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Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy

Carla LoPinto-Khoury

Department of Neurology, Thomas Jefferson University, Carla.LoPinto@mail.tju.edu

Michael R. Sperling

Department of Neurology, Thomas Jefferson University, Michael.Sperling@jefferson.edu

Christopher Skidmore

Department of Neurology, Thomas Jefferson University, Christopher.Skidmore@jefferson.edu

Maromi Nei

Department of Neurology, Thomas Jefferson University, maromi.nei@jefferson.edu

James Evans

*Department of Neurosurgery, Thomas Jefferson University**See next page for additional authors*

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Authors

Carla LoPinto-Khoury, Michael R. Sperling, Christopher Skidmore, Maromi Nei, James Evans, Ashwini Sharan, and Scott Mintzer

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Surgical outcome in PET-positive, MRI-negative Patients with Temporal Lobe Epilepsy

LoPinto-Khoury, Carla¹; Sperling, Michael R.¹; Skidmore, Christopher¹; Nei, Maromi¹; Evans, James²; Sharan, Ashwini²; Mintzer, Scott¹

¹. Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA.

². Department of Neurosurgery, Thomas Jefferson University, Philadelphia, PA, USA.

Corresponding author:

Carla LoPinto-Khoury

900 Walnut Street Suite 200

Philadelphia PA 19107

(215) 955 - 1222

Fax: (215) 955-0606

Email: carla.lopinto@gmail.com

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SUMMARY

Purpose: FDG PET hypometabolism is important for surgical planning in patients with temporal lobe epilepsy (TLE), but its significance remains unclear in patients who do not have evidence of mesial temporal sclerosis (MTS) on MRI. We examined surgical outcomes in a group of PET-positive, MRI-negative patients and compared them with those of patients with MTS.

Methods: We queried the Thomas Jefferson University Surgical Epilepsy Database for patients who underwent anterior temporal lobectomy (ATL) from 1991-2009 and who had unilateral temporal PET hypometabolism without an epileptogenic lesion on MRI (PET+/MRI-). We compared this group to the group of patients who underwent ATL and who had MTS on MRI. Patients with discordant ictal EEG were excluded. Surgical outcomes were compared using percentages of Engel Class I outcomes at 2 and 5 years as well as Kaplan-Meier survival statistic, with time to seizure recurrence as survival time. A subgroup of PET+/MRI- patients who underwent surgical implantation prior to resection were compared to PET+/MRI- patients who went directly to resection without implantation.

Key Findings: There were 46 PET+/MRI- patients (of whom 36 had 2-year surgical outcome available) and 147 MTS patients. There was no difference between the two groups with regard to history of febrile convulsions, generalized tonic-clonic seizures, interictal spikes, depression, or family history. [Mean age at first seizure was higher in PET+/MRI- patients \(19±13 vs. 14±13 years, Mann-Wittney test, p=0.008\) and disease duration was shorter \(14 years±10 vs. 22±13, student's t test, p=0.0006\).](#) Class I surgical outcomes did not differ significantly between the PET+/MRI- patients and the MTS group (percentages of 2 and 5 year outcomes were 76% and

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75% for the PET+/MRI- group, and 71% and 78% for the MTS group); neither did outcomes of the PET+/MRI- patients who were implanted prior to resection versus those who went directly to surgery (implanted patients had 71% and 67% Class I outcomes at 2 and 5 years, while nonimplanted patients had 77% and 78% Class I outcomes, $p=0.66$ and 0.28). Kaplan-Meier survival statistics for both comparisons were nonsignificant at five years. Dentate gyrus and hilar cell counts obtained from pathology for a sample of patients also did not differ between groups.

Significance: PET-positive, MRI-negative TLE patients in our study had excellent surgical outcomes after ATL, very similar to those in patients with MTS, regardless of whether or not they undergo intracranial monitoring. These patients should be considered prime candidates for ATL, and intracranial monitoring is probably unnecessary in the absence of discordant data.

Key words: nonlesional, presurgical evaluation, postoperative outcomes, fluorodeoxyglucose, positron emission tomography, temporal lobectomy, depth electrode, implantation

INTRODUCTION

FDG-PET (fluorodeoxyglucose positron emission tomography) imaging was the first imaging modality found to be useful in the surgical evaluation of temporal lobe epilepsy (TLE). Magnetic Resonance Imaging (MRI) has now supplanted PET as the primary imaging tool used in the presurgical evaluation of TLE because of its high sensitivity (97%) and specificity (83%) for hippocampal sclerosis (HS), the most common pathological basis of TLE (Berkovic 1995). While it is established that mesial temporal sclerosis (MTS), the MRI correlate of HS, is the most reliable predictor of good surgical outcome (Berkovic 1995, Spencer 2005), only 58-72% of patients with TLE have MTS on MRI, with 16% of drug-resistant TLE patients demonstrating no MRI abnormality at all (Berkovic 1995) This leaves a sizable minority of TLE patients to be localized with other measures, including PET and intracranial monitoring.

At many epilepsy centers, interictal PET imaging is routinely used in the presurgical evaluation of TLE patients, as hypometabolism on FDG-PET has been shown to correlate with good surgical outcome (Willmann et al 2007). This empirical finding notwithstanding, we know little about the etiology of PET hypometabolism in these patients. Studies that correlate PET with pathology have found that the severity of cell loss in HS does not correspond to the degree of PET hypometabolism (Foldvary 1999, O'Brien 2007). It also appears that the pattern of temporal PET hypometabolism does not correspond to the severity of temporal atrophy or MTS on MRI (Chassoux 2004), and indeed the overall pattern rather than degree of focal hypometabolism predicts successful surgical outcome (Dupont 2000). Despite these differences between MRI and PET for presurgical evaluation, the asymmetry index for focal hypometabolism in the mesial

temporal lobe is higher patients who attain seizure freedom postoperatively (Delbeke 1996). PET hypometabolism ipsilateral to scalp EEG onset also has a high correlation with intracranial EEG onset, which caused Engel to conclude that those patients may go on to surgery without intracranial monitoring (Engel 1990). This conclusion predated the era of modern MRI scanning, however.

Thus, the question remains whether PET positive, MRI negative patients should undergo intracranial EEG monitoring, or whether they may proceed directly to surgical resection if all other data is concordant. One case-control study matched 30 such PET positive, MRI negative patients who underwent standard or hippocampal-sparing resections to 30 age and gender matched patients with MTS on MRI, concluding that surgical outcome was equivalent between groups (Carne et al 2004). At our center, 28 PET positive, MRI negative cases were reviewed and found to have excellent surgical outcomes, although intracranially implanted patients were excluded (Mintzer 2004). The purpose of our study is to compare surgical outcomes in a large group of PET positive, MRI negative patients to those with MTS on MRI, as the latter is the group with most established excellent surgical outcome. We also included those who underwent intracranial electrode implantation, with the goal of determining whether invasive monitoring altered surgical outcomes in this group of patients.

METHODS

Approval for a retrospective study was obtained from our institutional review board. We queried the Thomas Jefferson Surgical Database from the Comprehensive Epilepsy Center for patients

who underwent standard anterior temporal lobectomy (ATL) from 1991-2009. We selected 1991 as a cutoff point because of lesser MRI quality prior to 1991 resulting in decreased sensitivity to MTS. Historical data, MRI, PET, aura and seizure types, interictal and ictal EEG, history of depression, and follow up data were obtained from the database, which is prospectively maintained. The methods of presurgical evaluations at our center have been previously described (Sperling et al 1996, Chandrasekar et al 2007). PET hypometabolism was defined qualitatively by visual inspection of a consensus of radiologists and epileptologists at surgical conference.

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Selection and Exclusion Criteria

We divided the patients into two groups: (1) *PET+/MRI-*, consisting of patients who had temporal PET hypometabolism ipsilateral to the surgical site and an MRI without an epileptogenic lesion (as described below), and (2) *MTS*, consisting of patients who had MRI findings of hippocampal atrophy, with or without increased mesial temporal signal intensity. We also queried the database for patients with the above imaging criteria who underwent intracranial implants only, who did not undergo surgery, or who underwent nonstandard ATL instead.

In order to limit the study to patients who were likely to have true TLE, we excluded patients with risk factors for multifocal epilepsy, including severe head injury with loss of consciousness, cerebral anoxia, central nervous system infection, or stroke. Patients with brain tumors on imaging or histopathology were also excluded, as the progressive nature of these conditions separates them from other TLE etiologies with regard to prognosis. We also excluded patients who had any extratemporal MRI findings that were potentially epileptogenic, including

hemiatrophy, stroke, encephalomalacia, or other cortical lesions. Patients who had PET hypometabolism in regions other than the temporal lobe, thalamus or cerebellum (as the latter two regions are commonly hypometabolic in TLE patients (Theodore et al 1987, Henry et al 1993)), were excluded as well. Non-specific white matter lesions typical of migraine or mild microvascular disease, and generalized brain atrophy were not considered exclusion criteria. Finally, we excluded patients who had ictal scalp EEG findings that were extratemporal, posterior temporal, or contralateral to the imaging abnormality.

Hippocampal Pathology

Owing to the age of much of the patient cohort and limitations of the dataset, reliable histopathologic data for the majority of our patients could not be obtained.

However, in addition to the information obtained from our surgical database, we were able to locate hilar neuron densities and dentate gyrus granule cell densities for a sample of our patients from 1992-1997. The methods have been previously described elsewhere (Dlugos 1999). Eight patients in the PET+/MRI- group and six patients from our MTS group had available data.

Statistical Analysis

Student's t test or Mann-Wittney test (for nonparametric variables) were used to compare age at surgery, age at disease onset, disease duration and mean hilar neuron and dentate granule cell densities between both groups. To compare the categorical variables, including febrile convulsions, a family history of epilepsy, gender, laterality, history of depression, seizure type

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and handedness, we used the Fisher's Exact test or Chi-Squared tests as applicable. To compare surgical outcomes, in addition to comparing percentages of patients with Class I outcomes at 2 and 5 years postoperatively with Fisher's Exact Test, we used Kaplan-Meier analysis with seizure free time as "survival time". Statistical analysis was performed with WinSTAT software [version 2009.1 R. Fitch, Germany].

RESULTS

A total of 193 patients met inclusion criteria and underwent standard ATL, with 46 patients included in the PET+/MRI- group, and 147 patients in the MTS group. Mean age at first seizure was higher in PET+/MRI- patients (19±13 vs. 14±13 years, Mann-Wittney test, p=0.008) and disease duration was shorter (14 years±10 vs. 22±13, student's t test, p=0.0006). The groups were not significantly different with regard to, history of febrile convulsions, presence of generalized tonic clonic seizures, history of depression, family history of epilepsy, handedness or surgical side (Table 1).

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The mean total years of postsurgical follow up were 5.4 for all patients (5.1 for the MTS patients and 6.3 for the PET+/MRI- patients). Of the PET+/MRI- patients, 36 had two or more years of follow up and 23 had five or more years of follow up; of the MTS patients, 115 had two or more and 71 had five or more years of follow up. In addition to the 193 patients who underwent surgical resection, an additional 33 patients (14.6%) in either group either had no surgery, underwent nonstandard ATL or underwent implantation without proceeding to surgical resection. Of the total group of 226 patients, 73% went directly to surgical resection and 12% underwent

implantation prior to resection. (These are summarized in Table 2.) Of the PET+/MRI- patients who underwent depth electrode implantation, 6/7 were performed before 1999, whereas the nonimplanted patients were equally split between the two decades.

A summary of the presence and types of auras among the two groups is given in Table 3. The only noteworthy difference in aura type appeared to be the presence of cognitive auras (including déjà vu, forced thoughts, or other cognitive phenomena), which were found in 8/46 (17%) of PET+/MRI- patients and in 9/145 (6%) of MTS patients ($p = 0.058$).

Class I surgical outcomes at 2 and 5 years were 76% and 75% for PET+/MRI- patients and 71% and 78% for MTS patients ($p=0.68$ for 2 years, 0.78 at 5 years using Fisher's Exact Test). The Kaplan-Meier survival curves using time to any seizure recurrence as a first event were not statistically different between PET+/MRI- patients and MTS patients at five years ($p=0.44$, see figure 1). In addition, the surgical outcomes between PET+/MRI- patients who underwent intracranial implantation prior to resection and those who did not were also similar: nonimplanted patients had 77% and 78% Class I outcomes at 2 and 5 years, respectively, and implanted patients had 71% and 67% percent Class I outcomes at 2 and 5 years ($p=0.66$ and 0.28 at 2 and 5 years). The Kaplan-Meier probability statistic for implanted versus nonimplanted patients was nonsignificant at $p=0.9$ (See figure 2).

Subanalyses were performed with regard to interictal EEG characteristics and with regard to hippocampal neuron densities. Detailed information on interictal spikes on scalp EEG recording was reviewed for 186 patients (Table 4). Patients were categorized into concordant, discordant

and null (no interictal spikes) groups. Patients with concordant interictal spikes were defined as having the majority of spikes (greater than 50%) seen in the ipsilateral sphenoidal, mid-temporal, inferior temporal or frontotemporal electrodes, with few or no extratemporal spikes. Patients who had interictal spikes not meeting these criteria were categorized as discordant. The majority of patients had concordant spikes (84% in the PET+/MRI- group, 86% in the MTS group). Of the discordant spikes in either group, there was no identifiable pattern to their locations – ie, PET+/MRI- patients did not appear to have in excess a posterior temporal or contralateral discordant interictal spike focus (see Table 4). A Kaplan-Meier survival analysis using time to first postoperative seizure recurrence was performed for patients in the PET+/MRI- group with concordant and discordant interictal spikes, which revealed no difference in postoperative surgical outcomes in those patients who had discordant interictal spike discharges (Figure 3). For the histopathological analysis, PET+/MRI- patients were similar to MTS patients in terms of their mean hilar neuron and dentate gyrus granule cell densities (dentate granule cell densities were $123,553 \pm 64,494$ for PET+/MRI- patients and $120,646 \pm 56,776$ for MTS patients, and hilar neuron densities were 2461 ± 2381 for PET+/MRI- patients and 2758 ± 2600 for MTS patients, units in cells/mm^3 , $p=\text{NS}$).

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Further review of PET+/MRI- patients who underwent intracranial monitoring without subsequent resection revealed two patients who were thought to have frontal seizures prior to implantation; one of these was eventually determined to have seizures arising from Broca's area, while the other had seizures which could not be localized on intracranial EEG. A third patient had anterior and posterior temporal interictal spikes on the right while ictal scalp EEG localized to the left; implantation revealed bitemporal seizures. Two other patients had non-localized ictal

scalp EEG which was not adequately localized after implantation.

In order to ensure that the survival analysis was not biased by differential dropout of particular groups of patients, demographic data including age of disease onset, disease duration, gender, handedness, laterality, family history of epilepsy and history of GTC seizures and the concordance of interictal spikes were compared between the patients who fell out of the survival analysis (ie, patients with five or fewer years of follow up who did not have a seizure recurrence) in the PET+/MRI- and MTS groups. No significant differences between those groups were found.

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DISCUSSION

We report the outcome of a large group of PET positive, MRI negative patients, with comparison of surgical outcomes in these patients to those in patients with mesial temporal sclerosis on MRI. Furthermore, we directly compared the surgical outcomes of patients who underwent surgical electrode implantation prior to resection to patients who did not. The mean and median follow up times for our patients were at least 4 years, thus providing good long term data on surgical outcome for a little-studied group, and allowing for survival analysis between groups.

Our study robustly showed that the PET+/MRI- group of patients have excellent postsurgical outcomes, with 75% categorized as Class I at 5 years. In particular, the five-year surgical outcomes for these patients were quite comparable to those of patients with MTS on MRI. These findings corroborate those found in a previous studies (Carne et al 2004, Struck et al 2011) and

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provide further evidence that the PET+/MRI- patients are very good surgical candidates.

In some centers, this group of patients generally undergoes intracranial implantation due to the absence of a structural abnormality. The PET+/MRI- patients in our center had a low rate of surgical implantation, yet still had excellent outcomes. Furthermore, those patients who were implanted surgically had equivalent outcomes to those who went directly to resection, with Kaplan-Meier survival outcomes having no significant difference at five years. Thus, it is likely unnecessary to undertake expensive and invasive surgical implantation for many otherwise uncomplicated cases of temporal lobe epilepsy with concordant PET and EEG, even when MRI is negative.

Further review of our PET+/MRI- patients who did not undergo resection after implantation showed that for most, their presurgical workup had relevant pieces of discordant or ambiguous data that made them less than ideal candidates for resection despite their concordant PET and ictal EEG findings. Thus, while most PET+/MRI- TLE patients may likely proceed directly to resection, there are some for whom intracranial monitoring may still be appropriate. In our patient population, the PET+/MRI- patients who were implanted and underwent surgery were mostly earlier cases, which is probably a result of more conservative practices in years past. Since we have found that those implanted patients who otherwise fit our criteria did well, it appears that a less stringent approach has been appropriate.

Another clinical implication from our findings is that any MRI-negative patient with TLE should be considered for a PET study. A recent meta-analysis showed that MRI-negative epilepsy

patients had a significantly lower seizure-free outcome compared to lesional cases (Télez-Zenteno et al 2010), but this does not preclude finding particular subgroups of MRI-negative epilepsy in whom surgical prognosis is better; our data suggest that PET+/MRI- patients without discordant data should have much higher rates of seizure freedom, likely equivalent to the lesional group. Among predictive factors for seizure outcome on a series of MRI negative patients, non-congruent PET was the strongest predictive factor for an Engel Class of III or IV (Immonen et al, 2010); this suggests that a PET scan may be considered to rule *out* candidates for surgery as well.

Our study is limited by the retrospective design, as is the case for most surgical outcome studies. Carrying out a prospective study for epilepsy surgery in which individualized judgments are superseded by randomization is not feasible, given the complexities of individual cases. We attempted to minimize the biases of complex cases by limiting our data to groups of “clean” cases with minimal discordant data and without risk factors for multifocality. We did include patients with discordant interictal spike discharges, as bitemporal spikes are commonly seen in TLE; but discordant interictal spikes did not correlate with worse surgical outcomes in our PET+/MRI- patients, nor was there a difference in distribution of interictal spikes between the PET+/MRI- patients and classic MTS patients. It is also worth noting that for those patients who did not undergo surgery — which occurred more frequently in the PET+/MRI- group — it is possible that there might have been similarly good postoperative outcomes had resections been pursued.

The two other limitations to our study are the absence of neuropsychological data detailing

cognitive outcomes for this group and histopathological diagnoses. Raw neuropsychological data for many of the patients operated on during the 1990's was not available, but a further analysis is being performed for a subset of patients and will be reported separately. Since clinicians often hesitate to resect a dominant nonlesional temporal lobe because of a theoretical potential for verbal memory dysfunction, this data will help guide practitioners on whether or not to implant the dominant PET+/MRI- patient based on actual postoperative cognitive outcomes. Regarding histopathologic data, while diagnoses were not available for most patients, we were able to obtain hippocampal cell density data for a small subgroup and found no difference in hippocampal cell densities in the regions of the hilum and dentate gyrus between the patients with MTS and the patients with temporal PET hypometabolism and normal MRI. These data provide further evidence that the distinction between MRI+ and MRI-/PET+ patients with TLE is likely not a function of differences in hippocampal cell density (Foldvary 1999, O'Brien 2007, Dlugos 2009).

The underlying etiology of PET+/MRI- TLE continues to be enigmatic. Carne et al found differences in the history of febrile convulsions and presence of hippocampal sclerosis, and concluded that their patients appeared to be a surgically remediable syndrome which was distinct from MTS (Carne et al 2004). The only significant clinical differences we found between these patients and those with MTS is that the PET+/MRI- patients developed epilepsy at a later age and had shorter disease durations at time of surgery, along with a trend towards more cognitive auras. While our results would indeed suggest that these patients are largely surgically remediable, their distinction as a homogeneous clinical entity is not supported by our findings. In fact, recent reports together have found heterogeneous causes of PET+/MRI- epilepsy such as

small temporal pole encephalocles (Abou-Hamden et al 2010) or Taylor-type focal cortical dysplasias (Chassoux et al 2010). Interestingly, a recent series showed that only one of three MRI- patients with HS had lateralized PET hypometabolism (Bien et al 2009); thus, it would appear that PET hypometabolism does not result from HS. In that same series, the MRI- patients categorized as indefinite histopathology who had lateralized PET had nonspecific irregularities of hippocampal architecture such as blurring of the gray-white matter junctions, gliosis or heterotopic neurons (Bien et al 2009, personal communication). Thus, it is possible that the PET+/MRI- TLE group represents a milder form of hippocampal abnormality than classic HS that is nonetheless equally remediable to surgical treatment.

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DISCLOSURE OF CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier survival plot of probability of postoperative seizure freedom in PET+/MRI- patients versus MTS patients, with survival as time to first seizure recurrence. No statistically significant difference was seen.

Figure 2. Probability of postoperative seizure freedom in PET+/MRI- patients who underwent surgical EEG electrode implantation prior to resection versus those who went directly to surgical resection. There was no difference in surgical outcomes.

Figure 3. Probability of postoperative seizure freedom in PET+/MRI- patients with concordant versus discordant interictal spike discharges. There was no difference in surgical outcomes between the two groups.

TABLES

Table 1. Summary of Demographic Data

	PET+/MRI-		MTS		p value
	percent	number	percent	number	
Total number of subjects		46		147	
Age of onset (<u>mean</u> in years)		<u>19</u>		14	<u>0.008</u>
Age at surgery		34		36	0.567
Disease Duration		14		22	<u>0.0006</u>
History of GTC seizures	52%	24	65%	97	0.091
Gender					
Men	41%	19	44%	65	0.865
Women	59%	27	56%	82	
Seizure lateralization					
Right	43%	20	53%	78	0.311
Left	57%	26	47%	69	
Handedness					
Right	85%	39	85%	125	0.888
Left	15%	7	13%	19	
Ambidextrous	0%	0	1%	2	
Nonresponders		0		1	
Family history of Epilepsy					
Positive	24%	11	91%	42	0.699
Negative	63%	29	63%	92	
Unknown		6		13	
History of Febrile Convulsions					
Positive	30%	14	44%	64	0.167
Negative	65%	30	56%	84	
Nonresponders		2		1	
History of Depression	35%	16	32%	47	0.72
Number of subjects who underwent intracranial monitoring	15%	7	14%	21	0.815

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Table 2. Patients fulfilling study criteria who did not undergo standard resection or only underwent surgical EEG electrode implantation.

	PET+/MRI-	percent	MTS	percent
Direct to surgery	39	67%	126	75%
Intracranial monitoring proceeding to standard ATL	7	12%	21	12%
no surgery	5	9%	5	3%
modified ATL	2	3%	11	7%
Intracranial monitoring without proceeding to resection	5	9%	5	3%
total	58		168	

Table 3. Auras in PET+/MRI- patients and MTS patients

	PET+/MRI- n=46	MTS n=145	p value
% without auras	21.7%	29.0%	0.337
% with auras	78.3%	71.0%	
type:			
cognitive, déjà vu or forced thought auras	17.4%	6.2%	0.058
epigastric/thoracic	17.4%	21.4%	0.41
nausea	10.9%	11.0%	0.612
"indescribable feeling"	15.2%	7.6%	0.243
other	17.4%	24.9%	

Table 4. Interictal Spike Data

	PET+/MRI-	MTS
Number with concordant interictal spikes	37	122
Number with discordant interictal spikes	4	14
discordant contralateral temporal	1	4
discordant ipsilateral anterior	2	2
discordant ipsilateral posterior	1	3
discordant contralateral extratemporal	0	1
bitemporal	0	2
discordant hemispheric	0	2
Null (no interictal spikes)	3	6
Totals	44	142