Notably, only 8 % of patients exhibiting no thalamic asymmetry (n=38) and 22 % with thalamic asymmetry (n=37) experienced post-surgical seizures. Patients with reverse thalamic asymmetry (n=5) demonstrated the strongest association; all of the patients experienced post-surgical seizures (Table 2) [52].

Another study reinforced this association, demonstrating that 35 % of patients with thalamic hypometabolism achieved seizure-free outcomes, as opposed to 59 % of patients with normal thalamic metabolism ($p < 0.05$) (Fig. 2). However, multivariate analysis revealed that thalamic hypometabolism was associated with, but not an independent predictor of, postoperative seizures [25]. This observation was corroborated by a subsequent study, which visually identified thalamic hypometabolism, but failed to establish a correlation with postoperative seizure outcomes [53]. When PET imaging was combined with 3D-SSP, thalamic hypometabolism was not found to be a significant predictor of post-surgical outcomes [49].

4.2.2.5. Ipsilateral temporal lobe hypometabolism. Several studies have concluded that hypometabolism in the temporal lobe ipsilateral to the resection site is associated with positive postoperative seizure outcomes [20,25,54–56]. One study reported that 89 % of patients with ipsilateral temporal hypometabolism achieved a favorable surgical outcome [25]. However, other research has suggested that ipsilateral temporal hypometabolism is likely a diagnostic indicator rather than an independent prognostic indicator [57].

An investigation which combined FDG-PET and 3D-SSP suggests hypometabolism in the ipsilateral temporal lobe is a significant predictor of positive surgical outcomes. Moreover, this study examined subregions within the temporal lobe and determined that the hippocampus and amygdala were the most significant predictors (P = 0.025, Fig. 3) [49].

Furthermore, a 2017 study found that FDG uptake asymmetry in the medial anterior temporal (r=0.36, P = 0.01) and medial posterior temporal lobe (r=0.30, P = 0.04) were significant predictors of seizure outcomes. It was observed that a greater degree of relative hypometabolism in these regions corresponded with improved seizure outcomes [47].

Table 2
Proportion of Patients Who Experienced Seizures Based on Differences in Thalamic Asymmetry. Patients with thalamic hypometabolism ipsilateral to the hypometabolic temporal lobe, also known as thalmic asymmetry had a seizure incidence of 22 % (8/29), while patients with thalamic hypometabolism contralateral to the hypometabolic temporal lobe, also known as reverse thalamic asymmetry had a seizure incidence of 100 % (5/5). Patients with no thalamic asymmetry had a seizure incidence of 8 % (3/35). Results adapted from Newberg et al., 2000.

Type of asymmetry	Seizures	No seizures	% Seizures
Reverse thalamic asymmetry (n = 5)	5	0	100
No thalamic asymmetry (n = 38)	3	35	8
Thalamic asymmetry (n = 37)	8	29	22

4.3. Methodological quality and limitations

Despite the introduction of new generation PET scanners that offer improved sensitivity and consequently, lower radiation doses, ionizing radiation exposure from PET imaging remains a limitation that warrants careful management [58]. Clinicians and technologists must strike a balance between the clinical benefits of PET imaging and the potential risks associated with radiation exposure. Despite PET being a reliable and stable imaging modality, the utilization of single-voxel proton MR spectroscopy (MRS) and MRI may offer safer, more accessible alternatives for locating seizure foci if the results of these imaging methods concur [31].

The accessibility of PET imaging can be limited due to the specialized equipment and facilities required. PET scanners are not as ubiquitous as other modalities, such as CT or MRI, which can result in longer waiting times or restricted access in certain areas. The requirement for on-site cyclotrons to produce radiotracers, such as ^{11}C and ^{15}O, further contributes to the limited availability of PET scans [59]. This limitation creates challenges for patients seeking rapid access to PET scans, potentially impacting the timeliness of diagnosis, treatment planning, and monitoring. Overcoming this constraint requires expanding

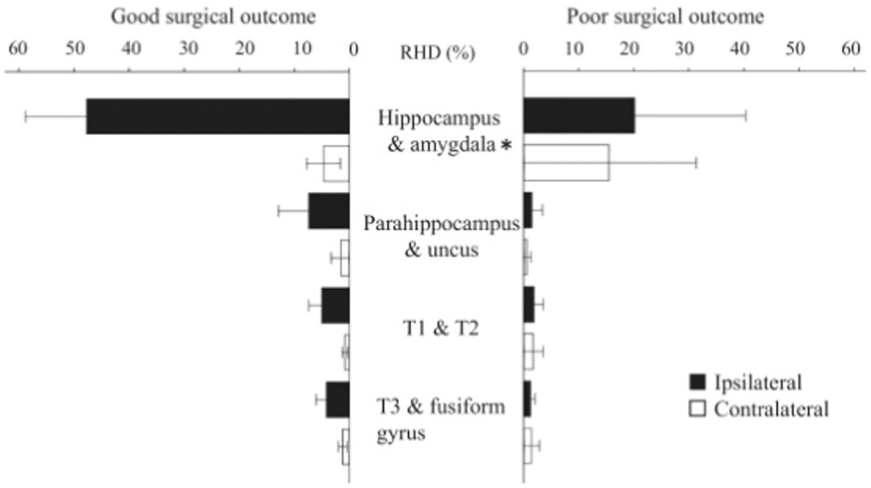

Fig. 3. Contrasting ratio of hypometabolism difference (RHD) between good and poor surgical outcome groups. In the good surgical outcome group, the RHD ipsilateral to the surgical side was significantly higher than that of the contralateral side in all regions of interest. However, the RHD was not significant in all regions of interest in the poor surgical outcome group (*$p<0.05$). Figure reproduced with permission from Higo et al., 2016.

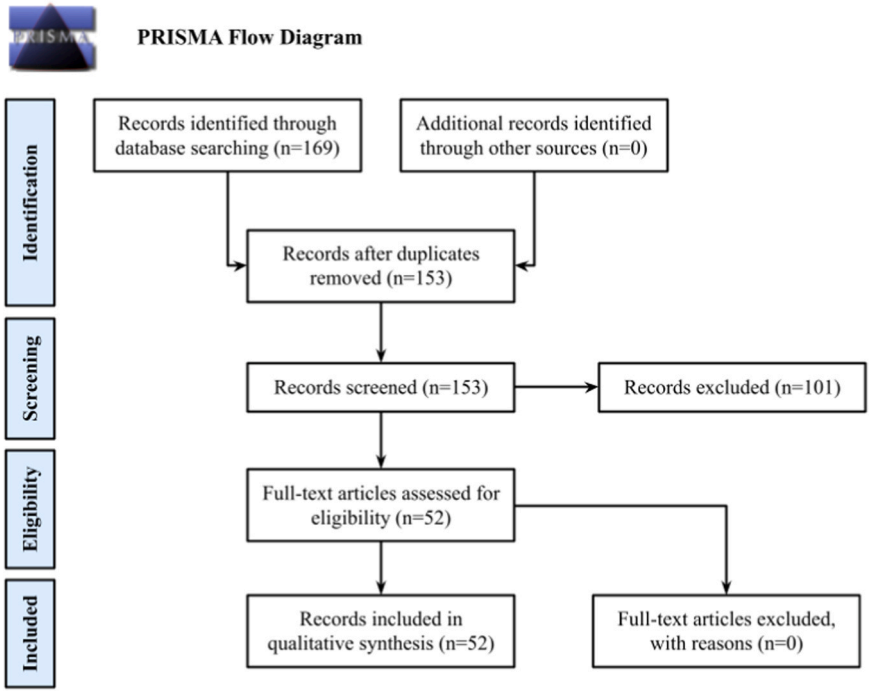

Fig. 4. PRISMA Flow Diagram.

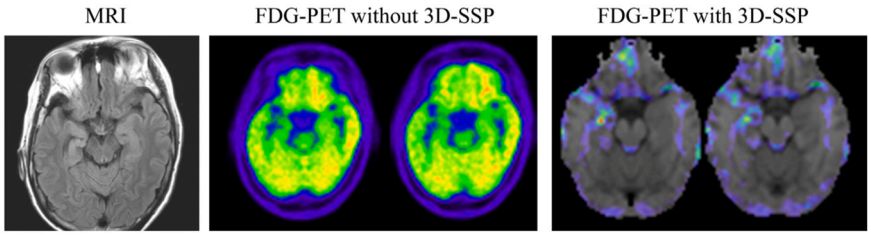

Fig. 5. MRI and FDG-PET findings with and without 3D-SSP in the patients with well-lateralized epileptic focus. In this case, atrophic mesial temporal structures on MRI-FLAIR imaging show hypometabolism on the FDG-PET with and without the 3D-SSP analyses. Adapted from Higo et al., 2016.

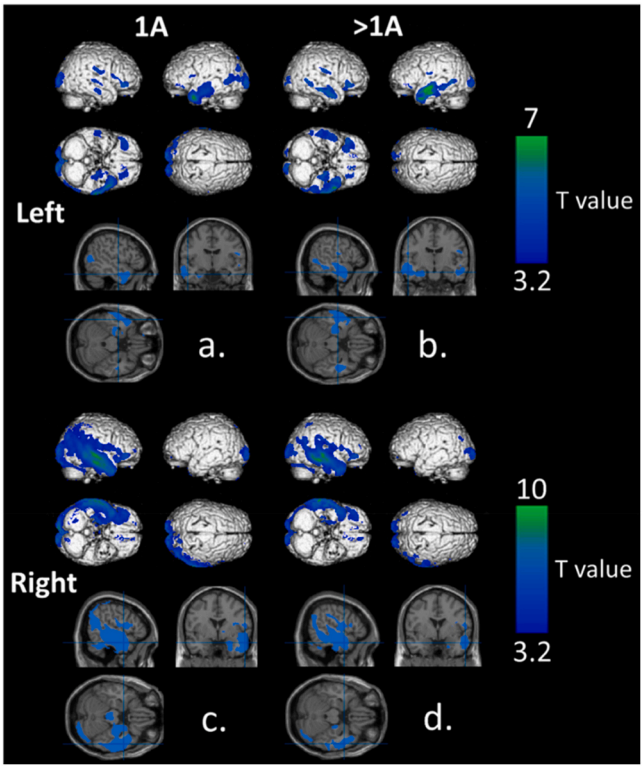

Fig. 6. Significant findings on whole-brain 3D-rendered volumes and main temporal clusters represented on slice sections of MRI template in the MNI space at a p-voxel value of 0.001 corrected for the cluster volume of voxel-to-voxel comparisons between the left IA (a) > IA (b) groups compared to healthy controls and the right IA (c) and > IA groups (d) compared to the healthy controls. Highlighted areas represent hypometabolic areas of TLE patients. Adapted from Doyen et al., 2022.

infrastructure and resources to enhance the accessibility of PET imaging.

The financial aspect of PET imaging may also present a limitation. The costs involved encompass a range of factors, including the production of radiotracers, the operation of specialized PET scanners, and the expertise required for accurate scan interpretation. The production of radiotracers alone can constitute a substantial part of the cost, with cyclotrons costing several million dollars to install and maintain [60]. The higher cost of PET imaging may limit its accessibility, present challenges for healthcare systems, and necessitate careful resource allocation to ensure cost-effectiveness.

4.4. Combination imaging

Presurgical planning is a key component for various aspects of ATL, such as localization of lesions as well as surgical decision-making. In a study that analyzed the relationship between preoperative evaluations and surgical outcomes for 47 patients with temporal lobe epilepsy that underwent ATL, the study concluded that while ATL is effective in achieving seizure control postoperatively, detailed and thorough presurgical evaluations are necessary, particularly for identifying the concordance of lesions and the epileptogenic foci [61]. Preoperative evaluations for these patients included serial EEG, MRI, MRS, FDG-PET, and neuropsychological assessment. In considering preoperative planning, several studies have shown that, when used alongside other imaging modalities, FDG-PET can play a role in enhancing pre-surgical planning (including localization) and justifying ATL [32,34].

4.4.1. FDG-PET and scalp-sphenoidal EEG

One study from 1990 indicates that the combination of FDG-PET and scalp-sphenoidal EEG is highly accurate in localizing epileptogenic regions in medically refractory patients. Of the 153 patients studied, FDG-PET was only misleading in three patients (1.96 %) due to the presence of nonepileptic structural defects that demonstrated extra-temporal/contralateral hypometabolism. As such, this study shows that the combination of FDG-PET and scalp-sphenoidal EEG is safe in the use of justifying anterior temporary lobectomy for patients with medically refractory epilepsy [27].

4.4.2. Interictal FDG-PET and Ictal SPECT

Other studies have compared the utility of ictal SPECT and interictal PET for the purpose of localizing the epileptogenic focus in patients with medically intractable complex partial seizures. In a retrospective analysis of 67 patients, the combination of ictal SPECT and interictal FDG-PET was utilized in 36 patients (53.73 %). For these patients, ictal SPECT and interictal PET were found to be equally sensitive; both modalities were reliable for localization in MRI-negative patients. Specifically, the sensitivity of ictal SPECT and interictal PET was 34/36 and 32/36, respectively, the difference was not statistically significant ($\chi 2$=0.18, DF=1, P=0.67) [30]. FDG-PET and SPECT also provide the neurosurgeon greater ability to visualize non-lesional foci, leading to better long-term postoperative outcomes as per a 2013 review of management and surgical outcomes for medically refractory epilepsy. Visualization is especially important because the resection of mesial structures with preservation of the neocortex allows for optimal seizure control while minimizing neurological deficits postoperatively [62].

In addition to better visualization, both techniques can be used in presurgical evaluations to: 1) determine the side of ATL and the area of multilobar resection without EEG recording during epileptic episodes, 2) discern high-probability sites of intracranial electrode placement for recording ictal onsets, and 3) determine prognosis following resection of the anterior temporal lobe. Of note, the sensitivity and specificity of both PET and SPECT can be increased via cross-referencing of structural and functional images (e.g. MRI) as well as by statistical comparison of patient data with normal data sets [21].

4.4.3. FDG-PET and MRI

Initial research suggests that the use of PET in combination with MRI can also, in specific circumstances, avoid the need for invasive techniques such as intracranial EEG. One study assessed whether non-invasive data could predict outcomes of intracranial EEG and ATL in patients with bitemporal independent seizures. The study found that lateralized findings on MRI and PET, a history of febrile convulsions, and shorter duration of seizures were associated with focal onset on intracranial EEG. The study also concluded that while non-invasive data did not predict surgical outcomes and while intracranial EEG is usually necessary for localization, patients with focal abnormalities on PET and MRI *and* a history of febrile convulsions may not need further workup [63].

Furthermore, a study that compared the use of ^{18}F-FCWAY PET and cerebral metabolic rate of glucose (CMRglc) PET for planning temporal lobectomy found that while MRI alone was not predictive of seizure freedom, both types of PET imaging offered utility in planning, with ^{18}F-FCWAY PET providing greater predictive value than CMRglc PET. The study demonstrated that the combination of any two lateralizing imaging studies was highly predictive of postoperative seizure cessatio [45].

FDG-PET can also be used to determine appropriate modifications to anteromesial temporal lobectomy (ATML) when used in combination with MRI. One study suggests that mesial structure-sparing resection for TLE (which spares the hippocampus and parahippocampal gyrus) may be worth considering for patients with temporal lobe foreign tissue lesions outside the mesial structures, as well as for those demonstrating temporal lobe hypometabolism on FDG-PET despite a normal MRI [63]. In these cases, FDG-PET can provide unique benefit in combination with MRI for MRI-negative patients given that mesial structure-sparing modifications can ultimately decrease functional consequences while

offering effective seizure control. In summary, the combination of PET and MRI offers the ability to predict seizure-free outcomes, potentially avoid invasive testing, and plan for beneficial modifications.

4.4.4. Interictal FDG-PET and Ictal stereo-EEG (SEEG)

The combined application of FDG-PET and ictal stereo-electroencephalography (SEEG) has enhanced our comprehension of the origin and mechanism of oroalimentary automatisms (OAAs). The authors of a 2019 study discovered that, through of analysis of interictal FDG-PET imaging and ictal SEEG, the rolandic operculum is most likely the symptomatogenic zone of OAAs in mTLE. The researchers also found that there is a unilateral functional connection from the hippocampus to the rolandic operculum during seizure onset in mTLE; this functional connection serves as the basis for OAA generation [65]. These findings, and similar applications of FDG-PET and ictal SEEG, can offer insight specifically into OAA generation and provide additional useful information for presurgical planning.

In conclusion, the use of PET imaging, with a focus on radiotracers such as FDG, H_2O, FMZ, MPPF, and FCWAY, brings about considerable potential for improving the precision and effectiveness of ATL procedures for TLE patients. PET imaging provides an invaluable tool in identifying seizure foci, establishing resection margins, and forecasting postoperative results. Amongst the radiotracers, FDG-PET has shown superior sensitivity in the detection of epileptogenic temporal lobes, often when structural abnormalities are not detected on MRI scans, and presents the potential for predicting verbal memory outcomes·H_2O-PET offers a highly sensitive technique to monitor blood flow changes during an ictal event. FMZ-PET has demonstrated value in MRI-negative TLE cases, providing higher sensitivity than FDG-PET in locating epileptogenic foci. The 5-HT_{1A} antagonists, radiotracers FCWAY and MPPF, show promise for localizing seizure foci, particularly in MRI-negative TLE, although their use is still relatively limited compared to traditional imaging techniques.

The fusion of PET with other imaging modalities such as EEG and MRI has shown to enhance localization accuracy and surgical outcomes. With the capability to optimize preoperative planning, provide justification for ATL, and direct surgical approach modifications, PET presents substantial promise. While challenges such as radiation exposure, limited accessibility, and financial constraints remain, PET imaging has the potential to improve outcomes, especially for TLE patients who are unresponsive to epilepsy medications.

The advent of PET-MRI as a novel modality presents a unique opportunity to further enhance the role of imaging in managing this disabling brain disorder. With superior anatomical detail from MRI and metabolic information from PET, this integrated approach may offer unparalleled insights into epileptogenic foci and peri-ictal changes, while minimizing the shortcomings of either modality alone. However, further research is necessary to ascertain the relative efficacy and optimal combinations of these existing and emergent radiotracers, alongside PET-MRI, in guiding ATL surgical planning and predicting postoperative outcomes for patients with TLE.

CRediT authorship contribution statement

Thomas Werner: Writing – review & editing, Software, Resources, Project administration, Methodology. **Yvonne Su:** Writing – review & editing, Formal analysis, Data curation. **Talha Khan:** Writing – review & editing, Investigation, Data curation. **Victoria Anderson:** Writing – review & editing, Investigation, Data curation. **Robert Subtirelu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Shiv Patil:** Data curation, Investigation, Writing – review & editing. **Eric Teichner:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mona-Elisabeth Revheim:** Writing – review & editing, Supervision, Conceptualization. **Abass Alavi:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Sahithi Talasila:** Writing – review & editing, Investigation, Data curation. **Arjun Ashok:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Chitra Parikh:** Writing – review & editing, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2024.108562.

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