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Quantitative brain surface mapping of an electrophysiologic/metabolic mismatch in human neocortical epilepsy

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Summary

The spatial relationship between an intracranial EEG-defined epileptic focus and cortical hypometabolism on glucose PET has not been precisely described. In order to quantitatively evaluate the hypothesis that ictal seizure onset and/or rapid seizure propagation, detected by subdural EEG monitoring, commonly involves normometabolic cortex *adjacent* to hypometabolic cortical regions, we applied a novel, landmark-constrained conformal mapping approach in 14 children with refractory neocortical epilepsy. The 3D brain surface was parcellated into finite cortical elements (FCEs), and hypometabolism was defined using lobe- and side-specific asymmetry indices derived from normal adult controls. The severity and location of hypometabolic areas vs. ictal intracranial EEG abnormalities were compared on the 3D brain surface. Hypometabolism was more severe in the seizure onset zone than in cortical areas covered by non-onset electrodes. However, similar proportions of the onset electrodes were located over and adjacent to (within 2 cm) hypometabolic regions (46% vs. 41%, respectively), whereas rapid seizure spread electrodes preferred these “adjacent areas” rather than the hypometabolic area itself (51% vs. 22%). On average, 58% of the hypometabolic regions had *no* early seizure involvement. These findings strongly support that the seizure onset zone often extends from hypometabolic to adjacent normometabolic cortex, while large portions of hypometabolic cortex are not involved in seizure onset or early propagation. The clinical utility of FDG PET in guiding subdural electrode placement in neocortical epilepsy could be greatly enhanced by extending grid coverage to at least 2 cm beyond hypometabolic cortex, when feasible.

Keywords

Neocortical epilepsy; Positron Emission Tomography; Glucose metabolism; Epilepsy surgery; Intracranial EEG

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Conflict of interest

None of the authors have any conflicts of interest to disclose.

1. Introduction

In patients with intractable neocortical epilepsy, 2-¹⁸F-fluoro-2-deoxy-D-glucose (FDG) PET is a valuable diagnostic tool to lateralize and even localize epileptic foci. Numerous early studies have demonstrated a good correlation between the general area of cortical glucose hypometabolism depicted by FDG PET and electroclinical localization of epileptic foci (Swartz et al., 1989, 1990; Henry et al., 1991). FDG PET can be particularly useful in patients with non-localizing MRI, as it can often lateralize and regionalize potentially epileptogenic cortical regions to guide intracranial electrode placement. According to previous studies, the presence of localized glucose PET abnormalities which are concordant with ictal EEG or resection site varies widely between approximately 40 and 90% (Gaillard et al., 1995a; da Silva et al., 1997; Kim et al., 2000; Hong et al., 2002; Hader et al., 2004; Lee et al., 2005; Kurian et al., 2007). Furthermore, previous studies have provided evidence that localizing FDG PET concordant with ictal EEG and/or site of resection, represents a clinically valuable prognostic factor for post-surgical seizure-free outcome (Lee et al., 2005; Yun et al., 2006; Knowlton et al., 2008).

The primary purpose of presurgical evaluation in cases of refractory neocortical epilepsy is to identify the epileptic zone to be resected in order to achieve seizure-freedom. However, the accurate location and extent of cortex necessary to be resected cannot (at present) be determined by a single diagnostic tool and, therefore, results from various diagnostic modalities are typically considered in reaching a final decision as to the extent of resection. The seizure onset zone has been considered to be the most important electrocorticography measure indicating the location of the epileptogenic zone (Rosenow and Luders, 2001) and the most important area to be resected for favorable surgical outcome (Asano et al., 2009). The seizure onset zone can be precisely detected by the optimal use of extraoperative subdural EEG monitoring whose clinical utility is highly dependent on subdural grid placement guided by other non-invasive diagnostic modalities. FDG PET, in conjunction with other imaging, as well as clinical and non-invasive electro-physiological data, is often used to lateralize the side of seizure onset and to guide intracranial electrode placement.

Although it is generally accepted that cortical metabolic abnormalities correspond well with epileptic cortex, including the seizure onset zone, in many cases interictal hypometabolic regions are larger and extend beyond the presumed epileptic zone or sometimes completely miss it (Henry et al., 1993; Gaillard et al., 1995b; da Silva et al., 1997; Juhasz et al., 2000; Muzik et al., 2000a). In a previous preliminary study, we reported that areas of seizure onset and seizure propagation often occur at the border of hypometabolic/normometabolic cortex (“metabolic borderzone”) rather than in the center of the hypometabolic region (Juhasz et al., 2000). Previous studies, however, did not analyze the presence and extent of epileptogenic cortex in normometabolic areas surrounding cortical hypometabolism.

Based on our previous observations, we performed a detailed, quantitative analysis of the extent and degree of cortical hypometabolism on FDG PET and their spatial relationship to ictal subdural EEG findings in children with intractable neocortical epilepsy. We used a novel multimodality software environment allowing three-dimensional (3D), quantitative surface mapping of metabolic abnormalities. The central goal of the present study was to quantitatively evaluate the concept of a spatial mismatch between ictal intracranial EEG findings and glucose PET abnormalities. We hypothesized that seizure onset and/or rapid seizure propagation commonly involves normometabolic cortex adjacent to hypometabolic cortical regions. In addition, we evaluated whether selected clinical variables are related to this metabolic–electrophysiologic mismatch.

2. Methods

2.1. Subjects

Fourteen children (7 boys, mean age at surgery: 9.0, range: 2.8–16.5 years) with intractable neocortical epilepsy were included in this retrospective study (Table 1). Inclusion criteria: (1) medically refractory epilepsy with partial seizures; (2) 2-stage epilepsy surgery with chronic subdural EEG monitoring, performed between 2001 and 2009 in the Children's Hospital of Michigan, Detroit; (3) the presence of focal cortical area(s) showing decreased glucose metabolism, ipsilateral to the EEG-defined epileptic focus, on the interictal FDG PET scan based on visual assessment; (4) identifiable seizure onset zone located on the lateral cortical surface; (5) no previous surgery. Exclusion criteria: (1) MRI showing an intracranial foreign mass or extensive (multilobar, hemispheric) cortical developmental abnormalities; (2) chronic subdural EEG recording showing only medial temporal seizure onset zones. Fourteen patients who satisfied both inclusion and exclusion criteria were studied. Presurgical evaluation included MRI, scalp and chronic intracranial (subdural) EEG monitoring, neuropsychology evaluation, as well as FDG PET and, in some cases, also PET scanning with [^{11}C]flumazenil or alpha[^{11}C]methyl-L-tryptophan. All patients subsequently underwent resective epilepsy surgery and histological assessment of the resected tissue. Antiepileptic medication at the time of PET scan included mono- or polytherapy with topiramate ($n = 5$), oxcarbazepine ($n = 6$), levetiracetam ($n = 3$), zonisamide ($n = 2$), lamotrigine ($n = 2$), carbamazepine ($n = 1$), valproate ($n = 2$), clorazepate ($n = 1$), clonazepam ($n = 1$), phenytoin ($n = 1$), vigabatrin ($n = 1$).

Tables 1 and 2 summarize the clinical data, imaging and EEG findings of the 14 patients. Duration of epilepsy was defined as the period between the first clinical seizure and the date of epilepsy surgery. Time of last clinical seizure prior to PET scan was obtained from parent interviews at the time of the PET scan, and was scored as follows: score 1 = last seizure within 1 day prior to scan, score 2 = last seizure between 1 and 6 days before the scan, score 3 = last seizure was more than 6 days before the PET scan. We also applied a ranking method for assessing the average spike frequency on EEG during the FDG uptake period. Score 0 = no spikes; score 1 = 0–1 spike/min, score 2 = 1–10 spikes/min, score 3 = more than 10 spikes/min. Age at epilepsy onset, duration of epilepsy and pathology findings were obtained from medical charts and clinical databases. The study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from patients over age 13 years and all patients' parents or legal guardians.

2.2. MRI scan protocol

MRI studies were performed clinically on a GE 1.5 T Signa 5.6 Unit (GE Medical systems, Milwaukee, WI). For the purpose of 3D surface reconstruction, a volumetric T1 weighted spoiled gradient echo (SPGR) sequence was used for each patient. The MRI scans were acquired between 2001 and 2009 with slightly differing acquisition parameters such as number of planes (100–164), orientation (sagittal or coronal) and plane thickness (1.2–1.5 mm). These differences did not have any major impact on 3D brain surface rendering.

2.3. FDG PET scan protocol

All FDG PET scans were performed for clinical indications as part of the presurgical evaluation. PET scans were performed in 2D-mode using the CTI/Siemens (Erlangen, Germany) EXACT/HR positron tomograph located at Children's Hospital of Michigan in 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 5.5 ± 0.35 mm at full-width-at-half-maximum and 6.0 ± 0.49 mm in the axial direction. Calculated attenuation correction was performed as described previously (Bergstrom et al., 1982). The

scanning protocol was similar to that described earlier (Juhasz et al., 1999). In short, 0.143 mCi/kg of FDG was injected intravenously as a slow bolus followed by a 30 min uptake period, during which EEG was continuously monitored. Subsequently, a static 20-min emission scan of the brain was acquired parallel to the canthomeatal plane. The median time interval between FDG PET scan and subdural electrode placement was 6 months (range: 2–40 months).

2.4. Chronic subdural EEG monitoring

Subdural electrode placement was determined at a multidisciplinary epilepsy surgery conference based on clinical data, information about seizure onset location determined by scalp ictal EEG, MRI and the location of FDG PET abnormalities (assessed visually at the time of decision). A total of 1199 electrodes (range: 64–106/patient) were placed covering the presumed epileptogenic cortex. In all but 1 patient (patient 4), at least three habitual seizures were captured and analyzed during intracranial video-EEG monitoring. In patient 4 only one seizure was captured, although it provided sufficient information to identify the epileptic cortex. Identification of electrodes involved in seizure onset (defined as a localized, sustained, rhythmic, semirhythmic, or spiking EEG pattern with frequency >2 Hz, visually distinguished from background activity and not attributed to the state of arousal) (Lee et al., 2000; Asano et al., 2004) of habitual clinical seizures was accomplished through long-term (3–5 days) subdural EEG monitoring in all of the cases by board-certified electroencephalographers (E.A, A.S). Electrodes involved in the early propagation of ictal activity (seizure spread area, defined as an area involved in seizure activity within 10s of seizure onset) could be reliably determined and further evaluated in 9/14 cases.

2.5. Image preprocessing

FDG PET and MRI images were initially co-registered using VINCI 2.50.0 (Max-Planck-Institut, Cologne, Germany) (Cizek et al., 2004), a well-established, multi-purpose software, using semi-automated three-dimensional registration technique. Subsequently, all extracerebral structures (including the cerebellum) were removed from the MR image volumes using either Mri-Cro (<http://www.sph.sc.edu/comd/rorden/mricro.html>) or Brain-Suite2 (Shattuck and Leahy, 2002) software. To better visualize cortical landmarks, the original cortical surface was then smoothed using alpha-shapes and a curvilinear shrink operation with varying depth was performed (Edelsbrunner and Mucke, 1994). This operation removed the outer layer of the cerebral cortex thus exposing the deep folding structures (sulci). As a result, sharp border zones between white and gray matter were rendered and subsequently projected onto the original (non-shrunk) cortex showing the location of the major and minor gyri and sulci.

Based on previous approaches (Drury et al., 1999; Gu et al., 2004; Hurdal and Stephenson, 2004) as well as on our recent work (Muzik et al., 2005), we have developed a computational framework for landmark-constrained conformal mapping of the brain surface, where the mapping accuracy is achieved through the matching of readily identifiable cortical landmarks (major sulci) (Muzik et al., 2007). These landmarks were manually defined in the subject's native space and subsequently conformally mapped into a canonical domain (sphere) where they are aligned by minimizing the surface harmonic energy. Once aligned, the surface of the sphere was parcellated into triangle shaped finite cortical elements (FCEs; 256 for each hemisphere) using a recursive parcellation scheme and the set of surface elements was reversely mapped into the subject's native space where they represented homotopic surface elements in brains of individual subjects and where all data analysis took place.

2.6. Quantitative assessment of PET abnormalities

Following parcellation of the brain surface, the normal surface vector was calculated for each surface voxel. By averaging the PET tracer concentration along the inverse normal vector in the co-registered PET image volume, the mean PET tracer concentration within a 10mm cortical mantle was calculated, color-coded and projected onto the smoothed brain surface. Using this methodology, abnormal FCEs with regard to decreased glucose metabolism were defined based on asymmetry indices (AIs) derived from homotopic FCEs according to a predefined cutoff threshold. AIs of each finite cortical element were calculated as $AI(\%) = [(I - C)/(I + C)/2] \times 100\%$, where I indicates the average PET tracer concentration in the ipsilateral (to the epileptic focus) and C represents that of the homotopic contralateral element. Moreover, to eliminate the application of arbitrarily predefined thresholds, lobe- and side-specific thresholds were calculated and utilized as follows.

MRI and FDG PET scans were acquired previously in 11 healthy, young adult controls (6 females, mean age: 32 years). The glucose PET studies were carried out using the same protocol applied for the epilepsy group. Their surface rendered volumetric MRIs were then parcellated into finite cortical elements with the method described above. Subsequently, the mean AIs of the elements in each lobe of both hemispheres were measured (Table 3). In the patient group FCEs having higher AIs than the corresponding lobe- and side-specific normal mean +2SD were considered abnormal (hypometabolic) and were marked with blue color on the 3D brain surface.

2.7. Determination of electrode position on brain surface

Definition of surface electrode locations was done by one author (B.A.) who was blinded to the intracranial EEG monitoring and PET results at that time. By utilizing digital skull X-ray images with the subdural electrode arrays in place, cortical surface views were generated using the 3D-Tool software package with the location of electrodes directly rendered on the brain surface (Muzik et al., 2001; Juhasz et al., 2009). The use of X-ray images (instead of grid-CT or MRI) is advantageous in children since this procedure is performed at bed-side and does not require transportation and sedation of the child. The accuracy of the co-registration procedure between the subdural EEG electrodes and the MRI image volume was reported to be 1.2 ± 0.7 mm with a maximal misregistration of 2.7mm (von Stockhausen et al., 1997). These electrode locations were then manually transferred to the 3D brain surface visualized by the landmark-constrained surface mapping software used in the present study. In addition, intraoperative digital images taken before dural closure showing the exposed brain surface with the placed electrodes were used to verify the spatial accuracy of electrode positioning on the 3D brain surface (Wellmer et al., 2002). Major anatomical landmarks (central sulcus, precentral sulcus, Sylvian fissure, gyral pattern, etc.) readily identifiable on both the photographs and the 3D rendered brain surface were used to verify the exact location of the electrodes (Fig. 1). In order to achieve reliable electrode positioning, “seed” electrodes with readily definable locations (e.g., the junction of central sulcus and Sylvian fissure) were chosen and used as starting points in the electrode placing procedure. Each electrode within one grid was placed next to each other evenly with an accurate distance of 1 cm (i.e., the standard intercontact distance between two adjacent electrodes in an electrode grid or strip). Finally, each electrode was color-coded according to its ictal characteristics (red = seizure onset, yellow = rapid seizure spread, green = no early ictal involvement).

2.8. Evaluation of metabolic and localization data

Using the above described methodology, we measured the *extent* of hypometabolic cortex in the epileptic hemisphere based on the number of FCEs with abnormal AIs, as well as the *degree* of hypometabolism (mean AI) in individual FCEs and user-defined regions encompassing a number of FCEs. Spatial relationship between seizure onset/propagation

electrodes and hypometabolic areas was evaluated by calculating the number of hypometabolic and normometabolic FCEs underlying onset electrodes, as well as calculating the number of onset and spread electrodes overlying hypometabolic or normometabolic triangles (FCEs). In addition, based on our previous concept of metabolic “borderzones” (Juhasz et al., 2000), we defined a specific “adjacent area” which consisted of the FCEs directly surrounding the hypometabolic areas and then calculated the corresponding AIs and the number of onset/spread electrodes overlying this area. Based on the size and geometry of FCEs, the borders of the adjacent area were within 2 cm of the hypometabolic area (Fig. 2). The analysis of metabolic vs. EEG relationships was confined to cortical regions covered by subdural electrodes (on average, $40 \pm 15.7\%$ of the total hypometabolic area); therefore, hypometabolic regions not covered by electrodes were not included in this part of the analysis.

2.9. Statistical analysis

Statistical analysis was performed using SPSS 17.0 (Chicago, IL) statistical software package. Initially an independent samples *t*-test was performed to test a possible difference between the extent of left and right hemispheric hypometabolic areas as well as the number of seizure onset electrodes in patients with left and right hemispheric seizure onset. The same test was used to test whether the severity of hypometabolism (characterized by AIs) was different in seizure onset zones as compared to areas covered by non-onset electrodes. Paired samples *t*-test was used to compare the *extent* (number of FCEs) of hypometabolic vs. normometabolic cortex involved in the onset of seizures. In addition, repeated measures ANOVA was applied to compare the number of onset and spread electrodes located over hypometabolic, adjacent areas and other normometabolic regions. Finally, to assess possible correlations between metabolic parameters (such as extent of seizure onset zone, hypometabolic/normometabolic part of onset zone, total hypometabolic area, AI in and around onset zone, AI of total hypometabolic areas, AI of areas covered by non-onset electrodes, proportion of onset electrodes overlying hypometabolic or normometabolic areas as compared to the total number of onset electrodes) and clinical variables, we performed Pearson’s parametric test for continuous and Spearman’s rank correlation test for ordinal variables. Since not all patients had seizure-free outcome, it could be argued that some results, indicating a mismatch between EEG and PET abnormalities, may be due to an inadequate identification of the epileptogenic zone. Therefore, statistical analysis was repeated in the subgroup of patients with seizure-free outcome [class I, according to the criteria of Engel et al. (1993)] where we had high confidence that the area of seizure onset was identified and resected completely. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Extent and severity of cortical hypometabolic areas

In the 14 patients the mean number of hypometabolic finite elements (FCEs) was 41 (range: 5–133), which, considering that the surface of a hemisphere is divided into 256 elements, represented on average approximately 16% of the hemispheric surface. Due to the high variance, there was no significant difference in the total number of hypometabolic elements between the subgroup of patients having right or left hemispheric seizure origin, although the mean extent of hypometabolism was higher in the left-sided subgroup (mean = 50 ± 45 vs. 25 ± 22 for the right-sided; $p = 0.19$). Furthermore, there was no significant difference between the number of seizure onset electrodes in the two groups (mean = 13 for the left-sided vs. 9 for the right-sided; $p = 0.29$). The average AI of the hypometabolic areas was $14.8 \pm 4.6\%$. The AI of cortical areas underlying seizure onset electrodes was slightly higher than that of the cortical areas covered by non-onset electrodes (10.8% vs. 4.4%, $p = 0.062$);

this suggested that the onset zone in general was slightly hypometabolic although it was not necessarily located in cortex with the most severe hypometabolism.

3.2. Location of seizure onset and early seizure propagation zones compared to hypometabolism

In 12 out of 14 patients studied, at least one seizure onset electrode was located on a hypometabolic FCE and in 2 patients all onset electrodes overlay hypometabolic areas. On average, $58 \pm 33\%$ of the hypometabolic regions showed no early seizure involvement (i.e., neither onset nor spread). There was no significant difference between the extent of hypometabolic and normometabolic areas covered by onset electrodes (mean number of FCEs: 4.6 vs. 4.9, respectively). Altogether $46 \pm 32\%$ of onset electrodes were detected by FDG PET as hypometabolic. Interestingly, an additional $41 \pm 27\%$ of the onset electrodes were located in the adjacent area (within ~ 2 cm) thus together detecting a total of $87 \pm 29\%$ of onset electrodes (see Table 2 and Fig. 3). Seizure onset electrodes were significantly more often located over either hypometabolic ($p = 0.039$) or adjacent ($p = 0.040$) areas than over other normometabolic areas. In addition, seizure spread electrodes were located preferentially over adjacent areas rather than over the hypometabolic area itself (51% vs. 22% , $p = 0.008$) or over other, remote normometabolic areas (27% , $p = 0.007$). In an additional analysis of those 8 patients who had their last seizure earlier than 24h prior to the PET scan showed a similar distribution of both seizure onset (hypometabolic: $39 \pm 35\%$, adjacent $39 \pm 29\%$) and seizure spread electrodes (hypometabolic: $15 \pm 15\%$, adjacent: $53 \pm 17\%$), suggesting that the majority of onset and spread electrodes were not hypometabolic even in patients with no recent seizures.

3.3. Correlation between metabolic parameters and clinical variables

The age at onset of seizures varied between early infancy and 11.6 years of age (mean: 3.6 years), duration of epilepsy ranged between 0.4 and 15.2 years (mean: 5.5 years) and the time of last clinical seizure before PET varied between 3 h and 2 months. Neither the total extent and severity of hypometabolic areas nor the metabolic parameters of onset zones correlated with any of the clinical variables. Spike frequency during PET was not associated with any metabolic parameters. In addition, no correlations were found between any metabolic variables and the time interval between the PET scan and epilepsy surgery.

3.4. Results of patients with seizure-free outcome

The main results remained the same in the subgroup of the 8 children with class I outcome. The AI of the seizure onset zone in this subgroup was higher than that of the regions underlying non-onset electrodes (mean: 11.9% vs. 2.5% , $p = 0.11$); however, the difference remained non-significant. There was no significant difference between the groups with class I and classes II–IV outcome in the proportion of onset electrodes overlying hypometabolism (46.0% vs. 42.2%). An additional $41.5 \pm 27.6\%$ of onset electrodes were located in the adjacent area; thus, detecting $87.5 \pm 35.4\%$ of seizure onset electrodes. There was also no significant difference between the extent of hypometabolic and normometabolic areas covered by onset electrodes (mean number of FCEs: 4.5 vs. 4.3) in this subgroup.

4. Discussion

The present study demonstrates a partial mismatch between ictal intracranial EEG and glucose metabolic abnormalities in human neocortex, by showing that, on average, more than 50% of seizure onset areas are located in cortex with normal metabolism. However, most of the seizure onset areas over normometabolic cortex are adjacent to (within 2 cm) hypometabolism and rapid seizure spread regions are preferentially located in this normometabolic surrounding area. Although the electrode coverage of hypometabolic cortex

was incomplete in most cases, our findings strongly suggest that a substantial proportion of hypometabolic cortex is actually *not* epileptogenic. This metabolic/electrophysiologic mismatch does not appear to be affected by basic clinical seizure variables or timing of surgery after PET scanning, although the limited number of cases precludes definite conclusions in this regard.

4.1. Interictal hypometabolism and epileptic cortex

Several previous studies have addressed the clinical utility of glucose PET in detection of the cortical regions responsible for seizure generation (Gaillard et al., 1995a; da Silva et al., 1997; Kim et al., 2000; Hong et al., 2002; Hader et al., 2004; Lee et al., 2005; Kurian et al., 2007). Most of these reports included only patients with nonlesional neocortical epilepsy and compared PET findings with the location of epileptic foci. Sensitivity of FDG PET was reported to be more than 50% in most studies; however, it varied widely across studies presumably due to differences in patient selection criteria, methods of image analysis and use of different outcome measures. These data in general demonstrate that FDG PET can be as sensitive to identify potentially epileptogenic cortical regions in patients with non-localizing MRI as in lesional cases. However, in many of the “non-lesional” cases, pathology revealed small cortical developmental abnormalities as the potential underlying substrate for the PET abnormality. Most previous studies assessed only the general correlation of PET abnormalities (defined on a lobar or regional level) and the presumed location of the epileptic focus (defined by ictal EEG, surgical resection site or seizure semiology). Utilizing our conformal surface mapping technique it has become feasible to measure the extent and degree of hypometabolism in small cortical regions and to assess the spatial relationship between metabolic and EEG abnormalities with a high spatial accuracy. Using this approach, our findings provide firm support for the notion that the origin of neocortical seizures often involves cortex adjacent to PET-defined hypometabolism. This observation has implications for both the basic understanding of metabolic abnormalities in neocortical epilepsy and for the clinical use of metabolic PET imaging.

4.2. The metabolic/electrophysiologic mismatch and potential underlying mechanisms

Using co-registration of high-resolution MRI, FDG PET and subdural electrodes we have previously demonstrated that both seizure onset electrodes and electrodes involved in rapid seizure propagation are often located at the edge of hypometabolic cortical zones rather than in the center of hypometabolic cortex, as one would initially presume. Our more sophisticated analytic approach allowed us now to develop this concept further in a different patient group, as we have now shown that a significant proportion of seizure onset and rapid spread electrodes are actually located *adjacent* to hypometabolic regions, mostly within 2 cm beyond its boundaries.

It is worthwhile to note that some hypometabolic areas, not involved in seizure onset or early spread, showed interictal spiking during the chronic EEG recording, although this was not analyzed in the present study as we focused on ictal electroclinical phenomena.

The exact mechanisms of interictal hypometabolism in and adjacent to the epileptic neocortex remain unclear. A plausible explanation could be that hypometabolism adjacent to cortical epileptic foci represents a metabolic manifestation of “surround inhibition”, a phenomenon reported first from recordings performed in cortex adjacent to experimental epileptic foci (Prince and Wilder, 1967). A metabolic correlate of this electrophysiologic phenomenon was later demonstrated using (¹⁴C)-2-deoxyglucose autoradiography (Collins, 1978), and it has been also shown that decreased (¹⁴C)-2-deoxyglucose uptake was associated with decreased synaptic activity and tonic hyperpolarization of the cells (Bruehl and Witte, 1995). Consistent with these data, in a rat model of focal penicillin-induced

epilepsy, hypermetabolic epileptic foci were surrounded by hypometabolic cortex whose size changed in a dynamic fashion depending on the activity of the epileptic focus (Witte et al., 1994). More recently, optical imaging of experimental epileptic foci showed an inverted signal, consistent with decreased blood flow and neuronal activity, in experimental epileptic foci (Schwartz and Bonhoeffer, 2001; Zhao et al., 2009). This hypometabolic inhibitory zone may protect these cortical areas from rapid seizure involvement by local propagation. This would be consistent with our observation that rapid seizure spread in our patients preferred cortical areas adjacent to hypometabolic cortex while less than 1/4 of electrodes showing rapid propagation were located over hypometabolic cortex. It should be noted that cortical metabolic abnormalities, measured by PET in patients with epilepsy, reflect a temporal summation of metabolic changes during a relatively long (about 40 min) uptake period; thus, the clinically measured metabolic abnormalities have a low temporal resolution, and a direct comparison with experimental data mapping rapid electrophysiologic and blood flow changes is difficult. Also, PET abnormalities are not measured simultaneously with intracranial EEG recordings. Thus, the extent of hypometabolic areas might have changed between the PET scan and the subdural EEG monitoring. We have previously reported that major changes in seizure frequency may contribute to longitudinal changes in the extent of cortical glucose hypometabolism (Benedek et al., 2006). In that study, enlargement of hypometabolic areas was related to persistently high or increasing seizure frequency, while decrease in the size of hypometabolism was seen in some children with a major decrease in seizure frequency. Thus, although we did not find any apparent effect of timing between PET and subdural EEG recordings on the observed PET/EEG relationships, a potential spatial shift of metabolic and/or electrophysiologic abnormalities cannot be excluded between the time of imaging and the time of subdural EEG recording. Nevertheless, it is unlikely that a potential enlargement of hypometabolic cortex during this time interval would lead to significant changes in the observed mismatch between metabolic and ictal EEG abnormalities, since hypometabolism likely expands to previously not involved non-epileptogenic areas. A study using PET scans obtained shortly before subdural EEG monitoring could further address this issue.

Decreased cortical glucose metabolism also could simply reflect neuronal loss leading to a decrease of active synapses. Impaired synaptic density is likely the underlying mechanism of typically low metabolic rates in cortical tubers in patients with tuberous sclerosis (Szelies et al., 1983; Lippa et al., 1993). However, decreased neuronal number and/or reduced synaptic density are not necessarily associated with epileptogenicity, suggested by the fact that not all cortical tubers appear to be epileptogenic (Rintahaka and Chugani, 1997). In addition, seizures often originate from mildly hypometabolic areas adjacent to tubers. Together, these potential pathophysiological mechanisms may contribute to the general matching of hypometabolic regions and epileptic pathology but at the same time explain the observed mismatch between them.

There could be also some methodologic reasons for an apparent metabolic/electrophysiologic mismatch. For example, a mismatch could occur if the subdural grid electrodes missed the true seizure onset and only detected propagation areas, which, in such cases, may be falsely identified as “onset” regions. Such a mis-identification, however, is not likely to explain our findings, since the analysis of patients with class I outcome (where the true seizure onset area was definitely found and removed) revealed the same mismatch between the seizure onset zone and hypometabolic cortex. Another potential source of error could be if some hypometabolic areas were falsely identified as normometabolic; this could occur in areas with bilateral, symmetric hypometabolism, since definition of hypometabolism was performed by an asymmetry-based analytic approach in the present study. To exclude this error, an objective, voxel-based analysis, using statistical parametric mapping (SPM) (Friston et al., 1995) was carried out to screen PET scans for bilateral

symmetric hypometabolism (detailed data not shown) in children older than 5 years of age ($n = 11$; SPM is not validated for younger children; Muzik et al., 2000b). This analysis failed to identify any hypometabolism in the homotopic area contralateral to the general area of the onset zone in any of the patients.

As almost half of the patients experienced a seizure within 24 h prior to the PET scan, it is conceivable that recent seizures affected the metabolic pattern. It has been suggested that PET and SPECT scans should be ideally performed at least 24 h after a clinical seizure (Vander Borgh et al., 2001), although the exact time frame of complete metabolic recovery after seizures is not known and is likely variable depending on the type and severity of seizures. Many children, who are evaluated for epilepsy surgery, have high seizure frequency with multiple seizures daily, thus it is often not possible to perform PET scanning after a period of at least 24 h without any clinical seizure. In our study, none of the patients had clinical seizures within 3 h prior the PET scan; thus, none of the PET images were obtained in the immediate postictal period, although presence of subclinical seizures could not be excluded. Analysis of those 8 patients who had their last seizure more than 24 h before the PET scan revealed similar quantitative findings, suggesting that this factor probably did not have a major impact on our final data. Altogether, our findings strongly suggest that, under common clinical circumstances, a partial mismatch between ictal EEG and glucose metabolic findings often exists, and this is important to keep in mind regardless of the actual mechanism of this finding.

4.3. Methodological advantages and limitations

Our method attempts to merge the benefits of both voxel-based (although confined to the analysis of the brain surface) and region-of-interest-based strategies, but at the same time avoid some of the problems associated with either of these methods. This new software environment has the capability to quantify metabolic abnormalities in the native space of surface rendered brain MRI of patients of any age regardless of brain size, unlike SPM, which may introduce artifacts below the age of 5–6 years due to spatial normalization of pediatric brain to an adult template (Muzik et al., 2000b). Furthermore, our method allows a quantitative, integrative analysis of multimodal data (e.g., EEG, PET).

The application of an asymmetry-based method is both advantageous and also poses some limitations. This approach eliminates the use of absolute or normalized values of tracer uptake for which we do not have a proper age-matched control group. In addition, cortical asymmetries are likely much less affected by age differences than absolute tracer concentration values. On the other hand, the use of AIs assumes that there is no major metabolic abnormality in the contralateral homotopic cortical region.

Our previous studies applied a predefined general threshold of 10% asymmetry (Muzik et al., 1998, 2000a; Juhasz et al., 2000); however, these investigations were carried out in a different software environment, which analyzed average asymmetries in small cortical segments on 2D images. Since there is a physiological metabolic difference between the two hemispheres (particularly present in the temporal and parietal lobes, showing lower metabolism on the left side), defining any abnormal cortical area based on a general threshold may yield an underestimation of the extent of hypometabolic cortex in the left hemisphere and overestimation in the right (Kawachi et al., 2002). Consistent with this, we have found that the proper asymmetry thresholds should be lower for the right side than for the left (Table 3); thus, use of side- and lobe-specific thresholds improved the accurate delineation of hypometabolic cortex in specific regions.

Another issue that needs to be considered is the spatial resolution of the parcellation procedure. Based on our calculations, the average extent of one FCE is approximately 1.3

cm². This spatial resolution appears to be adequate as it is comparable to the standard distance between intracranial electrodes in a grid, which is also 1 cm.

In the present study, the cortical regions involved in ictal onset and early seizure propagation were defined visually. Although visual assessment is subjective and varies among electroencephalographers, no optimal automated analytic method is currently available to identify various patterns of seizure onset and propagation. Each ictal intracranial EEG was reviewed first by one of the electroencephalographers and subsequently discussed at the multidisciplinary epilepsy surgery conference. The definition of rapid seizure spread is considered to be more difficult due to the often observed very fast, diffuse seizure spread without clear localization. The latency of seizure propagation shows wide interindividual variations and also depends on focus localization (Götz-Trabert et al., 2008). The 10 s used as a time limit in definition of rapid seizure spread in our study is arbitrary, and many neocortical, particularly frontal lobe foci show propagation within a few seconds after seizure onset (Götz-Trabert et al., 2008). The present study focused on the relationship between seizure onset and PET hypometabolism. Thus, our findings regarding the location of rapid seizure spread should be interpreted cautiously.

Patients without neocortical abnormality apparent on glucose PET or with seizure onsets localized exclusively in the interhemispheric or other anatomically hidden places, such as the medial temporal lobe, were not included in our study. Our findings also do not apply to PET-negative cases.

4.4. Clinical implications

The role of FDG PET in the presurgical evaluation of patients with medically intractable epilepsy, particularly in patients with non-localizing MRI or discordant scalp EEG and MRI findings, is generally accepted. Although our results indicate that the location of glucose metabolic abnormalities does not correspond accurately with the epileptic focus, the utility of PET may be enhanced if we are aware of the spatial and functional relationship between metabolic and neurophysiological abnormalities. Our findings suggest that more complete detection of the epileptic cortex could be achieved by extending intracranial electrode coverage to at least a 2 cm area around the hypometabolism. Considering that the extent of feasible electrode coverage is limited, in cases of large hypometabolic cortex, localization information from other modalities (scalp EEG, seizure semiology, SPECT, MEG, etc.) should be used to optimize grid coverage and thus, to increase the chance of properly sampling epileptogenic cortex for resection, which is a major prerequisite to achieve seizure-freedom in this difficult group of patients with intractable epilepsy.

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Figure 1. Determination of electrode locations. The intraoperative digital photos (A and B) show the cortical surface before and after subdural grid placement in a 3-year-old girl (patient 1). The skull X-ray (C) with the three fiducial markers [two ipsilateral (solid line arrows), one contralateral (dotted line arrow)] was used for initial co-registration of the lateral electrode grids with the 3D MRI. Electrode grids placed to anatomically hidden areas, such as the interhemispheric grid seen on the X-ray, were not used for analyses in this study. The intraoperative photos were used to verify and refine the location of electrodes on the surface rendered 3D MRI image based on some readily identifiable landmarks (e.g., central sulcus, Sylvian fissure) delineated on the images (dotted black lines). Seizure onset (red) electrodes were located in the left frontal lobe and overlapped partially with the corresponding hypometabolic area. Rapid seizure spread could be identified in electrodes posterior to the onset zone (yellow electrodes). Green circles represent electrodes with no early ictal involvement (blue triangles, D).

Figure 2. Definition of the “adjacent area” surrounding hypometabolism. Intracranial electrodes and decreased glucose metabolism are displayed on the three-dimensional, parcellated MRI surface of an 8-year-old girl (patient 13). Hypometabolic cortex is marked with blue color. Triangles outlined with magenta represent the adjacent area around the hypometabolism. Seizure onset (red) and spread (yellow) electrodes in this case did not overlap with the glucose PET abnormality; however, the most of them were located in the adjacent area.

Figure 3.

Partial mismatch between the onset zone and the hypometabolic cortex. The original transaxial FDG PET images (A) of a 15-year-old girl with refractory partial seizures (patient 7) show extensive glucose hypometabolism in the left hemisphere including all four lobes (red arrows). Hypometabolic cortex is marked with blue color on the parcellated 3D surface display (B). Although the hypometabolic cortex was not covered completely with subdural electrodes, the detected onset zone (red electrodes) overlapped only partially with the hypometabolic cortex. Several electrodes over the hypometabolic cortex did not show seizure onset or rapid propagation (green electrodes). On the other hand, all seizure onset and most propagation electrodes were located over hypometabolic or adjacent cortical areas.

Table 1

Clinical data of the patients.

Patient No.	Gender/age (y)	Age at onset (y)	Duration of epilepsy (y)	MRI finding	Last seizure score	Spike frequency, I/C	Pathology
1	F/2.8	2.4	0.4	Normal	1	3/2	Gliosis
2	M/6.0	5.5	0.5	Normal	1	2/2	Gliosis
3	M/7.0	2.5	4.5	Normal	1	3/2	FCD, gliosis
4	M/9.8	5.0	4.8	Normal	1	2/2	FCD
5	M/10.6	2.0	8.6	RO dysplasia	2	1/0	FCD, heterotopia
6	M/14.9	7.0	7.9	RP cortical dysplasia	2	3/3	FCD
7	F/15.6	0.4	15.2	LF polymicrogyria-like cortex	2	2/1	Gliosis
8	F/16.5	11.6	4.9	Normal	3	0/0	Gliosis
9	M/5.8	0.0	5.8	Asymmetric gyral, sulcal pattern	3	2/1	FCD
10	M/14.1	5.0	9.1	Normal	3	3/2	Gliosis
11	F/4.8	0.3	4.5	Symmetric cortical thickening	2	2/2	Heterotopia, polymicrogyria
12	F/7.1	5.8	1.3	Normal	1	2/0	Gliosis
13	F/7.8	2.0	5.8	Normal	2	1/1	FCD
14	F/3.8	0.4	3.4	Mild bilateral periventricular signal abnormality	1	3/3	Gliosis

Abbreviations: FCD: focal cortical dysplasia, y: years, F: female, M: male, R: right, L: left, F: frontal, T: temporal, P: parietal, O: occipital, I: ipsilateral to PET abnormality, C: contralateral to PET abnormality.

Scoring of last clinical seizure prior to PET scan: score 1: last seizure within 1 day prior to scan, score 2: last seizure between 1 and 6 day interval before the scan, score 3: last seizure was more than 6 days before the PET scan.

Scoring of spike frequency during EEG/PET: score 0: no spikes, score 1: 0–1 spike/min, score 2: 1–10 spikes/min, score 3: >10 spikes/min.

Table 2

PET, intracranial EEG findings and onset electrode locations of the patients.

Patient No.	Locations of PET abnormality	Subdural EEG seizure onset/spread	Number of onset electrodes in areas		
			Hypometabolism	Adjacent	Other normometabolic
1	LFTP	LF/LP	3	4	0
2	LFTP	LF/LFTP	1	2	0
3	RFP	RFP/RFP	6	5	0
4	LFP	LF	2	4	0
5	RTO	RO	6	0	0
6	RP	RPT/RPT	4	6	0
7	LTPO	LFP/LFP	18	10	0
8	RPO	RPO/RPO	0	0	13
9	LTPO	LPO	2	5	8
10	RTP	RTP/RTP	1	2	0
11	LF	LF	9	5	0
12	LFTPO	LF/LF	3	0	0
13	LFP	LP/LP	0	7	2
14	LFTPO	LTPO	22	9	1

Abbreviations: R: right, L: left, F: frontal, T: temporal, P: parietal, O: occipital. Electrodes showing rapid seizure spread could be clearly identified in 9/14 cases.

Table 3

Lobe- and side-specific thresholds for detecting hypometabolism derived from normal controls, expressed as an asymmetry index (%) (AI).

Lobe/region	Mean AI	SD	Threshold
FRONL	-1.25	4.05	-9.35
FRONR	1.25	4.05	-6.85
OCCIL	-0.91	4.31	-9.54
OCCIR	0.91	4.31	-7.71
PARIL	-1.88	5.06	-12.00
PARIR	1.88	5.06	-8.24
TEMPL	-1.91	5.37	-12.66
TEMPR	1.91	5.37	-8.84

Thresholds for defining hypometabolism were calculated as the mean AI +2SD in each lobe. Abbreviations: FRONL: left frontal lobe, FRONR: right frontal lobe, OCCIL: left occipital lobe, OCCIR: right occipital lobe, PARIL: left parietal lobe, PARIR: right parietal lobe, TEMPL: left temporal lobe, TEMPR: right temporal lobe.