# Application of an Objective Method for Localizing Bilateral Cortical FDG PET Abnormalities to Guide the Resection of Epileptic Foci 

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#### Abstract

Purpose-In order to improve the objective localization of bilateral cortical abnormalities in positron emission tomography (PET) image volumes, we developed a new three-dimensional image processing technique. The accuracy of this approach with respect to invasive subdural electroencephalography (EEG) data was assessed in a group of children with neocortical epilepsy. Methods-Glucose PET image volumes were obtained from 12 epileptic children (mean age $5.2 \pm$ 4.3 years). Bilateral cortical areas of abnormal glucose metabolism were objectively determined using two conditional criteria assessed against a normal database. The normal database was derived from a group of 15 adult controls (mean age 27.6 years). The spatial relationship between seizure onset electrodes and PET abnormalities was assessed using a conventional receiver operating characteristic (ROC) analysis as well as using a newly defined spatial proximity index (SPI), which characterizes the association between adjacent, but not coincident, abnormalities.

Results-ROC analysis at the 2 standard deviation (SD) threshold, revealed an accuracy of 65\% to detect seizure onset areas with a sensitivity of $64 \pm 17 \%$ and a specificity of $66 \pm 24 \%$. Sensitivity decreased to $46 \pm 24 \%$ at the 3 -SD threshold with a specificity of $80 \pm 21 \%$ (accuracy $75 \%$ ). The average value for the SPI was determined as $3.82 \pm 1.65$ which was $20 \%$ lower than the SPI value calculated using a simple in-plane two-dimensional asymmetry between homotopic cortical segments (4.52 $\pm 3.82$ ).

Conclusion-The presented image processing technique improves localization of cortical abnormalities and provides valuable imaging clues for placement of subdural EEG grids prior to surgical resection.


## Keywords

Bilateral abnormalities; guided surgery; image data processing; neocortical epilepsy; positron emission tomography

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## Introduction

THE MAIN objective of presurgical evaluation of patients with medically refractory epilepsy is to define the boundaries of epileptogenic regions to be resected. Toward this goal, invasive subdural electroencephalography (EEG) evaluation remains the gold standard. However, the accuracy of foci localization using subdural electrodes depends greatly on selection bias. In order to guide the placement of subdural electrodes, noninvasive functional imaging such as positron emission tomography (PET) is used and provides the surgeon with imaging clues which considerably improve localization of epileptogenic brain regions [1], [2]. It was the goal of this study to develop an objective method for the definition of the spatial extent and location of PET abnormalities.

Previous attempts to apply statistical parametric mapping (SPM) in order to objectively define regions of tracer abnormality in young children showed limited success [3], although several groups have applied SPM successfully in adults [4]. The results of our earlier studies [3] indicated that the spatial normalization of pediatric brains to an adult template leads to a high level of artifacts in statistical parametric maps caused by the excessive amount of warping necessary. In our attempt to objectively define PET abnormalities in children with epilepsy, we previously developed a two-dimensional (2-D) technique which was based upon left/right asymmetries derived from homotopic cortical areas within the same plane [5]. Despite the overall usefulness of this method, which we have extensively used to semi-objectively define the size and location of cortical abnormalities in children with epilepsy [6], [7], this approach proved to be suboptimal as it requires a priori knowledge with respect to the side of abnormality. In contrast to the old method, our newly developed three-dimensional (3-D) approach does not rely exclusively on a single intra-subject asymmetry measure, but employs in addition to an asymmetry measure a comparison between normalized tracer concentration observed in individual patients against a normal database.

In the current study we applied this new approach to a group of children with epilepsy who underwent high resolution MRI and 2-deoxy- $2\left[{ }^{18} \mathrm{~F}\right]$ fluoro-D-glucose (FDG) PET imaging. Our goal was to assess the spatial relationship between objectively defined cortical glucose abnormalities and the location of seizure onset electrodes as determined using the gold standard of invasive subdural EEG.

## II. Material and Methods

## A. Subjects

MRI and FDG PET scans were acquired in 15 young adult controls (mean age $27.6 \pm 4.5$ years), who were not taking any medication, and had no history of neurological or psychiatric disorder. Moreover, 12 children (mean age $5.2 \pm 4.3$ years, age range $1.0-14.8$ years; Table I) with medically intractable partial epilepsy were selected. All these children were diagnosed with unilateral seizure foci based on seizure semiology, scalp ictal EEG as well as FDG PET, which were performed as part of their presurgical evaluation. No cortical or subcortical lesions on MRI scans were observed. Once a unilateral seizure focus was established, patients were admitted for surgery and PET-guided intracranial EEG grid electrodes were implanted in order to verify the seizure onset zone to be resected. The region of epileptic focus as verified by intracranial EEG showed hypometabolism in all cases. All studies were performed in accordance with guidelines stipulated by the Ethics Committee of Wayne State University.

## B. MRI Data Acquisition

MRI studies were performed on a GE 1.5 Tesla Signa 5.4 unit (GE Medical Systems, Milwaukee, WI). Volumetric imaging was performed using a spoiled gradient-echo (SPGR)
sequence. The 3D SPGR sequence generates 124 contiguous $1.5-\mathrm{mm}$ sections of the head, matrix size of $256 \times 256$, and a field-of-view (FOV) of $240 \times 240 \mathrm{~mm}$ (pixel area $0.9375 \mathrm{~mm}^{2}$ ).

## C. PET Data Acquisition

The tracer FDG was synthesized according to the method of Hamacher et al. [8]. PET measurements were performed using the CTI PET-scanner EXACT HR (Hoffman Estates, IL), which allows simultaneous acquisition of 47 contiguous transaxial images with a slice thickness of 3.125 mm . The reconstructed image resolution obtained in this study was $5.5 \pm$ 0.35 mm at full-width at half maximum (FWHM).

Initially, a venous line was established for injection of FDG (5.3 MBq/kg). External stimuli were minimized during the FDG uptake period ( $0-40 \mathrm{~min}$ postinjection) by dimming the lights and discouraging interaction so that studies reflected the resting awake state. Scalp electrodes for the EEG were placed in all epileptic children according to the International 10-20 system to monitor electroencephalographic activity during the tracer up-take period. Sedation with intravenous nembutal or midazolam was used in the pediatric group, only after the uptake period was completed when necessary. Forty minutes after injection, patients were positioned in the scanner. Subsequently a static 20 -min emission scan in 2-D-mode was initiated. Calculated attenuation correction was performed on all images according to the method of Bergström et al. [9].

## D. Subdural EEG Evaluation

All children with intractable epilepsy underwent chronic EEG monitoring with subdural electrode grids. Subdural electrode placement were guided by seizure semiology, scalp EEG recordings and FDG cortical abnormalities established through visual analysis. In every case more than two habitual seizures were captured. Identification of electrodes involved in the seizure onset of habitual clinical seizures (defined as a localized, sustained, rhythmic / semirhythmic or spiking EEG pattern with frequency $>2 \mathrm{~Hz}$ ) during ictal episodes was determined by chronic subdural EEG monitoring.

## E. Image Data Analysis

## 1) Data Preprocessing

Image coregistration: All brain image volumes were coregistered using a well-established, multi-purpose, 3-D registration software (MPI-Tool) [10], [11]. The coregistration method is highly interactive and is based on simultaneous alignment of PET-MRI contours that are exchanged in three orthogonal cuts through the brain.

Normalization of PET tracer concentration: In order to normalize PET tracer concentration to the whole brain value, the coregistered MR image volume was used. All voxels in the PET image volume which corresponded to cerebral voxels in the MR image volume were averaged, yielding the average PET tracer concentration in the brain. Subsequently, all PET image voxels were divided by this average value, yielding a PET image volume representing normalized tracer concentration.

Determination of EEG electrode position on the cortical surface: We previously described a method which allows the localization of subdural EEG grid electrodes on the cortical surface [7]. In short, this method relies on the accurate alignment of a lateral planar X-ray image with a 3-D surface rendering of the cortex. Upon completion, a surface view of the cortex is created which corresponds to the planar X-ray image and where the location of grid electrodes can be directly defined on the brain surface. The accuracy of this method was reported to be $1.24 \pm 0.66$ mm with a maximal misregistration of 2.7 mm [12].

Creation of the gray matter mask: A gray matter mask was created based on the gray matter partial volume image ( $\mathrm{PV} \mathrm{GM}^{\text {calculated using a probabilistic segmentation of the SPGR image }}$ volume. Probabilistic segmentation of the SPGR image volume into its underlying components was accomplished through a series of steps following the procedure described previously [13]. This procedure yields three partial image volumes $\left(\mathrm{PV}_{G}, \mathrm{PV}_{W}, \mathrm{PV}_{C}\right)$ in which voxel intensities correspond to the partial volume of gray matter (GM), white matter, and cerebrospinal fluid, respectively. Validation of this method [13] using a complex agarose/ $\mathrm{CuSO}_{4}$ phantom showed good accuracy of computed partial volumes with a mean difference of $4.3 \%$ (range $0 \%-7 \%$ ).

## 2) Image Analysis

Midplane definition: The initial step in the analysis consisted of an automated definition of the midplane. For this, the center point of the brain was geometrically determined together with the closest transaxial plane to the center point. The contour of the brain in this transaxial plane resembles an ellipsoid with $V$-shaped edges in the direction of the long axis. In order to determine for each supratentorial plane the anterior and posterior points in the interhemispheric cleft, the distance between the center point and each brain contour point was determined within a range of $\pm 15$ degrees from the long axis. For each plane, the anterior and posterior points in the interhemispheric cleft were then determined by finding (in each direction) the point with minimal distance to the center. The so obtained points were then fitted with a plane equation.

Definition of anatomical territories on the rendered cortical surface: The previously created gray matter mask was surface rendered using the object graphics model provided by the IDL software package. Subsequently, taking advantage of anatomical landmarks, the user defined regions of interest (ROIs) directly on the cortical surface (Fig. 1). Five ROIs were defined unilaterally on the right side of the brain representing the anterior frontal, posterior frontal, parietal, occipital and temporal anatomical territory.

Creation and sampling of cortical volume elements: In order to allow localization of abnormalities within the large anatomical territories, smaller volume elements were created within these territories. These small volume elements were represented by cylinders with 7mm radius on a rectangular surface grid with $10-\mathrm{mm}$ spacing. The radius of these cylinders was chosen so that it coincided with the diagonal distance between the EEG grid surface points $\left(7=\left[5^{2}+5^{2}\right]^{1 / 2}\right.$; thus, the circles touched at the halfway point between two diagonal grid points (Fig. 2). This design guarantees complete coverage of the cortical surface and results in an overlap between neighboring cylinders of around $15 \%$. As the cylinders were limited to the cortical shell, the chosen dimensions generate a cylinder volume of about $1 \mathrm{~cm}^{3}$. In order to obtain homotopic volume elements in the contralateral hemisphere, surface grid points were mirrored along the previously determined midplane.

Once the location of the small cylindrical volume elements was established in both hemispheres, the coordinates were transferred to the coregistered PET image volume and the normalized tracer concentration in each volume element obtained. This data was then used to determine both the normalized tracer concentration in each volume element as well as the asymmetry index (AI) between homologous volume elements calculated as

$$
\begin{equation*}
\mathrm{AI}(\%)=\left\{\frac{\left[L_{v e}-R_{v e}\right]}{\left[0.5 *\left(L_{v e}+R_{v e}\right)\right]}\right\} * 100 \% \tag{1}
\end{equation*}
$$

where $L_{v e}$ and $R_{v e}$ represent homotopic volume elements on the right and left side of the brain, respectively.

Creation of a normal database: In order to determine the normal range of normalized tracer concentration and asymmetry in the five anatomical territories, we initially applied this approach to a group of normal adults. All small volume elements contained within an anatomical territory were averaged to yield the mean and standard deviation (SD) of normalized tracer concentration and asymmetry for a particular territory. Subsequently, normalized tracer concentration and asymmetry derived from small volume elements in children with epilepsy were compared against the database.

Marking of abnormal volume elements: To objectively define regional cortical abnormalities in children with epilepsy, two ordered conditional criteria were used. The firstorder criterion (asymmetry criterion) consisted of the AI defined in (1). If for an individual volume element the asymmetry criterion was matched, the second-order criterion (laterality criterion) was applied. Dependent on which of the two homotopic volume elements showed a normalized tracer concentration outside the normal range for a particular territory (as derived from the normal controls), it was marked according to severity on the cortical surface.

## F. Spatial Proximity Index (SPI)

Our previous results indicated that intracranial subdural electrodes showing electrophysiological ictal abnormalities (seizure onset) are either overlapping or in close proximity to functional abnormalities measured with FDG PET. Since the PET and ictal EEG abnormalities are many times adjacent, but not coincident, application of a standard ROC analysis is problematic as sensitivity and specificity are independent of the distance between the two measures. In contrast, the close proximity of the PET abnormality to the epileptogenic zone is of great value for the clinical management of epilepsy patients, as it triggers the insertion of an EEG grid which will include the PET abnormality border zone. In order to assess this relationship quantitatively, we developed a spatial proximity index (SPI) calculated based on the position of intracranial subdural EEG electrodes [Fig. 3(A)] relative to PET abnormal cortical areas [Fig. 3(B)].

The subdural EEG grid defines electrodes which are either positive or negative for seizure onset. Furthermore, electrodes located within the PET abnormality are designated as PET positive and those outside the PET abnormality as PET negative. In order to calculate the total distance score between seizure onset electrodes and PET positive electrodes, individual distances between each seizure onset electrode and its nearest PET positive electrode are summed. In addition, a penalty is assessed for each false positive PET electrode by adding a value of 1 to the total distance score. Finally, the (unitless) SPI is computed as shown in (2) at the bottom of the page. Because subdural electrodes are always arranged in a rectangular lattice, we used the "city-block" metric [16] to assess the distance between two electrodes. The cityblock metric is a special case of the general distance model, which is given as
$\mathrm{SPI}=\frac{(\text { total distance score })+(\# \text { of false positive PET electrodes })}{(\# \text { of seizure onset electrodes })}$

$$
D(p, q)_{\operatorname{dim}=N}^{\mathrm{metic}=r}=\left[\sum_{i=1}^{N}\left|p_{i}-q_{i}\right|^{r}\right]^{1 / r}
$$

with $p$ and $q$ being two points in $N$-dimensional space and $r$ being the applied metric. For $r=$ 1 this formula yields the city-block distance, whereas for $r=2$ we obtain the familiar Euclidian distance in two dimensions

$$
\begin{align*}
& D(p, q)_{\text {dim }=2}^{\text {metric }=1}=\left|p_{x}-q_{x}\right|+\left|p_{y}-q_{y}\right|  \tag{4}\\
& D(p, q)_{\operatorname{dim}=2}^{\text {metric }=2}
\end{align*}=\sqrt{\left|p_{x}-q_{x}\right|^{2}+\left|p_{y}-q_{y}\right|^{2}} .
$$

In this metric, the distance between two adjacent electrodes is 1 and the distance between two diagonal electrodes is 2 . Thus, perfect coincidence of PET positive and EEG positive electrodes results in a value of 0 and the larger the score, the poorer the localization.

## G. Study Design

Initially, the control group was used to determine the normal mean and SD with respect to the AI and the normalized tracer concentration within each anatomical territory. These values were saved into a database which was then used to determine functionally abnormal volume elements in the cortex of epileptic children. Subsequently, a ROC analysis [17] was performed with cutoff thresholds of 2.0 and 3.0 SD above the normal mean. As gold standard we assumed subdural electro-physiological grid readings characterizing each electrode as either onset or normal electrode. The number of true positive (TP, abnormal EEG electrode over marked region) and true negative (TN, normal EEG electrode over unmarked region) decisions was determined for all implanted electrodes. Sensitivity and specificity were computed as

$$
\begin{align*}
& \text { Sensitivity }=\frac{T \mathrm{P}}{\mathrm{PC}}  \tag{5}\\
& \text { Specificity }
\end{align*}=\frac{\mathrm{TN}}{\mathrm{NC}}
$$

where PC represents all positive cases (electrodes with abnormal EEG) and NC all negative cases (electrodes with normal EEG). Furthermore, in order to determine the reproducibility of this approach a subgroup of patients was analyzed independently by two observers. Based on the results obtained from the two observers we first determined the difference in the $\%$ of marked area determined in each anatomical territory. In addition, we also determined differences in the resulting sensitivity/specificity pairs for the two threshold levels (2.0, 3.0 SD). Significance of all differences was assessed using a two-sided paired $t$-test.

In a second analysis, we compared the performance of our newly developed 3-D approach with the previously used plane-by-plane analysis [5]. For both these methods, cortical areas of glucose concentration which exceeded an asymmetry threshold of 2 SD above normal mean were assumed as abnormal. The SPI was calculated twice for each patient, once using abnormal cortical areas defined using the new software tool $\left(\mathrm{SPI}_{3 \mathrm{D}}\right)$ and once with respect to abnormal cortical areas determined in-plane $\left(\mathrm{SPI}_{2} \mathrm{D}\right)$. The two indices were compared using a two-sided paired $t$-test. All values are given as mean $\pm 1 \mathrm{SD}$. Significance was defined as $p<0.05$.

## III. Results

## A. Clinical Findings

Table I summarizes scalp and intracranial electrophysiological findings as well as the location of PET abnormalities as determined using the newly developed approach. Interictal FDG PET studies were obtained in all 12 patients and showed foci of decreased glucose metabolism in close proximity to EEG defined onset.

## B. Normal Subjects

In the normal group the regional normalized tracer concentration was not significantly different between the two hemispheres ( $p=0.55$ ); thus; values were pooled for each anatomical territory. In contrast, tracer concentration differed significantly between the various anatomical territories $(p=0.05)$. Normalized tracer concentration was highest in the prefrontal $(1.24 \pm 0.05)$ and motor-frontal ( $1.23 \pm 0.04$ ) territories, followed by the parietal $(1.20 \pm 0.05)$, occipital $(1.14 \pm 0.04)$ and temporal $(1.09 \pm 0.05)$ territories. Furthermore, no significant difference was detected between the asymmetry indices (AI) in the five anatomical territories. The AI was slightly lower in the prefrontal $(3.8 \pm 1.0 \%)$ and motor-frontal $(4.2 \pm 1.2 \%)$ territories as
compared to the parietal $(4.8+2.1 \%)$, occipital $(4.7 \pm 1.9 \%)$ and temporal $(4.7 \pm 2.2 \%)$ territories.

## C. Epilepsy Patients

Detection of seizure onset-At least one electrode overlying the seizure onset zone corresponded to decreased FDG activity in all 12 patients. The accuracy to detect seizure onset areas was $65 \%$ at the 2 -SD threshold and increased to $75 \%$ at the 3 -SD threshold, however, this increase was mainly caused by a decrease in the false positive fraction accompanied by a sharp decrease in sensitivity. ROC analysis revealed at the 2-SD threshold a sensitivity of 64 $\pm 17 \%$ and a specificity of $66 \pm 24 \%$ to detect areas of seizure onset. The sensitivity decreased to $46 \pm 24 \%$ at the 3 -SD threshold with a specificity of $80 \pm 21 \%$.

## Spatial relationship between seizure onset areas and cortical glucose

 abnormalities-The average value for the SPI obtained from all patients was $3.82 \pm 1.65$ when cortical abnormalities were defined using the new approach $\left(\mathrm{SPI}_{3 \mathrm{D}}\right.$. This value was lower than the value calculated using the old in-plane approach $\left(\mathrm{SPI}_{2 \mathrm{D}}=4.52 \pm 1.86\right)$, however, the difference was not statistically significant ( $p=0.09$, paired $t$ ).Reproducibility of seizure onset-From the patient group, 6 patients were randomly selected in order to determine the reproducibility of the size and location of marked areas. From a total of 60 anatomical territories ( 6 patients $\times 10$ territories per patient), $43 \%$ included markings at the 2 -SD threshold whereas only $22 \%$ included markings at the 3-SD threshold. The difference in area marked was not significantly different at both thresholds ( $p=0.46$ for 2 SD and $p=0.28$ for 3 -SD threshold). Furthermore, both sensitivity ( $p=0.33$ for 2 SD and $p=0.18$ for 3 SD ) and specificity ( $p=0.67$ for 2 SD and $p=0.45$ for 3 SD ) did not differ for either threshold with all differences being less than $5 \%$.

Marked cortical areas on the side of the epileptic focus-Guided by semiology, scalp EEG and visual assessment of FDG PET images, intracranial subdural EEG grids were placed on cortical locations suspected to give rise to epileptic seizures for chronic monitoring. Fig. 3 (A) shows the implanted EEG grids relative to anatomical landmarks. The corresponding surface rendering of the patient's cortex is displayed in Fig. 3(B). The patient (\#4) showed the most severe cortical glucose abnormalities in the left parieto-occipital region, in close proximity to the electrophysiologically identified seizure onset area.

Marked cortical areas contralateral to the epileptic focus-Three out of twelve children showed additional increases or decreases of FDG tracer concentration in the hemisphere contralateral to the EEG-confirmed epileptic focus. The size of these abnormal regions ranged between $3 \%$ and $28 \%$ of the corresponding territory and were mostly confined to territories other than those containing the epileptic focus on the contralateral side. Fig. 4(A) shows abnormal increases of cortical tracer concentration in the left frontal, parietal and temporal regions (\#7). In this patient, scalp EEG and semiology indicated a right-sided focus in the frontal and parietal lobes (which was confirmed by FDG PET), therefore, no intracranial electrode data was available from the left hemisphere. However, abnormal increases of FDG tracer concentration were visually verified by comparing the location of tracer increase with axial crossections through the original PET image volume [Fig. 4(B) and (C)].

## IV. Discussion

Determination of abnormalities based on visually apparent hemispheric asymmetry is frequently used in clinical routine in order to aid physicians in the definition of abnormal image patterns [18], [19]. Although sufficiently sensitive to identify the approximate anatomical
location of abnormalities [20], [21], this method lacks the ability to objectively define the precise extent of abnormal cortical areas. Attempts to assess abnormal patterns of tracer concentration in a more objective way employ an AI similar to that in (1) applied to manually defined ROIs. These approaches work well when the observed defect affects a whole anatomical structure or at least a well-defined portion of it, such as in the case of medial temporal lobe epilepsy [22], [23]. However, when abnormalities in the brain are not confined to a well-defined anatomical structure, the defined ROIs are largely arbitrary. In addition, this method cannot provide any information about the lateralization of the defect or whether the observed asymmetry consists of an increase or decrease of tracer concentration. Instead, this information has to be obtained a priori from other diagnostic measures or clinical observations and is a prerequisite in order to interpret the observed asymmetries.

Aside from asymmetry, there are several other methods which have been successfully applied to objectively define cortical abnormalities in adult patients. Statistical parametric mapping (SPM) [24] has been shown to be useful in localizing epileptogenic zones by revealing hypometabolic areas in nonlesional epilepsy [3], [25], although the sensitivity of this method is suboptimal in young children due to the necessary smoothing and spatial normalization to an adult template. Furthermore, when more than one image data set is available (e.g., FDG and FMZ PET, ictal and interictal SPECT), Boussion et al. [26] applied fuzzy modeling and data fusion in order to extract location of epileptogenic foci. This method is based on the notion that mild abnormalities observed in independent images derived from the same subject represent complementary information which can be combined in order to expose the true epileptogenic area. In this study, we attempted to merge the benefits of both the voxel-based and region-of-interest-based strategies, but at the same time avoid the problems associated with either of these methods. In a sense, our cortical volume elements can be compared to the "resolution elements" used in the context of SPM analysis, as they constitute the smallest volume elements assessed to be either normal or abnormal. However, in contrast to the SPM method, no nonlinear spatial warping of an individual pediatric brain to a "standard" brain template is required. Although no warping is required, this approach still takes advantage of the normal pattern of glucose concentration, shown to be established around one year of age [27], [28]. Using a database derived from a group of normal adults, a priori knowledge about the normal range of asymmetry and tracer concentration as a function of brain location can be standardized and applied more objectively than was possible with previous methods.

## A. Detection of Seizure Onset Areas

Our results suggest (Table I), that the lobe of seizure onset as defined by intracranial ictal EEG is well predicted by the location of FDG PET abnormalities. However, in most patients FDG PET abnormalities are observed in other lobes either in the same hemisphere (remote) or in the contralateral hemisphere (bilateral abnormalities). At this time the clinical relevance of both the remote and bilateral PET abnormalities is unclear. One can speculate that these abnormalities outside the EEG verified epileptic focus represent potential secondary foci which may mature with time to represent independent epileptic foci [22]. Moreover, the process of maturation of these secondary foci might be a complex function of their duration, frequency and location and the observed PET abnormalities might represent an early sign of tissue epileptogenicity.

The situation is even more difficult when bilateral FDG PET abnormalities are detected. Usually only the side of PET abnormality which corresponds to scalp EEG or semiology is considered in order to guide the placement of an intracranial EEG grid. In fact, only patients with lateralized (> $80 \%$ of seizures arising from one hemisphere) and localized (onset confined to one or two lobes) seizure onset are considered for further invasive evaluation. In the three patients in whom bilateral abnormalities were detected (\#2, \#6, \#7), no correlation could be
found with preoperative neuropsychological deficits and all three patients were seizure free after resection of the unilateral (EEG confirmed) primary focus (Table I).

Our previous assessment of the proximity between hypometabolic cortical areas and epileptogenic cortex indicates that epileptogenic areas are frequently found adjacent to PET abnormalities, but are not overlapping [22]. Usually, EEG abnormalities are located adjacent to extensive FDG abnormalities and might be reversible after surgical intervention. This phenomenon is at present time poorly understood and possible mechanisms are discussed elsewhere [22], [23]. Thus, although there exist a strong spatial relationship between epileptic cortex and glucose abnormalities, both are distinct. In order to address this issue, we designed the spatial proximity index (SPI) measure and showed that our 3-D approach constitutes a slight improvement with regard to the detection of seizure onset areas as compared to the simple inplane approach.

## B. Methodological Considerations

As with every method, a few limitations need to be considered when applying this method in clinical routine. As indicated above, we used young adults to create a normal database, and this database was implicitly assumed to characterize accurately the normal tracer concentration pattern in young children. This approach is inevitable due to ethical guidelines which sanction the administration of radioactive substances only in children who may derive direct benefit from the study. However, there are strong indications that the pattern of FDG tracer concentration is very similar between children and adults. It is well known that, although there are large changes in the absolute glucose metabolic rate between one year of age and adulthood, the overall distribution of brain glucose metabolism at one year of age appears similar to that seen in adults [3], [27], [28].

Furthermore, as a consequence of using the asymmetry measure as the primary criterion, our method is able to detect only those bilateral abnormalities which consist of a combination of abnormally high and low tracer combination. To accurately assess bilateral abnormalities, every single cortical volume element has to be compared against the normal database. Future development at our institution using geometric parcellation of the brain with subsequent analysis of individual cortical volume element might allow detection of truly bilateral cortical abnormalities.

## C. Clinical Implications

The relevance of bilateral abnormalities for the assessment of the functional integrity of the hemisphere contralateral to the focus is high due to its predictive value on cognitive outcome following surgical resection [29]. However, it is important to guard against artifacts which arise as a result of anatomical or physiological variations in patient's brains. As an example, one of our patients (\#7) showed contralateral decreases in the inferior frontal cortex. Upon closer inspection of the original images this decrease could be attributed to an unusual thinning of the inferior cortical mantle causing an apparent decrease due to the partial volume effect. This implies that results obtained by our method must be critically assessed for unusual individual variations of brain structure or function.

Finally, the ultimate standard for successful identification of epileptogenic brain regions is the prolonged absence of seizures following surgical resection. In our patient population, $85 \%$ of the patients had at least a worthwhile improvement and two thirds of all children became seizure free after surgery. Given that all our patients suffered with nonlesional epilepsy, this outcome is very good. In the two patients who did not benefit from the surgical intervention (\#11 and \#12), FDG showed very extensive hemispheric abnormalities. In one patient (\#12), large frontal, temporal and parietal abnormalities were detected, however, scalp EEG suggested a
primarily fronto-temporal focus. Due to the extensive abnormal areas, the parietal abnormality was not addressed with intracranial electrodes during chronic monitoring and as a consequence this area was not resected. The omission to address the parietal abnormalities might have contributed to the unfavorable outcome in this patient.

In conclusion, the presented 3D analysis approach has the potential to augment the application of PET in children not only with FDG and epilepsy, but also with various other neurological disorders showing abnormal pattern of tracer concentration, and might impact upon a large number of children who are being evaluated for surgical resection.

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## Biography



Otto Muzik received the Ph.D. degree in electron and X-ray physics in 1988 from the University of Vienna, Vienna, Austria.

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## REFERENCES

1. Engel J Jr. Henry TR, Risinger MW, et al. Presurgical evaluation for partial epilepsy: Relative contributions of chronic depth-electrode recordings versus FDG-PET and scalp-sphenoidal ictal EEG. Neurology 1990;40:1670-1677. [PubMed: 2122275]
2. So EL. Role of neuroimaging in the management of seizure disorders. Mayo Clinic Proc Nov.;2002 77(11):1251-1264.
3. Muzik O, Chugani DC, Juhasz C, Shen C, Chugani HT. Statistical parametric mapping: Assessment of application in children. NeuroImage 2000a; 12:538-549. [PubMed: 11034861]
4. Kim YK, Lee DS, Lee SK, Chung CK, Chung JK, Lee MC. (18)F-FDG PET in localization of frontal lobe epilepsy: Comparison of visual and SPM analysis. J. Nucl. Med., vol 2002;43:1167-1174.
5. Muzik O, Chugani DC, Shen C, da Silva EA, Shah J, Shah A, Canady A, Watson C, Chugani HT. An objective method for localization of cortical asymmetries using positron emission tomography to aid in surgical resection of epileptic foci. Comput. Aided Surg 1998;3:74-82. [PubMed: 9784955]
6. Juhász C, Chugani DC, Muzik O, Watson C, Shah J, Shah A, Chugani HT. Electroclinical correlates of flumazenil and fluorodeoxyglucose PET abnormalities in lesional epilepsy. Neurol 2000;55:825835.
7. Muzik O, da Silva EA, Juhasz C, Chugani DC, Shah J, Nagy F, von Stockhausen H-M, Herholz K, Canady A, Gates J, Frost M, Ritter F, Watson C, Chugani HT. Intracranial EEG versus flumazenil and glucose PET abnormalities in children with extratemporal lobe epilepsy. Neurology 2000b;54:171179. [PubMed: 10636144]
8. Hamacher K, Coennen HH, Stoecklin G. Efficient stereospecific synthesis of no-carrier-added 2-[F-18]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J. Nucl. Med 1986;27(2):235-238. [PubMed: 3712040]
9. Bergstroem M, Litton J, Bohm C, Blomquist G. Determination of object contours from projection for attenuation correction in cranial positron emission tomography. J. Comput. Assist. Tomogr 1982;6:365-372. [PubMed: 6978896]
10. Pietrzyk U, Herholz K, Heiss WD. Three-dimensional alignment of functional and morphological tomograms. J. Comput. Assist. Tomogr 1990;14(1):51-59. [PubMed: 2298997]
11. Pietrzyk U, Herholz K, Fink G, Jacobs A, Mielke R, Slansky I, Wurker M, Heiss WD. An interactive technique for three-dimensional image registration: Validation for PET, SPECT, MRI and CT brain studies. J. Nucl. Med 1994;35:2011-2018. [PubMed: 7989986]
12. Thiel A, Herholz K, von Stockhausen HM, van Leyen-Pilgram K, Pietrzyk U, Kessler J, Wienhard K, Klug N, Heiss WD. Localization of language-related cortex with 15O-labeled water PET in patients with gliomas. Neuroimage May;1998 7:284-295. [PubMed: 9626669]
13. Reiss AL, Hennessey JG, Rubin M, et al. Reliability and validity of an algorithm for fuzzy tissue segmentation of MRI. J. Comput. Assist. Tomogr 1998;22:471-479. [PubMed: 9606391]
14. Lorenson C, Kline D. Marching cubes": A high resolution 3D-surface construction algorithm. Comput. Graph 1987;21:163-169.
15. Foley, J.; van Dam, A.; Feiner, S.; Hughes, J. Computer Graphics: Principles and Practise. AddisonWesley; Norwell, MA: 1990. p. 702-725.
16. Shepard RN. Attention and the metric structure of the stimulus space. J. Math. Psychol 1964;1:5487.
17. Metz CE. Basic principles of ROC analysis. Proc. Seminars Nuclear Medicine 1978;8:283-298.
18. Harris G, Links J, Pearlson G, Camargo E. Cortical circumferential profile of SPECT cerebral perfusion in Alzheimer's disease. Psych. Res. Neuroimag 1991;40:167-180.
19. Maurer A, Siegel J, Comerota A, Morgan W, Johnson M. SPECT quantification of cerebral ischemia before and after carotid endarterectomy. J. Nucl. Med 1990;31:1412-1420. [PubMed: 2384810]
20. Jayakar P, Duchowny M, Resnick TJ, Alvarez LA. Localization of seizure foci: Pitfalls and caveats. J. Clin. Neurophysiol 1991;8:414-431. [PubMed: 1761707]
21. Theodore WH, Sato S, Kufta C, Balish MB, Bromfield EB, Leiderman DB. Temporal lobectomy for uncontrolled seizures: The role of positron emission tomography. Ann. Neurol 1992;32:789-794. [PubMed: 1471870]
22. Juhász C, Chugani DC, Muzik O, Watson C, Shah J, Shah A, Chugani HT. Is epileptogenic cortex truly hypometabolic on interictal positron emission tomography? Ann. Neurol Jul.;2000 48(1):8896. [PubMed: 10894220]
23. Juhász C, Behen ME, Muzik O, Chugani DC, Chugani HT. Bilateral prefrontal and temporal neocortical hypometabolism in children with epilepsy and aggression. Epilepsia 2001;42:991-1001. [PubMed: 11554884]
24. Friston KJ, Holmes AP, Worsley KJ, Poline J-B, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general approach. Hum. Brain Map 1995;2:189-210.
25. Kim YK, Lee DS, Lee SK, Kim SK, Chung CK, Chang KH, Choi KY, Chung JK, Lee MC. Differential features of metabolic abnormalities between medial and lateral temporal lobe epilepsy: Quantitative analysis of (18)F-FDG PET using SPM. J. Nucl. Med 2003;44:1006-1012. [PubMed: 12843213]
26. Boussion N, Cinotti L, Barra V, Ryvlin P, Mauguire F. Extraction of epileptogenic foci from PET and SPECT images by fuzzy modeling and data fusion. Neuroimage 2003;19:645-654. [PubMed: 12880795]
27. Chugani HT, Phelps ME. Maturational changes in cerebral function in infants determined by [18] FDG positron emission tomography. Science 1986;231:840-843. [PubMed: 3945811]
28. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann. Neurol 1987;22:487-497. [PubMed: 3501693]
29. Chugani HT. The role of PET in childhood epilepsy. J. Child Neurol Oct.; 1994 9(Suppl 1):S82-S88. [PubMed: 7822756]


Fig. 1.
(A) Borders of anatomical territories defined directly on the cortical surface of a representative patient. The view of the brain was interactively changed during region drawing to allow definition of anatomical boundaries based on cortical landmarks such as the central sulcus (CS), sylvian fissure (SF) and the parieto-occipital fissure (PO). Regions defined include unilaterally the prefrontal $(\mathrm{pF})$, motor-frontal $(\mathrm{mF})$, temporal $(\mathrm{T})$, occipital $(\mathrm{O})$ and parietal $(\mathrm{P})$ cortex in the right hemisphere. (B) The figure shows a frontal view of the cortex with the midplane separating the two hemispheres. Borders of anatomical territories defined in the right hemisphere were mirrored along the midplane onto the left hemispheric brain surface.


Fig. 2.
Superior view of the cortical surface showing the position of a few small volume elements within an anatomical territory. The cylindrically shaped volume elements (circles) were located with their base at the cortical surface and extending into the brain perpendicular to the surface normal. The depth of the cylinders coincided with the thickness of the cortical gray matter at the corresponding location, however, was limited to a maximum of 20 mm . Volume elements located in the right hemisphere were mirrored along the midplane onto the left hemisphere and the AI was computed for each corresponding pair. In addition, the borders of the anterior and posterior frontal territory are shown.


Fig. 3.
(A) Photograph taken during the placement of the intracranial subdural electrode grid. Intracranial electrocorticography was performed prior to surgical resection of the epileptic focus. Electrode grids were inserted in the left parieto-occipital ( $8 \times 8$ grid), temporal ( $4 \times 5$ grid) and frontal ( $4 \times 8$ grid) lobes for chronic monitoring of seizures. The central sulcus (CS) and the sylvian fissure (SF) are shown. (B) Corresponding rendering of the marked surface obtained from MRI and FDG PET images in the same patient (patient \#4). Electrodes representing seizure onset are shown in grey. Areas of abnormally decreased FDG tracer concentration were determined in the parieto-occipital and temporal territories. The SPI determined for this patient was 3.33 . This relatively high SPI value is a consequence of the remote PET abnormality in the temporal lobe which was not confirmed by intracranial EEG.


Fig. 4.
(A) The figure shows abnormal increases of tracer concentration in the left frontal (gray arrow), parietal (white arrow) and temporal (striped arrow) region of a patient (\#7) with right-sided epileptic focus, as indicated by semiology, scalp and intracranial EEG. Because no intracranial electrodes were available in the left (nonepileptogenic) hemisphere, two transaxial planes were selected in order to visually confirm these abnormal increases. (B) A large area of abnormally high glucose concentration can be observed in the left Brodman area 8 (gray arrow) and a smaller area in the superior section of the parietal lobe (white arrow). (C) In addition, abnormally high glucose concentration can be also found in the anterior portion of the temporal lobe (striped arrow).
The Table Reports the Location of Electrophysiological and PET Abnormalities in the Four Lobes of the Brain (Frontal, Temporal, Parietal and Occipital). In Addition, the Area of Resection as Well as the Surgical Outcome Is Shown. The Patients Are Ordered According to Outcome and the Length of the Followup Time Period. Patients in Whom Bilateral PET Abnormalities Were Detected Are Marked With an Asterisk and the Lobes Highlighted

| Sex/Age | Scalp ictal EEG | Intracrani Onset | Spread | PET abnormality | Resection | Outcome <br> (follow-up) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1. M/3y5m | L hemisphere | L temporal L parietal |  | L frontal <br> L temporal <br> L parietal | L frontal L temporal L parietal | seizure free (40 months) |
| 2.* $\mathrm{M} / 4 \mathrm{y} 11 \mathrm{~m}$ | L temporal <br> L parietal <br> L frontal | L temporal <br> L occipital | L frontal L parietal | $L$ hemisphere R parietal | L subtotal hemispherectomy | seizure free (31 months) |
| 3. F/3y 5 m | L temporal | L temporal | L parietal | L temporal L parietal | L temporal L parietal | seizure free (28 months) |
| 4. $\mathrm{M} / 4 \mathrm{y} / 3 \mathrm{~m}$ | L temporal <br> L parietal <br> L occipital | L temporal <br> L occipital | L frontal <br> L temporal <br> L parietal | L temporal <br> L parietal <br> L occipital | L subtotal hemispherectomy | seizure free (25 months) |
| 5. M/5y7m | L frontal | L frontal | L frontal <br> L temporal <br> L parietal | L frontal <br> L temporal <br> L parietal | L frontal L temporal L parietal | seizure free (23 months) |
| 6.* F/2y5m | R temporal | R temporal | R temporal | $\mathbf{R}$ temporal L parietal | R temporal R parietal | seizure free ( 15 months) |
| 7.* $\mathrm{M} / 13 \mathrm{y} 7 \mathrm{~m}$ | R frontal R temporal | R temporal R parietal | R temporal R parietal | $\mathbf{R}$ temporal <br> R parietal <br> L temporal <br> L parietal <br> L frontal | R temporal R parietal | seizure free (15 months) |
| 8. $\mathrm{M} / 2 \mathrm{y} 5 \mathrm{~m}$ | L temporal <br> L parietal | L temporal <br> L occipital | L occipital | L temporal <br> L parietal | L temporal <br> L occipital | seizure free <br> (13 months) |
| 9. $\mathrm{M} / \mathrm{ly} 0 \mathrm{~m}$ | L parietal <br> L temporal <br> L frontal | L temporal <br> L parietal <br> L occipital | L hemisphere | L temporal <br> L parietal <br> L frontal | L subtotal hemispherectomy | $>80 \%$ seizure reduction (34 months) |
| 10. M/3y5m | L temporal | L temporal L parietal | L temporal <br> L frontal | L temporal <br> L parietal <br> L frontal | L temporal <br> L parital <br> L frontal | $>80 \%$ seizure reduction (19 months) |
| 11. $\mathrm{F} / 3 \mathrm{y} 7 \mathrm{~m}$ | L temporal <br> L parietal | L temporal | L frontal | L temporal <br> L parietal <br> L frontal | L subtotal hemispherectomy | no improvement <br> (27 months) |
| 12. F/14y9m | R frontal R temporal | R frontal | R frontal R temporal | R frontal <br> R temporal <br> R parietal | R frontal R temporal | no improvement <br> (17 months) |


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