Research Article

A Bivariate Model Predicts Hemispheric Lateralization of the Seizure Onset Zone on Inter- Ictal [18F]-FDG PET-CT Scans

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Introduction

Epilepsy is a chronic debilitating condition for which current medical therapeutics are frequently unsuccessful and associated with significant side effects. It has a significant socioeconomic impact on the individual patient as measured by WHO (World Health Organization) population health DALYs (Disability Adjusted Life Years) as well as a prominent health care cost burden [1-4].

Antiepileptic drugs (AED's) confer a substantial long-term health care cost as well as are associated with debilitating side effects [5,6]. To add to this many epilepsy patients and young females of childbearing age, in whom a pregnancy is contemplated may be affected directly or indirectly by their epilepsy condition itself or by the adverse effects and teratogenicity related to AED's [7]. And although most epilepsy patients in a children or an adult population may respond to one or two AED's. About one third of these epilepsy patients do not respond to AED's and continue to have debilitating seizures. This group of patients where medical treatment is limited may benefit from advanced resective surgical techniques. Surgical resection of the Seizure Onset Zone (SOZ) can frequently yield good outcomes, but is underutilized worldwide. Failure to delineate the SOZ is a common limiting factor. Currently, preoperative clinical evaluation of epilepsy patients and definition of the SOZ relies heavily on functional and anatomical imaging as well as Intracranial Electrocorticography (IEC).

Non-invasive techniques, which identify different processes including anatomical lesions, metabolism, flow and intracellular biochemical changes, are utilized in identifying the SOZ and guiding IEC. Developing techniques that are simple to use may be of some benefit. Lateralization of the SOZ may at least guide the IEC phase and is felt to be crucial in many cases where functional and anatomical imaging show bilateral findings, which is not uncommon.

We propose to introduce novel simple, reproducible semi-quantitative indices extracted from a standard [18F]-FDG Brain PET scan. If used individually or in a multivariate model, they could guide pre surgical IEC evaluations of medically refractory epilepsy patients.

Methods

We evaluated all serial epilepsy patients with Complex Partial Seizures (CPS) whom underwent a surface electroencephalogram in the setting of an inpatient video monitoring evaluation and for whom a final lateralization of the seizure focus was determined from scalp EEG recordings and clinical semiology. A review of 72 patients evaluated during the period between 2005 and 2011 and having undergone a brain [18F]-FDG PET-CT scan was performed. 37 patients with CPS and definitive clinical and EEG lateralization were correlated and included in our analysis. Semi-quantitative parameters were analyzed including Volumes of Interest (VOI) around various structures (Global Cerebral= whole brain VOI, temporal lobes, thalami, basal ganglia, and the cerebellum) as shown in Figure 1. SUVm (maximum standardized uptake value) was used for correlation.

A dichotomous value of either "Right" or "Left" was assigned to each binary variable, including   global cerebral hypermetabolism SUVm, temporal SUVm asymmetry hypometabolism, thalamic hypometabolism, basal ganglia SUVm/SD asymmetry hypometabolism and cerebellum decreased visually. Surface EEG and clinical semiology lateralization served as a gold standard for the side of seizure onset. Dichotomous value "Right" was assigned to seizures lateralizing to the right and "Left" for left sided seizures. A bivariate analysis was performed for which contingency tables were constructed to present the concordance between the gold standard and each binary variable. A simple Kappa coefficient was computed to assess the agreement. Fisher's exact test was performed to examine significant associations. The predictive value of a single semi-quantitative index/variable for each side was defined as a proportion of concordant cases among the total cases of seizure onset in that side per gold standard. Furthermore, a multivariate strategy was developed by combining information of global cerebral hypermetabolism SUVm, temporal SUVm asymmetry hypometabolism, and basal ganglia SUVm/SD asymmetry hypometabolism. The significance level was set as 0.05, two-sided. All analyses were performed using SAS 9.2 (Cary, NC).
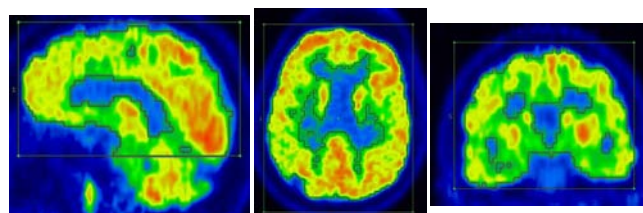

**Figure 1:** Whole Brain, Cerebral semi-quantitative VOI measurement.

Table 1: General patient characteristics. Data are presented as frequency (%) for categorical variables and mean ± SD for continuous variables.

Patient Characteristics	
Age	36.5 ± 15.0
Years since seizure diagnosed	14.5 ± 13.1
Sex	
Female	21 (59.8)
Male	16 (43.2)
Seizure Side	
Left	21 (56.8)
Right	16 (43.2)
Global Cerebral Hypermetabolism SUVm	
Left	20 (54.1)
Right	17 (46.0)
BG SUVm/SD Asymmetry Hypometabolism	
Left	21 (56.8)
Right	14 (37.8)
No Asymmetry present	2 (5.4)
Temp SUVm Asymmetry Hypometabolism	
Left	19 (51.4)
Right	16 (43.2)
No Asymmetry present	2 (5.4)
Cerebellum Down Visually	
No	11 (29.7)
Yes	26 (70.3)
Thalamic Hypometabolism Asymmetry	
Right	23 (62.2)
Left	12 (32.4)
No Asymmetry present	2 (5.4)
Left SUVm Basal ganglia location	
Putamen	20 (54.1)
Head/Caudate/Tail	17 (45.9)
Right SUVm Basal ganglia location	
Putamen	25 (67.6)
Head/Caudate/Tail	12 (32.4)
Surgery	
Yes	8 (21.6)
No	29 (78.4)

Results

The mean age of our population was 36.5 (SD: 15.0; range: 12.9-70.4). The mean duration of seizures since diagnosis was 14.5 years. We had 21 females and 16 males. Our population characteristics are detailed in Table 1.

As shown in Table 2, hemispheric cerebral hypermetabolism, determined by global cerebral hypermetabolism SUVm, was significantly associated with the contralateral side of the seizure onset (p=0.045) and showed significant moderate disagreement with seizure side with a negative kappa of -0.37 (95% CI: -0.66, -0.07). This suggests that the hemisphere contralateral to the SOZ will have the maximum uptake of FDG as determined by an SUVm measurement. If we use the right side of global cerebral hypermetabolism to predict a left sided seizure and use left to predict a right sided seizure onset, the left predictive value was 61.9%, and the right was 75.0% ,i.e, 61.9% of left sided seizures had right sided global cerebral hypermetabolism while 75% of right sided seizures had left sided global cerebral hypermetabolism.
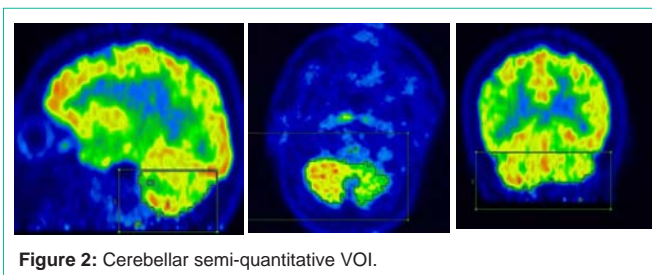

Figure 2: Cerebellar semi-quantitative VOI.

Temporal SUVm asymmetry hypometabolism showed significant moderate agreement with seizure side with kappa of 0.36 (95% CI: 0.05, 0.67). When temporal SUVm asymmetry hypometabolism was used to predict the side of seizure onset, we achieved a 70.0% and 66.7% (p=0.044) predictive value for left and right-sided seizures, respectively. In other words, 70.0% of left sided seizures or 66.7% of right-sided seizures was in agreement (on the same side) with temporal SUVm asymmetry hypometabolism.

Cerebellar hypometabolism was noted in 70.3% of our cases as noted through a visual assessment. Thalamic asymmetric hypometabolism was noted in 62.2% of cases but was not predictive of the seizure onset hemisphere either ipsi or contralaterally (p=1.00). Basal ganglia changes in metabolism, either increased or decreased were also not predictive of an ipsi or contralateral hemispheric seizure onset (p=0.74).

We then applied a multivariate strategy using composite variables including global cerebral hypermetabolism SUVm, temporal SUVm asymmetry hypometabolism, and basal ganglia SUVm/SD asymmetry hypometabolism (as shown in Table 3). An arbitrary post-hoc decision rule was implemented in order to explore the possible maximum predictive value that can be achieved. If the temporal SUVm asymmetry hypometabolism was on the right side, we used right side of global cerebral hypermetabolism SUVm to predict the left side of the seizure onset and the right side to predict the left side of the seizure onset. In contrast, if the temporal SUVm asymmetry hypometabolism was left sided then we predict a left side of seizure onset with the exception when all three variables were left side. For this exception, right side of seizure will be determined arbitrarily (as
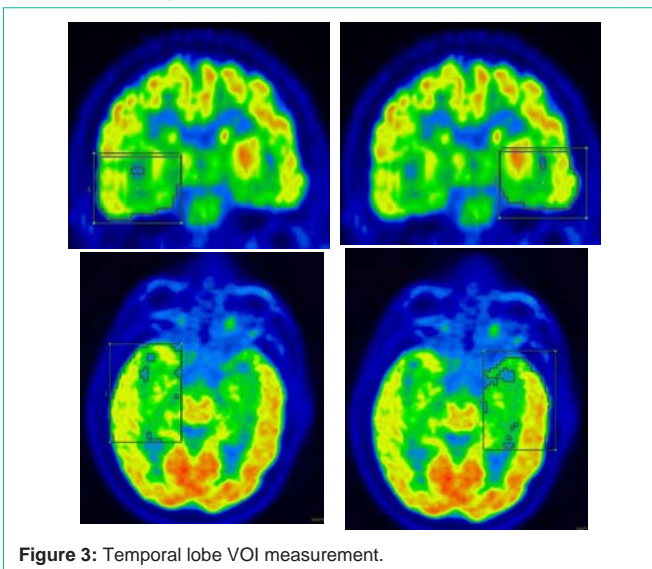
Figure 3: Temporal lobe VOI measurement.

Table 2: Agreement between seizure side and individual variables.

	Seizure side (Ax)		% Concordance	% Discordance	Left Predictive value (%)	Right Predictive value (%)	Simple Kappa a (95% CI)	Fisher's exact p value
	Left	Right						
Global Cerebral			32.4	67.6	38.1	25.0	-0.37	0.045
Hypermetabolism SUVrn, n=37			(8+4)/37	(12+13)/37			(-0.66, -0.07)	
Left	8 (38.1)	12 (75.0)						
Right	13 (61.9)	4 (25.0)						
Basal ganglia SUVmISD			48.6	51.4	57.2	35.7	-0.07	0.737
Asymmetry Hypometabolism, n=35			(12+5)/35	(9+9)/35			(-0.4, 0.26)	
Left	12 (57.2)	9 (64.3)						
Right	9 (42.9)	5 (35.7)						
Temporal SUVm Asymmetry			68.5	31.4	70.0	66.7	0.36	0.044
Hypometabolism, n=35			(14+10)/35	(6+5)/35			(0.05, 0.67)	
Left	14 (70.0)	5 (33.3)						
Right	6 (30.0)	10 (66.7)						
Cerebellum Down Visually, n=37			40.5 (5+10)/37	59.5 (16+6)137	23.8	62.5	-0.13 (-0.41, 0.15)	0.475
No	5 (23.8)	6 (37.5)						
Yes	16 (76.2)	10 (62.5)						
Thalamic Hypometabolism,			54.3	45.7	66.7	35.7	0.02	I.000
Asymmetry n=35			(14+5)135	(7+9)/35			(-0.30, 0.35)	
Left	14 (66.7)	9 (64.3)						
Right	7 (33.3)	5 (35.7)						

the red row shown in Table 3). Using this method, 80.0% and 69.2% predicted value for left and right side of seizure onset was achieved. Kappa coefficient improved to 0.49 (95% CI 0.19, 0.80) and p value was 0.01.

Discussion

Functional imaging with ^{18}F-FDG PET, ^{11}C-Flumazenil, ^{11}C AMT and ^{18}F-MPPF has been able to identify the SOZ necessary to be resected [8-33]. Outcomes studies have revealed that the longer patients have epilepsy prior to surgery, the worst their outcomes. This is supported by the fact that the longer the epilepsy duration is, the more extensive the area of hypometabolism seen on [^{18}F]-FDG PET [30,34-37]. Imaging glucose metabolism, central benzodiazepine receptors and serotonin availability has been shown to impact surgery planning and outcomes [8,9,13,16,18-25,27-29,31,34,35,38,39-62]. One of the major impediments to a wider utilization of resective surgical techniques is the challenging pre-surgical evaluation of epilepsy patients and the determination of the SOZ even in centers with extensive experience and advanced expertise. Pre- surgical evaluation frequently includes IEC in many instances to delineate the SOZ. This step is closely dependent on clinical and neuroimaging data guiding placement of the electrodes to the correct SOZ or its vicinity. Bilateral IEC is challenging and fraught with many complications, so although the ultimate goal of pre-operative investigations is to define a small area for IEC coverage, lateralization of seizures may sometimes be the only definitive deduction pre IEC placement in complicated patients. Most effective functional imaging analysis techniques use some aspect of advanced statistical parametric mapping. Either comparing patients to normal healthy control databases or different images from the same patient acquired at different time points or under different conditions. One of the challenges that can be encountered is that first these techniques are not readily available in numerous centers across the world. Secondly, they require multiple sophisticated steps (image registration, warping, subtraction and statistical analysis). A small error in any one of these steps could give erroneous results especially in non-expert hands. Finally, these advanced techniques do not always provide a clear answer and may show findings that would confound the SOZ with propagation and connectivity pathways. Developing techniques that are simpler to use may be of some benefit.

Our findings in this study are thought provoking. In pre-surgical epilepsy evaluation and IEC planning every clue and every element can be helpful. Usually epilepsy multidisciplinary surgical teams review clinical semiology, surface electrode EEG and imaging data and conclude on the seizure onset lobe area, or even hemisphere. Risks of IEC and surgery are also examined. This is further explored by IEC where a definitive SOZ is determined for surgical resection. Concordance of multiple elements' pre- IEC pointing towards a specific area is generally associated with better final localization and long- term outcomes. Our novel tool when used with currently generated techniques would be valuable. It does not require additional scans other than what is standard of care and could help especially in cases where multimodality and multidisciplinary evaluations are not conclusive or barely conclusive (and doubt remains). This would also be helpful in cases where the seizure onset area is known to be for example occipital but the side cannot be determined with certainty. Our technique may provide some assistance in lateralization. This technique using contralateral cerebral hypermetabolism and ipsilateral temporal hypometabolism to lateralize the epileptogenic zone (EZ) seems to be of same value in temporal and extra-temporal lobe epilepsy.

Table 3: Improvement in predict value combining global cerebral hypermetabolism SUVm, temporal SUVm asymmetry hypometabolism, and basal ganglia SUVm/SD asymmetry hypometabolism.

	Temporal SUVm Asymmetry Hypometabolism	Global Cerebral Hypermetabolism SUVm	Basal ganglia SUVm/SD Asymmetry Hypometabolism	Composite index	Seizure side	Frequency
Concordance	Left	Right	Left	Left	Left	8
	Left	Right	Right	Left	Left	2
	Left	Left	Right	Left	Left	3
	Right	Right	Right	Left	Left	2
	Right	Right	Left	Left	Left	1
	Right	Left	Left	Right	Right	4
	Right	Left	Right	Right	Right	3
	Left	Left	Left	Right	Right	2
Discordance	Left	Right	Left	Left	Right	2
	Left	Left	Right	Left	Right	1
	Right	Right	Right	Left	Right	1
	Right	Left	Left	Right	Left	2
	Right	Left	Right	Right	Left	1
	Left	Left	Left	Right	Left	1

	Seizure	side (Ax)	% Concordance	% Discordance	Left side predictive value (%)	Right side predictive value (%)	Simple Kappa α (95% CI)	Fisher's exact p value
	Left	Right						
Arbitrary rule			75.8 (16+9)/33	24.2 (4+4)/33	80.0 (16/20)	69.2 (9/13)	0.49 (0.19, 0.80)	0.010
Left	16(80.0)	4(30.8)						
Right	4(20.0)	9(69.2)						

Limitations

Using surface EEG as a gold standard to lateralize the SOZ with inpatient video monitoring can prove difficult in nonexpert hands and may occasionally be misleading, although in expert hands EEG performs very well when it detects epileptiform activity to lateralize the seizure. Specific localization within a hemisphere is more challenging. However we did not include any patient where lateralization was not achieved. Our small sample size is also an additional limiting factor and this even though we are a large surgical epilepsy referral center and only a multicenter study would be able to further validate our findings.

The fact that only 22% of our patients underwent surgery does not allow us to examine the ultimate question of outcomes and since this is a retrospective study we cannot assess accurately the impact on IEC mapping.

Conclusion

A bivariate model using contralateral cerebral hyper metabolism and ipsilateral temporal hypo metabolism can lateralize the epileptogenic zone. This would bring another layer of information to guide pre-surgical intracranial electrocorticography studies in severe medically refractory epilepsy patients, especially in difficult cases where multimodality work-up data shows conflicting results. This needs to be further validated in a larger cohort of patients in a multicenter fashion.

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