Quantitative Analysis of [^{18}F]FFMZ and [^{18}F]FDG PET Studies in the Localization of Seizure Onset Zone in Drug-Resistant Temporal Lobe Epilepsy

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Keywords

Seizure onset zone · Epilepsy · Positron emission tomography imaging · Fluoro-2-deoxy-D-glucose · Fluorofluminazil · Quantitative imaging · Stereo-electro-encephalography

Abstract

Background: Positron emission tomography (PET) imaging in epilepsy is an in vivo technique that allows the localization of a possible seizure onset zone (SOZ) during the interictal period. Stereo-electro-encephalography (SEEG) is the gold standard to define the SOZ. The objective of this research was to evaluate the accuracy of PET imaging in localizing the site of SOZ compared with SEEG. **Methods:** Seven patients with refractory temporal lobe epilepsy (Ep) and 2 healthy controls (HC) underwent 2 PET scans, one with 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) and another with 2'-[^{18}F]fluorofluminazil (FFMZ), acquired 1 day apart. FDG was acquired for 10 min (static scan) 1 h after administration. An FFMZ scan was acquired for 60 min from radiopharmaceutical administration in a dynamic mode. Each brain PET image was segmented using a standard template implemented in PMOD 3.8. The pons was used as the reference region for modeling

of the nondisplaceable binding potential (BP_{ND}) for FFMZ, and to obtain uptake ratios for FDG. SEEG studies of patients were performed as a part of their surgical evaluation to define the SOZ. **Results:** Well-defined differences between HC and Ep were found with both radiopharmaceuticals, showing the utility to identify abnormal brain regions using quantitative PET imaging. Lateralization of the SOZ findings by PET (lower uptake/binding in a specific brain hemisphere) matched in 86% for FFMZ and 71% for FDG with SEEG data. **Conclusion:** Quantitative PET imaging is an excellent complementary tool that matches reasonably well with SEEG to define SOZ in presurgical evaluation. © 2019 S. Karger AG, Basel

Introduction

According to the World Health Organization around 50 million people suffer from epilepsy, despite the many more that may be misdiagnosed [1], and 30–40% that are

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not controlled by any specific medication for the type of epilepsy and in adequate doses (refractory epilepsy) [2], hence becoming a public health problem. Patients with refractory epilepsy are candidates for surgical treatment. In cases with focal onset epilepsy, which are the great majority, accurate methods to localize the seizure onset zone (SOZ) are mandatory. These methods may also provide information on altered brain regions involved in the epileptogenic network that may help in understanding the physiopathology of the epileptic condition [1, 3].

Stereo-electro-encephalography (SEEG) is an invasive method, considered the gold standard for the spatiotemporal definition of the SOZ at the ictal period [4], identifying regions with high epileptogenesis [5], whereas positron emission tomography (PET) brain imaging is a non-invasive technique to study patients with epilepsy (Ep) during the interictal period. PET has proven to be a useful technique to localize the epileptogenic areas in patients with refractory Ep and noncontributory magnetic resonance image (MRI) [6–8]. PET image quantification is useful for the follow-up of different therapeutic trials, comparison between subjects or localization of the epileptogenic regions [6, 9]. Several radiopharmaceuticals have been shown to be useful for this purpose: flumazenil (FMZ) and other FMZ analogues labeled with ^{18}F [10, 11], ^{11}C -flumazenil [12, 13], ^{18}F -fluoro-2-deoxy-D-glucose (FDG) [14–16] and 2'-methoxyphenyl-(N-2'-pyridinyl)-*p*-[^{18}F]fluoro-benzamidoethylpiperazine, which identify epileptogenic regions by the reduced uptake of radiopharmaceuticals [17], whereas ^{11}C -carfentanil [6] and ^{11}C -PBR28 [18] show increased uptake in the affected areas. Nevertheless, although SOZ localization is the primary goal of these PET studies, their reliability on tackling that goal is still a matter of debate.

FMZ-based radiopharmaceuticals and FDG have been widely used in epilepsy PET imaging due to their low binding/uptake in the SOZ at the interictal period [6, 19, 20]. The above is because FMZ derivatives have shown a high affinity for benzodiazepine receptors, specifically to GABA A receptors, a system highly altered in epilepsy [11, 21], while FDG characterizes the brain glucose metabolism, also altered in the disease [14, 22, 23].

Although FMZ and its analogues have been reported to be more precise than FDG for identifying the SOZ [12], the importance of FDG-PET images monitoring brain activity [10] lies on its wide use and availability around PET centers compared with that of FMZ-based radiotracers. Furthermore, FDG is an accurate method in lateralizing the epileptogenic foci in temporal lobe epilepsy [23–26]. Despite all the advantages that have the wide availability

of FDG-PET around the world, most of the studies performed with this tracer are still being qualitatively analyzed by visual inspection. This is in part due to the lack of a reliable reference region for brain FDG-PET; the pons and cerebellum have been proposed as stable reference regions [26, 27], and for animal models of epilepsy, the pons has been successfully used as reference region [28, 29].

The utility of methods that allow accurate localization of the SOZ is essential for planning resection of the epileptogenic foci, which is the conventional treatment indicated in focal onset refractory epilepsy [13], such as mesial temporal lobe epilepsy associated with hippocampal sclerosis [30].

The aim of this research is to compare tridimensional SEEG ictal localization of the SOZ with a quantitative interictal localization of areas with decreased uptake of an ^{18}F -labeled FMZ analogue and FDG by PET imaging. In addition, an evaluation of affected areas using automated image segmentation as a precise and user-independent quantification technique is presented.

Materials and Methods

Subjects and Acquisition

Seven patients (Ep; 2 male, 5 female) diagnosed with intractable temporal lobe epilepsy with hippocampal sclerosis resistant to antiepileptic drugs and 2 healthy controls (HC; 1 male [33 years old], 1 female [30 years old]) were included in this research study. The patients are followed at the Epilepsy Clinic at the General Hospital of Mexico and required to have MRI, SEEG, and PET scans as part of their presurgical evaluation. The Scientific and Ethical Committees of the General Hospital of Mexico and of the Facultad de Medicina of Universidad Nacional Autónoma de México (UNAM) revised and approved the protocol. Patients and family were informed and asked to sign a written consent. Demographic and clinical characteristics of patients are shown in Table 1.

PET Scans

Radiopharmaceuticals used in this research were FFMZ ([^{18}F] fluoroethyl-8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-benzo-[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate, also known as 2'-[^{18}F]fluoroflumazenil) and FDG (2-[^{18}F]fluoro-2-deoxy-D-glucose). Despite the availability of a broad variety of FMZ-based radiopharmaceuticals, it was decided to use FFMZ given its convenient labeling procedure and specific binding properties [11, 21].

One month before SEEG evaluation, each patient underwent 2 PET scans at the PET/CT Unit, one with FDG (370 ± 37 MBq) and the other with FFMZ (300 ± 110 MBq), acquired 1 day apart. FFMZ data were acquired for 60 min from radiopharmaceutical administration following a dynamic mode acquisition (frames: 20×15 s, 10×30 s, 5×120 s, 4×600 s). FDG was administered 60 min before the acquisition in a 10-min static scan. Before each scan, pa-

Fig. 1. 3D MRI (left) segmented into the AAL atlas space (right).

Table 1. Demographic and clinical characteristics of patients

	P1	P2	P3	P4	P5	P6	P7
Age, years/sex	52/f	32/f	18/f	30/f	26/m	31/m	18/f
Seizure duration, years	15	25	16	17	14	31	17
Max. seizures/month	6	8	22	8	18	8	7
Hippocampal sclerosis	left	right	bilateral	bilateral	bilateral	bilateral	bilateral

tients rested in a quiet, dimly lit room, without physical activity. Images were acquired using a PET/CT Siemens Biograph 64 scanner. A CT scan was acquired for coregistration and to perform attenuation correction of the PET image.

PET images were reconstructed using a 2D-ordered subset expectation maximization algorithm with a pixel size of 2×2 mm on a matrix of 128×128 pixels and 95 planes, corrected by detector dead time, radioactive decay, scatter, and random events.

Intracranial Electrode Implantation

Preoperative MRI studies were fused to a CT scan performed with the stereotactic frame in place (Z-D Leibinger, Freiburg, Germany), and electrode trajectories were planned to the basal-medial parahippocampal cortex through a 3A Plus Praezis software (Heidelberg, Germany). Medtronic 3391 recording-stimulation electrodes that have 4 contacts with a 1.0-cm center-to-center distance were inserted through an occipital parasagittal approach, leaving percutaneous extension for SEEG recording during the subsequent days. A postoperative MRI confirmed the position of the electrodes.

The patients were left OFF anticonvulsive medication for the recording SEEG period until at least 3 seizures were recorded in each patient, identifying the electrode contacts that recorded the SOZ. Three-dimensional reconstruction of images for electrode contact stereotactic location was performed through the Steadth planning S7 stations using the Cranial 3.0 software (Medtronic Inc., Minneapolis, MN, USA).

Image Processing

MRIs were used for automatic image segmentation of each brain, using the implemented tool in PMOD 3.8 (PMOD Technologies Ltd., Switzerland) and the Automated Anatomical La-

beling (AAL) atlas [31]. MRI segmentation was used as a mask to coregister the PET data, as shown in Figure 1, for identifying brain regions and for data modeling. Before quantitative analysis, FFMZ dynamic images were realigned to the last frame. The simplified reference tissue model [32] was used to calculate the non-displaceable binding potential (BP_{ND}) for FFMZ (using the pons as the reference region). In the case of FDG, a semiquantitative ratio analysis was made by standardized uptake value ratios (SUVr) using in the pons (pons Varolii) as the reference region for normalization.

MRI-PET Fusion

The MRI scans acquired after electrode insertion were superimposed on the preprocessing PET scans using the PMOD Fuse It tool. Once each image was coregistered, 3D volume of interest (VOI) spheres of 4 mm in diameter were manually drawn in the center of each electrode as shown in Figure 2 in order to obtain PET values at the electrode localization. The size of the analyzed VOIs could be a limitation given the small number of evaluated voxels in each VOI, which could be susceptible to noise; however, this size of the VOI was chosen in order to avoid overlapping of the PET signal in the electrode's positions. Note that PET acquisitions were made before electrode insertion. In HC, corresponding VOIs in parahippocampal regions were obtained.

Statistical Analysis

Plots were made using GraphPad Prism 6.0; an unpaired t test ($\alpha = 0.05$) was made to compare HC versus patients, BP_{ND} and SUVr at the SOZ, and three regions obtained from the AAL atlas (temporal inferior, parahippocampus and hippocampus).

Fig. 2. Schematic representation of VOIs (over each contact) drawn into the MRI space and fused to parametric PET images.

Fig. 3. Representative transversal PET brain images of an Ep (left) and an HC (right) comparing the uptake of FDG (SUVr) and FFMZ (BP_{ND}); arrows show abnormally low uptake/binding regions.

Results

Well-defined differences between HC and Ep PET scans were found with both radiopharmaceuticals in the affected area once parametric images were presented in SUVr for FDG and BP_{ND} for FFMZ. Figure 3 shows representative images where abnormal reduced uptake can be perceived in Ep (P5) compared to that in HC (1).

A decrease in PET quantitative values matching with the SOZ lateralization findings by SEEG was found in 5 patients for FDG studies and in 6 patients for FFMZ (data shown in Table 2). PET values of the SOZ of each patient and the values of the corresponding region in HC are shown in Table 2, where it is possible to observe a decrease in patient values compared with those in HC, with more remarkable differences for the BP_{ND} .

Fig. 4. SEEG recording of patient P1 showing a monopolar montage where right (RH1, RH2, RH3, RH4) and left (LH1, LH2, LH3, LH4) parahippocampal contacts are referred to the ipsilateral ear. The arrow is pointing to a low-voltage fast-seizure onset, starting in the first two channels of the left electrode. Epoch = 30 s.

Table 2. Lateralization found by SEEG analysis compared with lateralization found by PET studies

	P1	P2	P3	P4	P5	P6	P7	HC1	HC2
Ictal SEEG	left	right	bilateral	right	bilateral	right	left	n.a.	n.a.
Interictal SEEG	left	right	bilateral	right	right	bilateral	bilateral		
FDG-SEEG agreement	yes	yes	no	yes	yes	yes	no	n.a.	n.a.
FFMZ-SEEG agreement	yes	yes	yes	yes	yes	yes	no	n.a.	n.a.
Min. SUVr ¹⁸ F _{FDG}	0.86	0.94	0.91	0.72	0.91	0.63	1.06	1.10	1.15
Min. BP _{ND} ¹⁸ F _{FFMZ}	0.35	0.33	0.01	0.34	0.38	0.36	0.31	0.74	0.65

n.a., not applicable.

SEEG recording for each patient was made in order to locate the SOZ; Figure 4 illustrates recording of the 8 contacts of 1 patient at the ictal period.

SUVr and BP_{ND} values obtained for each patient at the 8 spherical VOIs (corresponding to each contact position) are shown in Figure 5. The focus localization was obtained from SEEG data. Figure 5 represents the contact positions in each patient, indicating in blue-colored spheres the contacts that recorded the SOZ, and the corresponding SUVr and BP_{ND} values obtained at the place of each contact for FDG-PET in white and FMZ-PET in gray numbers.

PET values of both radiopharmaceuticals at foci, and in the temporal inferior region, parahippocampus, and hippocampus of the most affected side of patients and of both hemispheres of HC are shown in Figure 6. The significance level is associated with a symbol: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$. Note that BP_{ND} values have better power to classify HC from Ep, but SUVr values are also able to classify HC with statistical significance at the evaluated regions.

Fig. 5. Representation of VOIs at contact position on the left (L) and right (R) side of each patient. Gray spheres represent VOI at contact, while blue spheres indicate the SOZ detected in the ictal period. White values of each sphere correspond to SUVr values at this position, while gray values indicate the corresponding BP_{ND}.

Fig. 6. Unpaired *t* tests of Ep and HC for FDG (left side) and FFMZ (right side) in the SOZ, temporal inferior, parahippocampus, and hippocampus regions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

Discussion

Epilepsy is a complex disease; the different invasive and noninvasive methods that allow the finding of anatomical and functional abnormalities will be useful to understand the underlying processes involved in the disease. Advances in technology, especially in computer science, have been useful to develop tools to analyze and compare different neuroimaging techniques. As an example, automatic user-independent PET-MRI fusion and segmentation are used to locate and quantify physiological and physiopathological processes at high precision levels of the same patient. Although a complex neuron network is involved in the disease [33, 34], diagnosis methods are focused on SOZ localization due to their utility for presurgical evaluation.

PET imaging was used in the present study as part of a deep brain stimulation (DBS) protocol in the temporal lobe, for the treatment of refractory temporal lobe epilepsy in patients with hippocampal sclerosis. It has been reported that DBS of the sclerotic hippocampus was less effective to induce a significant decrease in the number of seizures than in patients without sclerosis [35]. Moreover, evaluation of GABA receptors through autoradiography in surgical specimens of anterior temporal lobectomy demonstrated that GABA activity in the parahippocampal cortex was restored more than in the hippocampus in patients who had received a trial of electrical stimulation of the hippocampus as compared with patients who had intracranial electrodes but did not receive stimulation [36]. Therefore, the utility of quantitative PET imaging to locate sites in the parahippocampal cortex that might be useful to orient the placement of DBS electrodes was evaluated. In this research, the personalized MRI segmentation was crucial to find those regions where the uptake/binding of radiopharmaceuticals was abnormal in the patient's brain space, and in a user-independent way. An advantage of comparing quantitative data from images of patient's versus HC is the possibility to find abnormal uptake/binding regions that could be masked based on bilateral abnormal uptake or whole brain abnormal uptake. Previous research works have compared the uptake of epileptogenic foci versus uptake on the contralateral side or in other cortical regions [10, 11, 20, 21] in a user-dependent way, increasing bias due to human error. Comparing PET images from patients versus HC improves the proficiency of discriminating both groups as exemplified in Figure 3, where PET images are in quantitative scale and it is easy to visualize affected regions of patients.

Using the pons as reference tissue has the advantage of eliminating errors in quantification due to the fact that it is a reference inside the brain, making the scale comparable

between subjects, instead of using parameters such as the standardized uptake value that depends on the dose administration and weight of patients, among many other factors affecting the accuracy of this semiquantitative value. The pons is a large structure, easy to locate, and given the large amount of voxels contained in this region of the brainstem, it provides a trustful reference region. Another advantage of the use of the pons as reference tissue is that, even when the binding/uptake is lower compared with other brain regions, it is high enough to maintain the noise at acceptable levels due to the low signal. The method is able to accurately locate abnormal regions anatomically segmented, giving specialists an effective tool to make a first and fast diagnosis, is useful to locate potentially affected regions (anatomical and nonanatomical) of abnormal uptake/binding; however, since PET quantitative analysis showed affected areas in other regions beyond the SOZ, the analysis in this research study is limited to the parahippocampal region where the DBS electrodes were placed for SEEG recording.

Other alternatives have been proposed in order to compare Ep versus HC using a statistical parametric mapping atlas to locate regions with statistical differences between groups [13] in a user-independent way, showing that it is possible to find significant differences between patients and HC, and predicting an individual postoperative outcome; nevertheless, it was also found that these methods did not always predict seizure status for individual outcome. Although statistical parametric mapping allows inter- and intrasubject comparisons, anatomical deformation may introduce bias, overall in PET studies where it is required to robustly locate anatomically abnormal areas. As an alternative, the proposed AAL-based segmentation method is a good alternative to anatomically locate abnormal areas in the same patient and compare them with HC. The information obtained from the segmentation allows us to discriminate patients from HC with both radiopharmaceuticals in an anatomical region and a focus level with both evaluated radiopharmaceuticals as it is shown in Figure 6.

Previous works have used FDG-PET and/or PET with FMZ analogues to locate the focus regions [14, 19, 29, 37, 38]. Nevertheless, finding extended (not focal) regions and PET images were used only to find lateralization or confirm affected lobules. Other works have compared PET imaging with SEEG recording [15, 27, 39] but were not able to find a clear correlation between SEEG and PET studies at anatomical structures. Automated brain segmentation has been used to locate successfully the foci [23, 40] in a structure region. In the present research work, at the electrode contact recording, the SOZ was found in good agreement with decreased FFMZ BP_{ND} in 86% of the

cases and for the FDG SUVr in 71% (Fig. 5; Table 2), suggesting an agreement between quantitative PET and SEEG; however, a large population must be evaluated to confirm the prediction. The patient who does not show a correlation between PET and SEEG (P3) had the maximal number of seizures per month; neither correlated ictal and interictal SEEG, suggesting complex patterns of FDG uptake, FFMZ binding, and electric activity for this patient.

Table 2 shows the minimum values for BP_{ND} and SUVr at the electrode position of each patient compared with the same region of HC; note that quantitative data obtained with both radiopharmaceuticals are able to discriminate affected areas, making quantification a suitable and useful tool for the analysis of FDG and FFMZ PET images in epilepsy.

Previous works have shown that radiopharmaceuticals based on FMZ derivatives perform better than FDG in the delimitation of the SOZ [6, 10, 13]; however, to obtain a good accuracy, it is necessary to acquire dynamic PET studies (1 h or more of data acquisition). The limited availability of non-FDG radiopharmaceuticals around PET centers makes semiquantitative FDG imaging normalized to the pons (as shown in this work) a good alternative to locate abnormal regions in epileptic patients, as shown in Figure 3, where the affected area is visually similar for both evaluated radiopharmaceuticals.

A limitation of this study is the low number of subjects participating in this protocol, so the method is presented as a proof of principle. However, the method evaluated in this research allowed us to find and quantify the uptake at the SOZ, making it an excellent tool to guide physicians in finding abnormal regions in the brain that can help to plan surgery, to follow up treatments and the natural evolution of the disease, or to compare with HC. In addition, the method allows, in an easy way, to accurately quantify the uptake in other brain regions in order to localize extra-SOZ regions of upregulated metabolic activity.

This research shows that semiquantitative or quantitative analysis of PET data allows not only to find similarities in the upregulated system between patients (suggested an abnormal metabolic and neurotransmission neural network), but also to find large differences between patients to perform a better classification of the disease facilitating a better prognosis and a personalized treatment.

Conclusions

The quantification of PET images allows to discriminate abnormal uptake regions from healthy regions. The information obtained from the analysis is useful as a pre-

surgical guide to localize the epileptogenic foci or to follow up the efficacy of new treatments. Abnormal uptake regions were localized with both radiopharmaceuticals FDG and FFMZ, identifying accurately the epileptic foci and also localizing other possible affected regions in an automatic and user-independent way.

FFMZ is a useful radiopharmaceutical to accurately delimitate the SOZ through quantitative analysis of dynamic images, with precision that surpasses visual inspection even by an experienced observer. FDG semiquantitative analysis normalized to the pons (SUVr) provides a worthy visual contrast between HC and Ep.

PET imaging showed agreement in an acceptable level (71% for FDG and 86% for FFMZ) with SEEG evaluation, making interictal PET imaging a potential noninvasive technique to locate SOZ and other affected areas. However, more studies with a larger cohort and in other brain regions have to be performed to confirm a possible correlation between neural electric activity at the ictal period and its correlation with abnormal uptake/binding obtained by PET at the ictal period.

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Statement of Ethics

The subjects gave their written informed consent. We confirm that we have read the Journal's position on issues involved in ethical regulations and affirm that this report is consistent with those guidelines.

Disclosure Statement

The authors have no conflicts of interest to declare.

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