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^{18}F-FCWAY and ^{18}F-FDG PET in MRI Negative Temporal Lobe Epilepsy

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Abstract

Background—Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) shows widespread hypometabolism even in temporal lobe epilepsy (TLE) patients with mesial temporal foci. ^{18}F-trans-4-fluoro-N-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexanecarboxamide (^{18}F-FCWAY) PET may show more specific 5-HT$_{1A}$ receptor binding reduction in seizure initiation than propagation regions. ^{18}FCWAY PET might be valuable for detecting epileptic foci, and distinguishing mesial from lateral temporal foci in MRI negative TLE patients.

Methods—We performed ^{18}F-FCWAY-PET and ^{18}F-FDG-PET in 12 MRI negative TLE patients who had had either surgery or subdural electrode recording, and 15 healthy volunteers. After partial volume correction for brain atrophy, free fraction-corrected volume of distribution (V/f1) measurement and asymmetry indices (AIs) were computed. We compared ^{18}F-FCWAY-PET and ^{18}F-FDG-PET results with scalp video electroencephalography (EEG), invasive EEG and surgical outcome.

Results—Mean ^{18}F-FCWAY V/f1, compared with normal controls, was decreased significantly in fusiform gyrus, hippocampus and parahippocampus ipsilateral to epileptic foci, and AIs significantly greater in hippocampus, parahippocampus, fusiform gyrus, amygdala and inferior temporal regions. Eleven patients had clearly lateralized epileptogenic zones. Nine had congruent, and two non-lateralized, ^{18}F-FCWAY PET. One patient with bitemporal seizure onset had non-lateralized ^{18}F-FCWAY-PET. ^{18}FFDG-PET showed congruent hypometabolism in 7/11 EEG-lateralized patients, bilateral hypometabolic regions in one, contralateral hypometabolism in one, as well as lateralized hypometabolism in the patient with bitemporal subdural seizure onset. Patients with mesial temporal foci tended to have lower superior and mid temporal ^{18}F-FCWAY V/f1 binding AI than those with lateral or diffuse foci.

Conclusion—^{18}F-FCWAY-PET can detect reduced binding in patients with normal MRI, and may be more accurate than ^{18}F-FDG-PET.

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Keywords

Epilepsy; Positron Emission Tomography; Serotonin Receptors; Temporal Lobe; Glucose Metabolism

Introduction

Thirty to forty percent of medically refractory temporal lobe epilepsy (TLE) patients have no evidence of hippocampal sclerosis or other focal lesions on brain magnetic resonance imaging (MRI) (Cascino et al 1991, Carne et al 2004). For these patients, non-invasive pre-surgical identification of seizure foci is particularly challenging. Reported hypometabolism on ^{18}F-FDG-PET in MRI-negative TLE varies widely (Swartz et al 2002, Willmann et al 2007).

Moreover, previous studies have shown that ^{18}F-FDG-PET may not differentiate mesial from lateral neocortical temporal lobe foci even if non-invasive lateralization is possible (Uijl et al 2007, Willmann et al 2007). In these patients, invasive evaluation with depth and subdural electrodes may be needed, increasing the risk, discomfort, and cost of presurgical evaluation. In order to evaluate a new imaging modality in MRI-negative TLE, we performed PET with 18F-*trans*-4-fluoro-*N*-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl-*N*-(2-pyridyl) cyclohexanecarboxamide (^{18}F-FCWAY), a selective $5HT_{1A}$ receptor antagonist.

Serotoninergic neurons have cell bodies in the midbrain dorsal raphe nuclei, projecting to limbic system and neocortex. $5HT_{1A}$ receptor concentration is highest in limbic regions, especially the CA1 segment of the hippocampus, moderate in neocortex, and lowest in cerebellum (Barnes and Sharp 1989). $5HT_{1A}$ receptor activation leads to CA1 membrane hyperpolarization and reduces seizure activity in several partial seizure animal models (Barnes and Sharp 1989, Gasbarri et al 1989).

Several previous studies have reported $5HT_{1A}$ receptor binding is reduced ipsilateral to temporal lobe seizure foci (Toczek et al 2003, Savic et al 2004, Giovacchini et al 2005). The degree of reduction was greatest in the seizure onset zone, and less marked in regions of seizure spread (Merlet et al 2004a). These data suggest that ^{18}F-FCWAY-PET might be valuable for delineating mesial temporal foci, and distinguishing them from lateral temporal neocortical foci in MRI negative TLE patients.

Methods

We studied 12 patients (4 women; mean age ± SD, 30 $\pm$ 9 years) with medically refractory TLE, who were referred to the Clinical Epilepsy Section, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH). Four patients had been included in our previous study (Giovacchini et al 2005). All patients underwent prolonged surface ictal video-EEG recording and either temporal lobe resection (nine) or subdural invasive monitoring (ten). Epilepsy duration was 12 ± 7 years. Medications at the time of scan included carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, phenytoin, and valproic acid. Three patients were taking a single drug; the others were taking two drugs. We also studied 15 normal healthy volunteers (10 men; 5 women; mean age ± SD, 37 ± 8 years), screened with history, general physical examination and routine laboratory tests. Ten of the volunteers were included in our previous studies (Toczek et al 2003, Giovacchini et al 2005). The study was approved by the National Institutes of Health Institutional Review Board and the Radiation Safety Committee, under 45 US Code of Federal Regulations part 46.

^{18}F-FCWAY-PET was performed on a General Electric Advance Tomograph (GE Healthcare), with full width at half maximum [FWHM] resolution 6–7 mm, scanning 35 simultaneous slices with 4.25-mm slice separation. Ten millicuries of ^{18}F-FCWAYwere injected over 60 seconds and dynamic frames (1–5 min) acquired in 3D mode for 120 minutes. Thirty radial arterial blood samples were taken to quantify ^{18}F-FCWAY concentration and selected samples used to measure the ^{18}F-fluorocyclohexanecarboxylic acid metabolite (^{18}F-FC) (Giovacchini et al 2005). Unbound ^{18}F-FCWAY fraction plasma protein was measured with ultracentrifugation (Giovacchini et al 2005). All patients underwent ^{18}F-FDG-PET for CMRglu measurement within 2 days of ^{18}F-FCWAY-PET scans. None had experienced seizures for at least two days before PET studies, and patients were observed carefully during scans to exclude ictal activity. CMRglu parametric images were co-registered to MR images. ^{18}F-FDG-PET was not performed on normal volunteers due to radiation dosimetry restrictions. However, control FDG data were available from previous NIH studies (Theodore et al 2001).

1.5-T GE Signa MRI with fluid attenuated inversion recovery (FLAIR), spoiled grass (SPGR), , , T1 and T2-weighted imagines were performed on all patients and controls. All MRIs were read by neuroradiologists who were unaware of ictal EEG and PET results. Anatomical regions of interest (ROI) were drawn on each patient's -co-registered T1, 3D-SPGR MRI, while ^{18}F-FCWAY radioactivity frames were registered to MRI. Brain tissue activity frames were corrected for brain acid metabolite ^{18}F-FC uptake, vascular radioactivity, and ^{18}F-fluoride metabolite spillover from skull. A previously described MRI-based partial volume correction (PVC) algorithm was applied to correct for brain atrophy (Giovacchini et al 2005).

We used V/f1 (where V is receptor volume of distribution, and f_1 is the ^{18}F-FCWAY plasma free fraction.) as the outcome measure, rather than binding potential:

$$\mathrm{BP}=(\mathrm{V_{ROI}}-\mathrm{V_{Cerebell}})/\mathrm{f_1}=\frac{B_{\max}}{K_{\mathrm{D}}}$$

For tracers, such as ^{18}F-FCWAY, with low non-specific binding, $\mathrm{V_{Cerebell}}$ / f1 is very low, and V/f1 very close to BP. Moreover, it has the advantage of obviating potential cerebellar measurement inaccuracies related to spill-over of [^{18}F]fluoride activity, or cerebellar atrophy due to epilepsy or AEDs with consequent binding heterogeneity (Carson et al 2003, Parsey et al 2005).

Asymmetry Indices (AIs) were computed as $200\cdot(I-C)/(I+C)$ within amygdala, hippocampus, fusiform gyrus, parahippocampus, insula and superior, middle and inferior temporal lobes, where I and C represent PET values in regions ipsilateral and contralateral to the seizure focus, respectively. A more negative number indicates greater 5HT1A binding (on ^{18}F-FCWAY-PET) or CMRglc (on FDG-PET) reduction ipsilateral to the epileptic focus. In control subjects, the right side was arbitrarily called ipsilateral. Two-sample T-tests were used for ^{18}F-FCWAY binding potential and Asymmetry Index comparison between patient and normal controls. For the single subject analysis, mean ±2 SD AI of ^{18}F-FCWAY and ^{18}F-FDG in each ROI in normal controls was used to define the cut-off point for abnormal binding potentials in patients.

Results

All patients had MRIs that showed no evidence of increased signal or structural atrophy. Seven patients had a left, six a right, and one bitemporal epileptogenic zones, confirmed by scalp ictal video EEG, subdural, or intraoperative recordings.

The ^{18}F-FCWAY plasma free fraction (f1) was higher in TLE patients than in healthy controls (0.13±0.04 vs. 0.09± 0.07, respectively, $P < 0.10$). Mean ^{18}F-FCWAY V/f1, compared with normal controls, was decreased significantly in fusiform gyrus, hippocampus and parahippocampus ipsilateral to epileptic foci, with trends for ipsilateral insula, contralateral insula, and contralateral hippocampus (Table 1). AIs were significantly greater in hippocampus, parahippocampus, fusiform gyrus, amygdala and inferior temporal regions (table 2).

Eleven patients had clearly lateralized epileptogenic zones. Nine had congruent lateralized, and two non-lateralized, ^{18}F-FCWAY-PET, defined by an AI greater than two standard deviations beyond the control mean (table 3) (figure 1). One patient with bitemporal seizure onset on subdural electrode recording had non-lateralized ^{18}F-FCWAY-PET. ^{18}F-FDG-PET showed hypometabolism ipsilateral to the epileptogenic zone in seven of the eleven EEG-lateralized patients (including one with negative ^{18}F-FCWAY-PET), equivocal findings in one (#2) contralateral hypometabolism in one (patient #4), and lateralized hypometabolism in the patient (#12) with bitemporal subdural seizure onset..

Nine patients had a resection. Five were seizure-free after at least one year, and two additional patients had experienced only rare post-operative seizures. Preoperative ^{18}F-FCWAY-PET detected decreased ipsilateral binding in six, and ^{18}F-FDG-PET hypometabolism in six, of these patients (table 3). Both PET scans found reduced activity ipsilateral to the epileptic focus in one patient who had fluctuating post-operative seizure frequency stabilizing in persistent seizures at night (#3). ^{18}F-FDG-PET found contralateral hypometabolism in one who had only moderate improvement, but was able to become employed after surgery (# 4).

In order to examine the value of the two PET scans for distinguishing mesial from lateral temporal neocortical foci, we compared AI between patients with mesial foci alone (table 3: #2, 7, 8, 11), and lateral or diffuse epileptogenic zones. Patients with mesial temporal foci had lower superior temporal ^{18}F-FCWAY V/f1 AI of 0.02 ± 0.10, and mid temporal AI of −0.03 ± 0.13. Patients with lateral or diffuse foci had superior temporal AI of −0.18 ± 0.21), and mid temporal AI of −0.14 ± 0.27. These trends were non-significant In mesial temporal regions, AI did not differ between the patient groups. ^{18}F-FDG-PET also showed no AI differences in either mesial or lateral temporal regions. . Patients with mesial temporal foci have less reduction of lateral temporal $5HT_{1A}$ binding ipsilateral to the epileptic focus than those.with lateral (or both lateral and mesial) temporal foci, but it is difficult to derive firm conclusions from a small patient sample.

Discussion

We found decreased ipsilateral temporal ^{18}F-FCWAY-PET 5-HT_{1A} receptor V/f1 and ^{18}F-FDG-PET hypometabolism in comparable proportions of patients with MRI negative temporal lobe epilepsy. Our ^{18}F-FDG-PET results are similar to previous reports that described hypometabolism ipsilateral to EEG foci in 30–90% of patients with MRI-negative TLE (Lamusuo et al 2001, Carne et al 2004, 2007). Thus, both ^{18}F-FCWAY-PET and ^{18}F-FDG-PET may be helpful for locating epileptogenic zones in non-lesional TLE. ^{18}F-FDG-PET did not distinguish mesial from lateral temporal foci, while ^{18}F-FCWAY-PET showed less lateral temporal binding reduction in patients with mesial than lateral foci. ^{18}F-FDG-PET appeared to show potentially misleading data in two cases.

^{18}F-FDG-PET tends to show lateral neocortical hypometabolism even in patients with mesial TLE (Sackellares et al 1990, Kim et al 2003). Patients with mesial foci defined by foramen ovale electrodes had greater mean depression of mesial metabolism than the group with lateral foci, but within the mesial focus group itself lateral hypometabolism was as prominent as mesial

(Hajek et al 1993). Patients with mesial temporal sclerosis (MTS) and microdysplasia may have greater lateral temporal hypometabolism than those with MTS alone (Diehl et al 2003). A study using statistical parametric mapping found that medial hypometabolism was less extensive or severe in the lateral than mesial TLE patients, and patients with lateral temporal neocortical foci, as a group, had relatively greater lateral temporal hypometabolism. However, individual variation was too great for ^{18}F-FDG-PET to be used for clinical localization (Kim et al 2003). Pure lateral temporal hypometabolism makes mesial seizure onset less likely.

^{18}F-FDG-PET has been reported to be sensitive to time since last seizure, and to extent of seizure spread, which could have affected the results in two of our patients (#2 and 4) although they had not had seizures detected within two days of the scan (Leiderman et al 1994; Franceschi et al 1995; Savic et al 1997). Occasional hypometabolism contralateral to EEG foci has been reported (Carne et al 2004).

In contrast, ^{18}F-FCWAY-PET results may be related to the specific distribution of receptors, which have their highest concentration in the limbic system and relatively reduced concentration in neocortex (Hall et al 1997). Previous studies showed greater $5HT_{1A}$ reduction in mesial than lateral temporal lobe in patients with TLE (Toczek et al 2003, Savic et al 2004, Merlet et al 2004a, Giovacchini et al 2005). Thus, patients with both mesial and lateral temporal foci may have mesial ^{18}F-FCWAY binding reduction.

In contrast to previous studies, we did not find significant hippocampal asymmetry ipsilateral to the epileptic focus in the patients with hippocampal sclerosis on pathological examination (Toczek et al 2003, Savic et al 2004, Merlet et al 2004a, Giovacchini et al 2005, Ito et al 2007). This was likely due to the presence of bilateral reduction in hippocampal ^{18}F-FCWAY binding in these patients, also reported in previous studies (Hasler et al 2007). The overall hippocampal AI, was, however, greater than control.

Other factors in addition to the seizure focus itself may lead to reduced $5HT_{1A}$ binding in patients with TLE. More extended binding reduction may be related to seizure propagation networks (Merlet et al 2004b, Ito et al 2007). Patients with major depressive disorders in addition to epilepsy have reduced binding in ipsilateral and contralateral regions beyond the epileptogenic zone (Hasler et al 2007, Theodore et al 2007). These effects may make the use of asymmetry indices less sensitive for detecting seizure onset regions. In order to use absolute values to detect clinically important abnormalities a larger control population will be needed. However, in a study of nine patients who had depth electrode recordings, $5HT_{1A}$ receptor binding was significantly lower in seizure onset regions than areas with only interictal or no discharges (Merlet et al 2004a). Even when MRI was normal, $5HT_{1A}$ receptor binding correlated with the seizure activity. Our results generally support these findings.

PVC could have affected our results in two ways. It appears to have a greater effect on neocortical than mesial temporal structures, possibly because lateral temporal gyral folding leads to greater partial volume effects in uncorrected images (Givoacchini et al 2005). However, ^{18}F-FCWAY BP variability is increased by the procedure. This might have reduced our statistical power, particularly for individual analysis, leading to the slightly greater sensitivity of ^{18}F-FDG-PET. However, the gain in specificity appears to outweigh a small loss of sensitivity.

We found a difference in ^{18}F-FCWAY free fraction between patients and controls, probably due to a protein binding interaction. Although some antiepileptic drugs (AEDs) may have mild influence on serotoninergic neural transmission, they are unlikely to have affected our results. Any drug effect would be likely to be bilateral, and thus not lead to greater binding reduction in the epileptic focus. Moreover, previous studies showed that, after correction for free fraction,

there were no significant AED effects on ^{18}F-FCWAY volume of distribution (Theodore et al 2006).

Several patients in our study proved to have hippocampal neuronal loss and focal gliosis on pathological examination, suggesting that reduced $5HT_{1A}$ receptor binding may occur in early or mild states of MTS. Serotonin receptor loss has been implicated in the hippocampal atrophy that occurs in patients with depression, and might be a contributing mechanism in epilepsy as well (Chugani and Chugani 2003, Husumu et al 2006). $5HT_{1A}$ receptor activation promotes cell proliferation in the hippocampus by a direct post-synaptic effect, as well as by affecting sensitivity of proliferating cells in the dentate gyrus to corticosterone (Huang and Herbert 2005). Antagonists, including WAY-100635, lead to significant reduction in dentate gyrus proliferating cells, and to cell survival in pilocarpine-induced status epilepticus (Radley and Jacobs 2002, 2003). $5HT_{1A}$ receptor loss might be an early step in the development of MTS.

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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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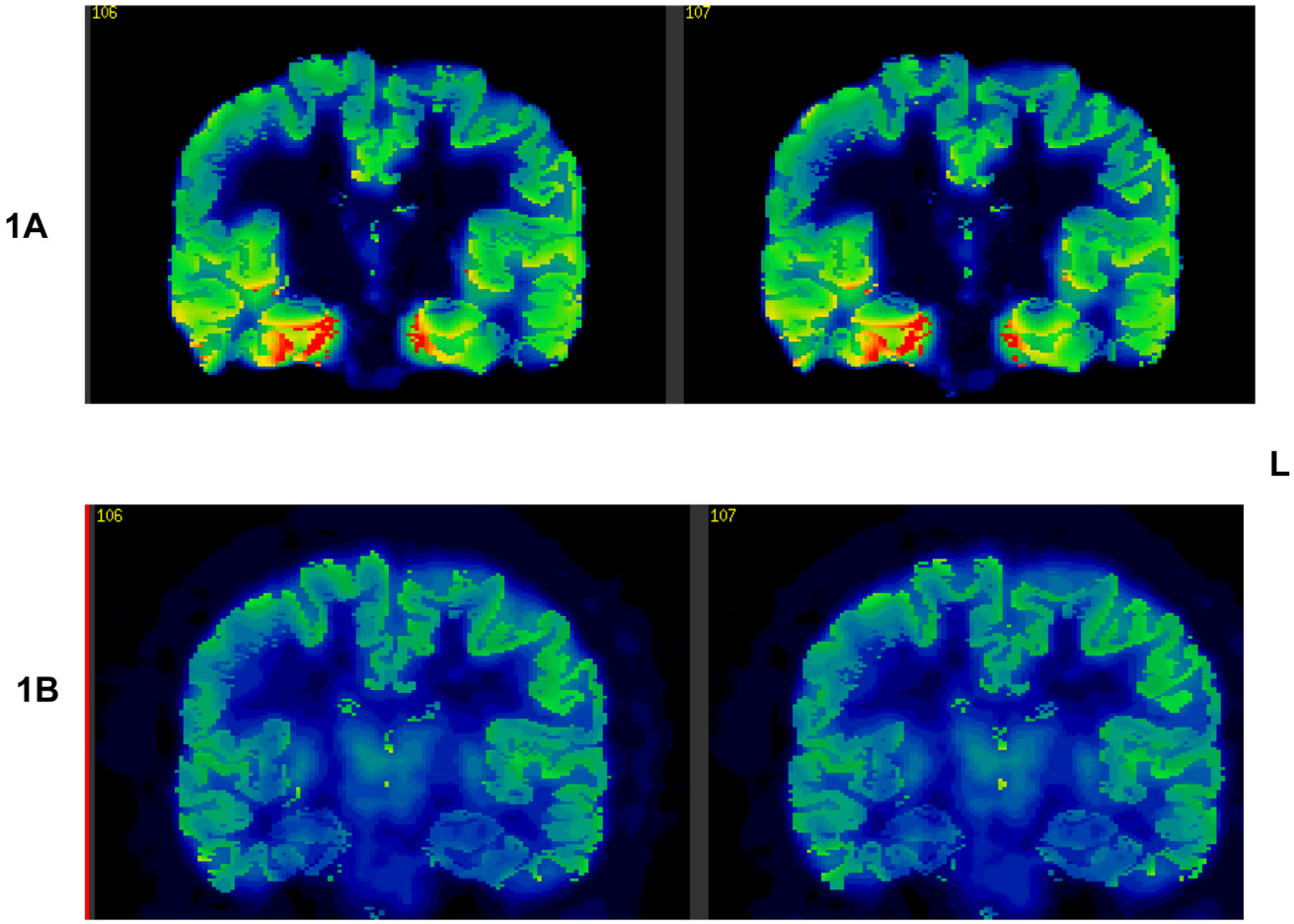

Figure 1.
1A: FCWAY PET showing decreased binding potential in the left mesial temporal region.
1B: FDG PET showing no metabolic asymmetry.

Table 1

Free-fraction-corrected FCWAY Volume of distribution in healthy controls and patients with TLE

Region	Controls (n=15)			Patients (n=11)[#]			p
I. frontal	69.0	±	23.7	62.7	±	14.0	0.45
C. frontal	68.3	±	22.0	63.0	±	15.1	0.50
I. insular	85.2	±	39.7	64.1	±	16.9	0.08
C. insular	87.1	±	38.3	68.6	±	15.7	0.11
I. hippocampus	116.2	±	43.1	81.3	±	23.3	0.02[*]
C. hippocampus	116.5	±	43.7	90.5	±	25.6	0.07
I. amygdala	70.8	±	26.4	58.8	±	24.9	0.25
C. amygdala	73.7	±	26.9	69.0	±	23.9	0.64
I. parahippocampus	125.8	±	56.2	86.7	±	17.2	0.02[*]
C. parahippocampus	125.6	±	58.0	99.6	±	21.5	0.13
I. superior temporal	81.1	±	35.8	71.7	±	19.3	0.40
C. superior temporal	81.4	±	30.6	80.2	±	14.3	0.89
I. middle temporal	88.5	±	36.8	77.3	±	22.4	0.38
C. middle temporal	87.8	±	31.1	88.1	±	17.3	0.98
I. inferior temporal	95.5	±	36.7	81.0	±	24.7	0.27
C. inferior temporal	98.0	±	32.7	94.8	±	25.1	0.79
I. fusiform	115.1	±	47.1	82.2	±	22.0	0.03[*]
C. fusiform	112.9	±	43.0	101.3	±	22.2	0.38

[#] patient 12 was excluded

I.=ipsilateral to seizure focus (arbitrarily right for controls).

C.=contralateral to seizure focus.

[*] $P<0.05$, unpaired t-test, patients vs. controls.

Table 2

18F-FCWAY volume of distribution Asymmetry Index (AI)

Region	Controls (n=15)			Patients (n=11)			p
Frontal							
insular	0.04	±	0.06	0.08	±	0.10	0.23
hippocampus	0.00	±	0.11	0.11	±	0.11	0.02*
amygdala	0.04	±	0.11	0.18	±	0.17	0.03*
parahippocampus	0.01	±	0.10	0.14	±	0.12	0.01*
superior temporal	0.03	±	0.14	0.13	±	0.20	0.22
middle temporal	0.02	±	0.11	0.12	±	0.22	0.21
inferior temporal	0.04	±	0.15	0.16	±	0.14	0.05*
fusiform	0.01	±	0.13	0.22	±	0.15	0.01*

* p <0.05 unpaired T-test

table 3

Patient	Age	Sex	Epilepsy duration	Regions with FCWAY Vd Δ	Regions with CMRglc Δ	Predominant Subdural focus	Pathology	Surgery outcome
1	40	M	29	R ST ↓	R Amyg, supT midT ↓,	Right Subtemporal and lateral T	HS	1 postoperative seizure
2	22	M	7	R Ins, amyg ↓	R infT ↓; L supT ↓	Right mesial T	cortical dysplasia	Seizure-free
3	31	M	12	R Ins, parahipp, midT ↓	R midT ↓	Right T	Cortical gliosis	Only nocturnal seizures
4	25	M	5	none	L midT, L infT ↓	Right Lateral T	Cortical gliosis	75% seizure reduction
5	28	M	7	L Fr, ins, amyg, hipp, parahipp, supT, infT, midT ↓	L Fr, amyg, supT, infT, fusif ↓	Left Lateral T	Cortical gliosis;	Rare postoperative seizures
6	45	F	14	L supT, infT ↓	L infT, fusif ↓	Left Lateral T	Cortical gliosis	Seizure-free
7	18	M	4	L Amyg ↓	L Parahipp, infT ↓	Left mesial T	HS	Seizure-free
8	43	F	4	L Ins, parahipp, fusif ↓	none	Left mesial T	HS	Seizure-free
9	24	M	9	L Hipp, supT, midT, fusif ↓	L Fr, ins, infT, fusif ↓	Left mesial and lateral T	No surgery	
10	23	M	19	L Fr, ins, amyg, infT, fusif ↓	none	Left Inferior frontal, mesial temporal	No surgery	
11	27	F	13	None	L Ins, fusif ↓	Left mesial T	Diffuse LT and HF Gliosis	Seizure-free
12	36	F	26	None	L Hipp, fusif ↓	bitemporal	No surgery	

MT: mesial temporal
LT: lateral temporal
T: temporal lobe
HS: hippocampal sclerosis

ST: superior temporal gyrus
Amyg: amygdala
Parahipp: parahippocampal gyrus