POSITRON EMISSION TOMOGRAPHY IN PRESURGICAL
LOCALIZATION OF EPILEPTIC FOCI

PhD Thesis

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BACKGROUND

Approximately 0.5% to 1.0% of the population suffer from some form of epilepsy, and in 15%-20% of cases the seizures are intractable, i.e., refractory to medical treatment with anticonvulsants. In such cases surgical treatment is increasingly being performed. However, the outcome of epilepsy surgery with respect to seizures widely varies depending upon the type of epilepsy and operation performed. The success rate of cortical resection in epilepsies of neocortical origin, especially those originating from extratemporal regions, continues to be disappointing. The success rate is even worse when no structural lesion can be identified during presurgical evaluation.

The most important aspect of presurgical evaluation is the identification of a discrete epileptogenic region, i.e. the area of brain necessary and sufficient for generation of habitual spontaneous seizures. Surgical resection of this region, by definition, will lead to complete seizure control. A major source of surgical failure is that boundaries of this region can be only assumed, but not directly defined, from complementary structural and functional information derived from the epileptic brain. The decision to recommend epilepsy surgery is based on convergence of data from an analysis of seizure semiology, scalp EEG, anatomical and functional neuroimaging data, and neuropsychological evaluation. When these data are non-convergent, the patient is not a surgical candidate or may be subjected to invasive intracranial EEG monitoring with depth or subdural electrodes. Chronic intracranial EEG evaluation remains the “gold standard” in defining the boundaries of the epileptogenic region to be
resected in order to achieve complete seizure control. Adequate coverage of the epileptogenic region, however, is heavily dependent on the localization information provided by non-invasive electro-clinical and imaging data.

Recent advances of neuroimaging have lead to an improved non-invasive localization of epileptogenic brain regions. Development of new magnetic resonance imaging (MRI) techniques provided a new insight into the variety of structural brain abnormalities associated with epileptogenicity. In epilepsies of neocortical origin, applications of inversion recovery techniques, high resolution MRI imaging with thin slices, and multiplanar three-dimensional reconstruction have improved the sensitivity of MRI for detecting cortical dysgenesis, which has been reported in up to 30% of epilepsy surgery specimens and is believed to represent the central pathologic substrate responsible for seizures. Intractable epilepsies with normal MRI and those with multifocal lesions, however, remain to be a major challenge during presurgical evaluation. It has been also increasingly recognized that epileptogenic cortical regions can variably extend beyond the visible lesion. Further, the presence of unsuspected dual pathology, i.e. co-existence of an epileptogenic cortical lesion and hippocampal sclerosis, can also lead to surgical failure. In such cases, functional neuroimaging can be applied to further delineate the epileptic cortex.

Several functional neuroimaging techniques, including proton magnetic resonance spectroscopy (1H-MRS), functional MRI, magnetic source imaging, single photon emission tomography (SPECT), and positron emission tomography (PET) with different radiotracers are being intensely investigated in regard to their clinical value for localization of epileptogenic brain regions. The present studies have focused on the application of PET
in intractable partial epilepsies, with special emphasis on the most difficult ones with neocortical origin.

PET is a noninvasive imaging method that can be used to image and quantify local biochemical processes within the brain and other organs. The most widely used PET tracer is 2-deoxy-2-[\textsuperscript{18}F]fluoro-D-glucose (FDG), that is used to measure brain glucose metabolism. Interictal FDG PET has proven to be a reliable clinical test for identifying dysfunctional cortical regions of hypometabolism that often correspond, in general, to the location of epileptic foci. However, areas with abnormal glucose metabolism are not specific for epileptic regions: they often extend far beyond epileptic areas, involving remote cortical and subcortical structures. For example, in patients with unilateral medial temporal lobe epilepsy, hypometabolism often occurs not only in the affected temporal region, but also in the ipsilateral parietal and frontal cortex, as well as thalamus. FDG PET shows decreased frontal glucose metabolism in up to 85% of patients with frontal lobe epilepsy, however, whether these areas should be completely resected to achieve seizure control, remained to be unclear.

In addition to FDG PET, several new PET tracers targeting various brain neurotransmitter receptors have been introduced and proposed to be more sensitive and/or specific for epileptogenic cortex. Among these, [\textsuperscript{11}C]flumazenil (FMZ) emerged as one of the most promising ones. FMZ is a ligand which binds to the \( \gamma \)-subunits of the \( \gamma \)-aminobutyric acid\(_{A} \) (GABA\(_{A} \)) receptor complex, the major binding site of GABA. GABA is the major inhibitory neurotransmitter in the human brain and it plays a key role in regulating central nervous system excitability and susceptibility to seizures. Involvement of GABAergic mechanisms in the pathophysiology
of human epilepsy is now widely accepted. Initial studies in temporal lobe epilepsy found FMZ PET to be more sensitive and accurate in delineating the seizure focus than FDG PET. In frontal lobe epilepsy, areas with decreased GABA_A receptor binding were reported to be generally less extensive than the abnormalities of glucose metabolism shown by FDG PET. Nevertheless, although FMZ PET became available in a number of epilepsy surgery centers worldwide, the electrophysiological correlates and clinical significance of cortical FMZ PET abnormalities, similarly to those of FDG PET, remained to be poorly understood.

**OBJECTIVES**

1. To apply three-dimensional (3D) MRI/PET/EEG co-registration and surface rendering, and to determine intracranial electrophysiological correlates of objectively identified FDG and FMZ PET abnormalities in patients with non-lesional epilepsy of neocortical origin.

2. To determine electro-clinical correlates of FDG and FMZ PET abnormalities in patients with intractable neocortical epilepsy and MRI-verified brain lesion, and to assess the value of FMZ PET in detection of dual pathology (coexistence of hippocampal sclerosis and a potentially epileptogenic cortical lesion).

3. To determine the relationship of pre- and postsurgical (non-resected) FDG and FMZ PET abnormalities to the outcome of cortical resection.
SUBJECTS AND METHODS

Subjects. All patients included in these studies underwent presurgical evaluation due to medically intractable epilepsy. These evaluations always included prolonged video-EEG monitoring using scalp/sphenoidal electrodes, multisequence MRI (including high resolution volumetric studies), FDG PET scanning as well as neuropsychological evaluation. Further studies, such as intracranial EEG monitoring, intraoperative electrocorticography, and FMZ PET have been also performed, where indicated.

PET studies. PET studies were performed using the CTI/Siemens EXACT/HR whole body positron tomograph located at Children's Hospital of Michigan, Detroit. This scanner has a 15 cm field of view and generates 47 image planes with a slice thickness of 3.125 mm. The reconstructed image in-plane resolution obtained is 6.5 ± 0.35 mm at full-width-at-half-maximum (FWHM) and 7.0 ± 0.53 mm in the axial direction for the FMZ PET and 5.5 ± 0.35 mm at FWHM and 6.0 ± 0.49 mm in the axial direction for the FDG PET. EEG was monitored throughout all PET examinations. A venous line was established for injection of FDG (0.143 mCi/kg) or FMZ (0.4 mCi/kg) produced, using a Siemens RDS-11 cyclotron (Knoxville, TN). All patients had their PET performed in interictal state. For the FMZ PET, a 60 min dynamic PET scan of the brain was performed, beginning at the time of injection. Summed images representing activity concentration between 10-20 minutes were used to display GABA\textsubscript{A} receptor binding in
brain. For FDG PET, a 20 min static emission scan was initiated 40 min after tracer injection.

**MRI studies.** MRI studies were performed on a GE 1.5 Tesla Signa 5.4 unit (GE Medical Systems, Milwaukee, Wisconsin). For PET co-registration and partial volume correction, volumetric imaging was performed utilizing a spoiled gradient echo (SPGR) sequence. The 3D SPGR sequence generates 124 contiguous 1.5 mm coronal sections of the entire head using a field of view of 240 mm. In studies on patients with brain lesion, axial and coronal fluid-attenuated inversion recovery (FLAIR) images were also used where the lesion could not be adequately visualized and delineated on the volumetric images. In patients with dual pathology, unilateral hippocampal atrophy was identified by MRI-based hippocampal volumetry.

**MRI/PET coregistration.** Matching of PET and MRI image volumes was performed using a multi-purpose 3D registration technique (MPItool) developed by the Max-Planck-Institute in Cologne. This co-registration method is highly interactive and is based on the simultaneous alignment of PET/MRI contours, which are exchanged in three orthogonal cuts through the brain. The co-registered PET and MRI image volumes were then transferred to an SGI OCTANE workstation. MRI-based *partial volume correction* of the PET images was performed in lesional studies.

**PET image analysis.** Objective definition and 3D surface rendering of cortical PET abnormalities. The extent of regional cortical abnormalities of brain glucose metabolism and FMZ binding was determined using an
objective method based on a semi-automated software package applied to all supratentorial axial planes of the PET image volume. This procedure allows the definition of abnormal cortical areas of glucose metabolism or FMZ binding based on an asymmetry index (AI) derived from contralateral homotopic cortical areas according to a predefined cutoff threshold, determined using PET images of healthy normal controls (AI >10% was used in all studies). A "marked file" containing the cortical regions with abnormal asymmetry was created for each PET study. The co-registered volumetric MRI and marked PET files were further processed using the 3D-Tool software package (Max-Planck Institute, Cologne, Germany), where the brain was automatically segmented from MRI data using morphological operations, and 3D surface views were created. Functional data obtained from the marked PET image volumes were projected onto the MRI-reconstructed brain surface.

**Spatial comparison of cortical structural vs. functional (PET) abnormalities.** In studies of patients with cortical lesions, the location and extent of the lesion was also displayed on the 3D reconstructed brain surface, thus allowing a direct comparison between the size and location of structural vs. functional abnormalities. Using this method, the surface extent of the structural lesion as well as that of the marked PET abnormalities could be obtained and expressed in cm². A similar procedure was employed for *postoperative* MRI images, where the location and extent of cortical resections were displayed on the 3D cortical surface reconstructed from the co-registered preoperative MRI image volume.

**Spatial comparison of intracranial EEG findings with the surface rendered PET abnormalities.** The exact surface location of subdural electrodes was determined and visualized on the 3D reconstructed brain surface by
utilizing digitalized radiographic (X-ray) images acquired with the subdural electrode arrays in place. In brief, three metallic fiducial markers were placed at standard locations on the patients’ head and a planar X-ray image was acquired. The X-ray was then digitized and the fiducial markers were identified on it as well as on the corresponding 3D reconstructed MRI image volume. An iterative algorithm minimized the differences between the two sets of coordinate triplets by adjusting the three euler-angles and the image zoom. As a result, a cortical surface view was created allowing the location of electrodes to be directly defined on the MRI 3D brain surface.

Analysis of FMZ PET abnormalities in patients with dual pathology using regions of interest (ROIs). In studies of FMZ PET abnormalities of patients with dual pathology, an MRI-based ROI analysis was applied to measure FMZ binding in the whole hippocampus and three hippocampal subregions (anterior, middle and posterior hippocampus). The ROIs were manually defined on each coronal SPGR MRI image plane where the given structure could be clearly visualized, using a previously defined protocol. All ROIs defined on MRI images were copied to the co-registered, partial-volume corrected FMZ PET images, and a weighted average concentration for each structure was obtained. Asymmetries of FMZ binding were then calculated using an asymmetry index (AI). Normal asymmetries of FMZ binding were defined by FMZ PET measurements of 6 normal healthy subjects (mean + two standard deviations). Cortical sites of decreased FMZ binding were also evaluated using AIs for regions with MRI-verified cortical lesions and for non-lesional areas with visually detected asymmetry.
EEG procedures. All patients underwent prolonged video-EEG recordings with scalp/sphenoidal electrodes. Furthermore, patients with neocortical epilepsy underwent intracranial EEG monitoring with subdural electrodes or intraoperative electrocorticography (ECoG), where indicated. Subdural electrode placement was guided generally by the seizure semiology, the seizure onset area as determined by scalp ictal EEG, and by the location of PET (and MRI, if applicable) abnormalities. During chronic intracranial EEG monitoring, at least three habitual seizures were captured and analyzed, and electrodes involved in seizure onset, rapid seizure spread (<10 s within seizure onset) and frequent interictal spiking were recorded. On intraoperative ECoG, the spiking area was defined as neocortex showing at least 10 spikes/min.

RESULTS

1. Ictal intracranial EEG correlates of cortical FDG and FMZ PET abnormalities

A. FMZ PET is more sensitive than FDG PET in detection of seizure onset as defined by intracranial EEG monitoring. Ten patients with neocortical foci (mean age: 11 years, age range 2 - 19 years; seizure focus: 6 frontal, 3 fronto-parietal 1 temporo-parietal) underwent both FDG and FMZ PET, and performance of these two PET modalities was compared to ictal intracranial EEG data. Using objectively marked PET images co-registered and surface rendered with high-resolution MRI scans, we found that FMZ
PET detected at least part of the seizure onset in all cases, whereas FDG PET missed the area of seizure onset in two children. A receiver operating characteristics (ROC) analysis showed that the area under the ROC curves was higher for FMZ than FDG PET for both seizure onset (p=0.01) and frequent interictal spiking (p=0.04). Sensitivity of FMZ PET for detecting areas of seizure onset at the 10% asymmetry threshold was 81 ± 9%, which was associated with a 74 ± 7% specificity. In contrast, we found a low sensitivity for both FMZ and FDG PET for detecting cortical areas of rapid seizure spread. Analysis of PET abnormalities marked remote from the area of seizure onset (i.e. non-continuous abnormality outside the lobe of seizure onset) in 7 patients with frontal lobe foci showed a non-continuous parietal area of decreased FMZ binding in 4 patients. Further, a temporal FMZ PET abnormality, mostly involving the middle temporal region, appeared in 6 (both parietal and temporal remote areas appeared in 3 subjects). Of these 10 remote areas with decreased FMZ binding, 7 were partially or fully covered by subdural electrodes, and were involved in rapid seizure spread in 6 cases. Based on the location of remote FMZ PET abnormalities, these areas may represent cortical regions synaptically connected with the primary seizure onset region and targeted by rapid cortico-cortical spread of the seizures.

B. Seizure onset occurs most often at the border of cortex with glucose hypometabolism. We performed a study on 12 young patients (mean age 10.8 years; age range 2-19 years) with neocortical epilepsy (seizure focus: 5 frontal, 3 fronto-parietal, 3 temporal and 1 temporo-parietal) and normal MRI, where subdural electrodes were classified according to their location over cortical areas which were defined as hypometabolic, normometabolic
or at the border between hypometabolic and normal cortex (metabolic “borderzones”) based on FDG PET. Ictal onset occurred in electrodes overlying metabolic borderzones significantly more frequently than in electrodes over hypo- or normometabolic regions (26% vs. 8.9% and 4.6%; respectively, p<0.01 [ANOVA]). Early seizure spread also occurred in electrodes overlying metabolic borderzones more often than in electrodes overlying hypometabolic regions (26.2% vs. 7.1%; p=0.013). Seizure spread occurred significantly more frequently than seizure onset over normometabolic areas (1.5 vs. 4.6%, p=0.0078).

2. Electroclinical correlates of FDG and FMZ PET in patients with intractable epilepsy and MRI-verified brain lesion

A. FMZ PET is more accurate than FDG PET in detection of perilesional epileptic cortex Seventeen subjects (10 adults and seven children, mean age 21.7 years, age range 5-42 years) with brain lesion and intractable epilepsy of neocortical origin underwent presurgical evaluation including FDG and FMZ PET studies. We found that the mean surface extent of FMZ PET abnormalities (after partial volume correction) was significantly larger than the corresponding structural lesions (p=0.015; paired t-test), but it was significantly smaller than corresponding areas of glucose hypometabolism measured using FDG PET (p=0.005). The size of FDG abnormalities was in average 1.9 (range 1.03 - 9.4) larger than that of the corresponding FMZ abnormalities. The size of perilesional FDG PET abnormalities showed a significant correlation with the estimated life-time number of seizures (Kendall’s tau=0.47, p=0.019) as well as with the estimated life-time number of partial seizures (Kendall’s tau=0.45, p=0.025). The extent of
perilesional FMZ PET abnormalities did not change as the function of seizure number, but showed an excellent correspondence with spiking cortex (sensitivity: 80%, specificity: 89%), the resection of which resulted in seizure-free outcome in all but one operated patients. Remote FMZ PET abnormalities (found in 6 patients) were significantly associated with early age of seizure onset (3.5 ± 4.1 years vs. 15.1 ± 12.7 years, p=0.048; unpaired t-test), and a similar tendency was found for long duration of epilepsy (patients with remote FMZ PET abnormalities had in average 7.5 longer duration of epilepsy; p=0.09). No similar differences could be found for the presence vs. absence of remote FDG PET abnormalities.

B. FMZ PET is highly sensitive for detection of dual pathology. Twelve patients (mean age 25.4 years, age range 15 - 41 years) with intractable epilepsy and MRI-verified dual pathology were included in this study. The FMZ binding calculated for the whole volume of the hippocampus was abnormal in 9 cases, whereas subregional analysis showed abnormal values in at least one portion of the atrophic hippocampi in all patients. Cortical regions of decreased FMZ binding were detected by visual evaluation in every patient. The localization of these regions corresponded well to MRI-defined structural lesions. AIs for these cortical regions with MRI abnormality were between 12.3 and 123% (mean: 49.2 ± 39.6%). The highest AI values were found over ROIs with infarcts (n=4), cysts (n=2) and ganglioglioma (n=1), all of them showing AIs above 40. In 4 cases, FMZ PET showed decreased binding on visual evaluation in additional cortical areas, where MRI did not reveal structural abnormality. AIs for these cortical regions were between 8.9 and 19.0 (mean: 12.8 ± 3.8), and
these were significantly lower than those for lesional ROIs measured in the same patients.

3. Relationship of PET abnormalities to the outcome of neocortical epilepsy surgery

We analyzed the data of 15 young patients (mean age 12.2 ± 7.0 years, age range 1.5 - 21 years) with intractable epilepsy of neocortical origin. The patients underwent cortical resection following preoperative MRI (normal in nine and showing structural lesions in the remaining six), surface (n=15) and subdural (n=11) EEG monitoring as well as FDG and FMZ PET examinations. All patients underwent postoperative MRI examination. Postoperative follow-up time was at least 12 months (mean: 21.5 ± 9.5 months, median: 17 months, range: 12-41 months). Postoperative outcome (class I-IV) was determined according to the criteria of Engel. After surgery, 8 patients (53 %) became seizure-free (class I outcome), 1 had class II outcome, 4 showed a worthwhile improvement (class III) and 2 had class IV outcome (no worthwhile improvement). Preoperative size of total FMZ PET abnormalities showed a significant correlation with the outcome (r=0.57, p=0.025; Spearman’s rank correlation). No similar correlation was found between outcome and the total size of FDG PET abnormalities (r=0.29, p=0.30). The total size of preoperative FDG abnormalities was not different in patients who became seizure-free as compared to those who continued to have seizures.

The size of non-resected cortex with perifocal FMZ PET abnormalities showed a positive correlation with the outcome scores
(r=0.66, p=0.007), i.e., larger residual cortex with FMZ PET abnormalities in the lobe of seizure onset was associated with a worse outcome. No similar correlations were found for non-resected cortex with perifocal FDG PET abnormalities (p=0.61). The correlation between non-resected perifocal FMZ PET abnormalities and the outcome scores persisted in patients with extratemporal resection (r=0.73, p=0.007) and also in patients with no lesion on MRI (n=10; r=0.60, p=0.049). In a logistic regression analysis, the percent size of non-resected perifocal cortex with FMZ PET abnormalities had a marginally significant (p=0.055) effect on seizure-free outcome, whereas neither the localizing value of MRI and/or surface EEG findings (p=0.71), nor the non-resected remote FMZ PET abnormalities (p=0.66) had a significant effect on seizure-free outcome. Finally, the effect of non-resected FDG PET abnormalities on seizure-free outcome was non-significant (p=0.50 for perifocal, and p=0.27 for remote FDG PET abnormalities).

CONCLUSIONS

1. Objectively marked, 3D surface rendered PET abnormalities enable direct comparison of functional cortical abnormalities detected by PET with those provided by intracranial EEG. Using this method, FMZ PET proved to be significantly more sensitive than FDG PET for detection of cortical regions showing seizure onset and frequent interictal spiking in patients with epilepsy of neocortical origin. Thus, application of FMZ PET during presurgical evaluation can enhance coverage of the epileptogenic zone. Decreased FMZ binding remote from the area of seizure onset may
represent, in some cases, functional involvement of directly connected regions, which may be targeted by rapid seizure propagation.

B. In patients with non-lesional neocortical epilepsy, seizure foci are often located at the border of cortical areas with decreased glucose metabolism seen on FDG PET, rather than in the center of hypometabolic areas. This finding is at odds with the generally accepted concept that focal areas of hypometabolism represent epileptic cortex. In fact, our study demonstrates that ictal electrophysiological changes often skip or “flow” around truly hypometabolic areas, which appear to be often protected against seizure involvement. Thus, cortical areas with hypometabolism should be interpreted as regions most likely not involved in seizure onset, while surrounding cortex should be carefully addressed in presurgical evaluation, if FDG PET is used to guide subdural electrode coverage.

2. A. In patients with epilepsy and cortical lesion, 3D surface rendered FMZ PET is able to delineate perilesional epileptic cortex as defined by intracranial EEG, and it may be especially useful to localize such areas in patients with large perilesional glucose hypometabolism. Perilesional FDG PET hypometabolism extends beyond epileptic cortex, and correlation of extent of perilesional hypometabolism with the life-time number of seizures may indicate progressive cortical dysfunction due to chronic epilepsy.

B. FMZ PET is very sensitive for detection of dual pathology. Volumetric MRI-defined hippocampal atrophy, even if it is mild, is always associated with decreased FMZ binding, although the latter may be localized to only one subregion of the hippocampus. Thus, FMZ PET can
be useful in selected patients with a potentially epileptogenic brain lesion when presence of dual pathology is suspected or to be excluded, e.g., from discordant EEG, clinical, and structural imaging data.

3. Extensive cortical abnormalities on FMZ PET predict poor outcome in neocortical epilepsy surgery. Resection of FMZ abnormalities in the lobe of seizure onset is associated with excellent outcome even in the absence of a structural lesion. In contrast, although FDG PET abnormalities correctly regionalize the epileptogenic area in most cases, their size is not related to the extent of epileptogenic tissue to be removed. Thus, FMZ PET can be used to delineate epileptic cortex to be resected when other localizing information including FDG PET is not sufficient to tailor cortical resection.


Published abstracts and presentations related to the theses


9. Juhász C, Muzik O, Chugani DC, Chugani HT. GABA$_A$ receptors in epileptic children: age-related changes and effect of


**Other full-length papers**


Book chapters
