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5-HT_{1A} receptor binding in temporal lobe epilepsy patients with and without major depression

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Abstract

Background—Major depressive disorder (MDD) is the most common comorbid psychiatric condition associated with temporal lobe epilepsy (TLE). Preclinical and clinical studies suggest that 5-HT_{1A} receptors play a role in the pathophysiology of both TLE and MDD. There is preliminary evidence for an association between decreased 5-HT_{1A} receptor binding in limbic brain areas and affective symptoms in TLE patients. The objective of this study was to compare 5-HT_{1A} receptor binding between TLE patients with and without MDD. For the first time, 5-HT_{1A} receptor binding was measured in a sample large enough to permit sensitive comparisons between TLE patients with and without comorbid MDD diagnosed by clinical and structured psychiatric interviews.

Methods—Thirty-seven epilepsy patients with temporal lobe foci confirmed by ictal video-EEG monitoring were recruited from the Clinical Epilepsy Section, NINDS. We performed interictal PET scanning, using [¹⁸F]FCWAY, a fluorinated derivative of WAY100635, on a GE Medical Systems Advance scanner with continuous EEG monitoring. 5-HT_{1A} receptor binding was estimated by partial volume-corrected [¹⁸F]FCWAY V/f_j values.

Results—In addition to decreased 5-HT_{1A} receptor binding in the epileptic focus itself, comorbid MDD was associated with a significantly more pronounced reduction in 5-HT_{1A} receptor binding in TLE patients, extending into in non-lesional limbic brain areas outside the epileptic focus. Focus side and the presence of mesial temporal sclerosis were not associated with the presence of comorbid depression.

Conclusions—Reductions in 5-HT_{1A} receptor binding may help elucidate the neurobiological mechanisms underlying the TLE-MDD comorbidity.

Keywords

temporal lobe epilepsy; major depressive disorder; [¹⁸F]FCWAY-PET; 5-HT_{1A} receptor binding; psychiatric comorbidity; serotonin

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Introduction

Community studies show depression is the most common comorbid psychiatric condition associated with epilepsy, with a severe impact on quality of life (14,23,25). Prevalence for clinically-relevant, current depressive symptoms range from 20% to 55% in epilepsy, higher than those for other chronic health conditions including asthma and diabetes (15). Patients with temporal lobe epilepsy (TLE) show the closest association with depression (14). One study of 174 patients with epilepsy, using standardized assessment methods based on DSM-IV, found *current* Axis I disorders in 49%, with anxiety (30.4%) and mood (21.8%) disorders being the most common categories; major depressive episode were the most common individual diagnosis (17.2%) (24). Of depressed patients with epilepsy, the majority suffer from unipolar depression (48). Longitudinal studies in epilepsy and depression reported a bidirectional temporal association between the two conditions: epilepsy was frequently followed by depression, and a history of depression was a considerable risk factor for subsequent epilepsy onset (17,22). Bidirectional temporal relationships of comorbid conditions suggest shared etiologic explanations (27). Both conditions are associated with common biological characteristics including reduced hippocampal volume (18), neuropathological changes in amygdale (1,10), and hypothalamic-pituitary-adrenal (HPA) axis dysfunction (21,53).

Decreased serotonergic function appears to constitute a major pathogenic mechanism underlying development of depression (21), and serotonin also may play a role in epilepsy (50). The 5-HT_{1A} receptor system in particular has been implicated in the pathophysiology of depression, and antidepressant drug mechanisms. Depressed subjects showed blunted response to 5-HT_{1A} agonists in vivo and decreased 5-HT_{1A} receptor binding postmortem (29-31). Drevets et al. (11,12) and Sargent et al. (45) found reduced 5-HT_{1A} receptor binding potential in subjects with familial depression relative to controls in regions including raphe and mesiotemporal cortex.

Evidence for 5-HT_{1A} receptor system dysfunction in epilepsy previously was limited to preclinical studies. Genetic epilepsy-prone rats showed reduced hippocampal 5-HT_{1A} receptor density. These rats showed depressive-like behaviors (as measured on the forced swimming test) that responded to antidepressants, and abnormal stress responses (8,9,46). Serotonin-induced anticonvulsive effects were mediated specifically by hippocampal 5-HT_{1A} receptors (32). Patients with TLE have reduced 5-HT_{1A} receptor binding (52). The reductions in serotonin receptor binding were not limited to disease-specific brain regions, or explained by brain atrophy (19).

Two studies showed a significant correlation between current depressive symptoms in TLE patients and reduced 5-HT_{1A} receptor binding in limbic regions including ipsilateral hippocampus (19) and ipsilateral anterior cingulate cortex (47). These studies assessed only depressive symptoms, and did not consider whether TLE patients had met diagnostic criteria for a major depressive episode. In primary major depressive disorder, 5-HT_{1A} receptor binding reduction proved independent of current mood-state (4,5). Thus it remained unclear whether the association between limbic 5-HT_{1A} binding reduction and comorbid depressive symptoms in TLE was dependent on a history of major depressive episodes or current mood state.

The goal of this study was to examine the relationship between 5-HT_{1A} receptor binding potential and comorbid depression in TLE. We hypothesized that in limbic brain regions including anterior and posterior cingulate cortex, anterior insula, and hippocampus, and raphe nuclei, TLE patients with a lifetime diagnosis of major depression would have lower 5-HT_{1A} receptor binding than patients without major depression.

Methods and Materials

Sample and clinical assessments

Thirty-seven patients with temporal lobe epilepsy (TLE) were recruited from the Clinical Epilepsy Section, National Institute of Neurologic Disorders and Stroke, NIH, where they were evaluated for refractory TLE. Fourteen had been included in a previous study (19). Patients had clinical interviews and physical examination by board-certified neurologists. Seizure onset was localized with ictal scalp video-EEG; only patients with complex partial seizures of temporal origin were included. Pregnant and nursing women, and patients with structural lesions other than mesial temporal sclerosis (MTS), progressive neurologic disorders, or taking medications other than antiepileptic drugs were excluded. No patient experienced seizures at least two days prior to PET scanning, and none experienced a secondarily generalized tonic clonic seizure for at least one month prior to PET scanning. The diagnosis of major depressive disorder was established by both an unstructured psychiatric interview and the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (16); both interviews were conducted by a psychiatrist (G.H.). Subject classification was based upon lifetime diagnosis of major depression instead of current mood state because previous studies suggested mood-state independence of this abnormality in primary major depressive disorder (4,5). The clinical evaluation also included physical examination, electrocardiography, and laboratory tests, including liver and kidney function tests, hematology profile, and urinalysis. Subjects enrolled after a full explanation of the study purpose and procedures, and written consent had been obtained as approved by the NINDS Institutional Review Board and NIH Radiation Safety Committee.

MRI

Structural MRI scans of the entire brain were acquired on a 1.5-T Horizon scanner (GE Medical Systems, Waukesha, WI) using standard T-2, Fluid attenuated inversion recovery, and T1-weighted pulse sequence (repetition time, 27 ms; minimum echo time; flip angle, 20°) to detect structural abnormalities, and facilitate localization, coregistration, and PET partial volume correction (PVC). Spatial resolution was $0.94 \times 0.94 \times 1.5$ mm ($256 \times 256 \times 124$ slices). We used the method MRI segmentation described in (19).

PET imaging

Interictal PET scanning was performed, using [^{18}F]Tans-4-Fluoro-N-(2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl)-N-(2-pyridyl)cyclohexanecarboxamide ([^{18}F]FCWAY), a fluorinated derivative of WAY100635, on an Advance scanner (GE Medical Systems, Waukesha, WI) with continuous EEG monitoring as described previously (19). Thirty-five slices with 4.25 mm slice separation were acquired in 3-dimensional mode, septa retracted, spatial resolution 6 to 7 mm full-width half-maximum in all planes, with a transmission scan for attenuation correction. Dynamic scans were acquired for 120 min after bolus injection of ~10 mCi of [^{18}F]FCWAY. Specific activity at injection was 18.5 TBq/mmol (500 Ci/mmol). Tissue radioactivity concentrations corrected for blood volume and acid metabolite uptake. Pixel-by-pixel estimation of distribution volume (V) was performed using data fitted to a 2 compartment 3 parameter model using metabolite-corrected input arterial function. ^{18}F -laeblleld metabolites were measured with thin layer chromatography (7).

Structural atrophy in patients with TLE (38) can affect PET findings. We used an MRI-based PVC algorithm to correct gray matter activity for spill-out of gray matter activity as well as spill-in of white matter activity into gray matter pixels (19). PET images were multiplied by a binary grey matter mask to limit regional measurements to gray matter pixels. Mean regional activity was obtained by transferring ROIs were drawn on MRI images to coregistered V images. Since raphe nuclei cannot be delineated on MRI, these structures were directly

identified on PET (raphe nuclei are the only structures within brainstem and adjacent cerebellar white matter that contain 5-HT_{1A} receptors). The inferior midbrain raphe border was identified by the interpeduncular cistern. Regions left and right from the midline were combined using a circular, fixed, 6-mm-radius ROIs placed over the area with highest radioactivity (11). We used MEDx (Medical Numerics INC, Sterling, VA) for image analysis.

Statistical analyses

We chose free fraction corrected V (V/f_1) as our binding measure. Antiepileptic drugs (AEDs) might influence [¹⁸F]FCWAY specific binding via receptor number (B_{max}), affinity (K_D), free fraction (f_1) or a combination. AEDs increase [¹⁸F]FCWAY f_1 but do not have substantial effects on B_{max} , K_D or 5-HT concentration (51). Failure to correct for f_1 can lead to spuriously low control binding, by underestimating the relative amount of tracer availability (7,37,43). Moreover, correction for non-specific binding using cerebellum could lead to inaccuracies due to the cerebellar atrophy that occurs in epilepsy, as well as spill-over of [¹⁸F]fluoride activity from adjacent skull, corrections for acid metabolite entering the brain, atrophy due to epilepsy or AEDs, or cerebellar binding heterogeneity (7,41,44). Moreover, cerebellar and occipital V , presumably representing non-specific binding, was very low (increasing the risk of measurement inaccuracy), and there were no significant differences in cerebellar or occipital V/f_1 between patients with or without MDD.

Fifteen regions were examined, but 5 were pre-selected as primary regions-of-interest (ROIs) based upon results of previous studies of primary MDD: anterior cingulate, posterior cingulate, raphe nucleus, anterior insula, and hippocampus (13). All data were examined for normality using the Shapiro-Wilks test and homogeneity of variance using Levene's test. Distributions were further examined for outliers using histograms and box plots as well as influence statistics and Cook's distance from ANOVA models. In order to reduce undue statistical influence by a small number of points, extreme outliers were adjusted to one point above or below the next closest point, as suggested by Tabachnik and Fidell (49). Differences between the results from adjusted and unadjusted analyses were minor and did not affect the interpretation of the results.

Demographic comparisons of epilepsy patients with depression and without depression were performed using Fisher's Exact tests for categorical variables and t-tests for continuous variables. Regions-of-interest were examined using repeated measures ANOVA where group was a between-subjects factor and laterality (brain hemisphere) was a within-subjects factor. Left and right sides were combined for anterior cingulate, posterior cingulate, and raphe nucleus to increase the reliability of those small regions, so one-way ANOVA was used for those regions. Post hoc simple effects tests were used to examine omnibus main effects and interactions.

Secondary analysis included examining influence of side of seizure focus and MTS separately in ANOVAs where each factor was added to the model from primary analysis. Additional analyses included using age, gender, age of seizure onset, and duration of epilepsy as covariates in separate statistics. Although there is a continuum of expression of depression and anxiety and the majority of patients with MDD have relevant anxiety symptoms or an anxiety disorder (34), one more analysis excluded patients with comorbid anxiety disorders. Another analysis excluded patients with a current major depressive episode due to limited sample size.

All p-values are 2-tailed original values prior to correction. Bonferroni corrections were applied to the 5 primary ROIs separately from the other 10 regions. Significant results after correction are noted.

Results

Table 1 shows demographic and clinical characteristics of TLE patients with and without MDD. There were no differences in any demographic factors, but the MDD group did have higher depression scores.

Average f_I values were 0.12 (SD=0.04) in TLE patients without MDD and 0.12 (SD=0.03) in TLE patients with MDD. Table 2 shows [^{18}F]FCWAY V/f_I values in TLE patients with and without MDD. Analysis of variance revealed that the effect of diagnostic group on V/f_I was statistically significant across all primary ROIs as well as in the medial and superior temporal lobe. Significant interactions of group and side were present for the hippocampus, amygdala, and parahippocampal gyrus. After Bonferroni correction, the non-depressed group had higher values in the anterior cingulate, right hippocampus, and medial and superior temporal lobe. Using [^{18}F]FCWAY V instead of [^{18}F]FCWAY V/f_I did not lead to important changes in results when comparing TLE patients with and without MDD. Only the results for the posterior cingulate and parahippocampal gyrus became non-significant. Also, adding gender, age, age of seizure onset, or duration of epilepsy as covariates to the primary analysis had little effect on the results. The medial temporal lobe lost significance when gender, age of seizure onset, or duration of epilepsy was a covariate. The parahippocampal gyrus lost significance when duration of epilepsy was a covariate. Table 3 shows the statistical comparison of [^{18}F]FCWAY V/f_I between TLE patients with and without MDD by side of seizure focus. Seizure focus side was associated with ipsilateral decreases in [^{18}F]FCWAY V/f_I in hippocampus, parahippocampal gyrus, left amygdala, left fusiform gyrus, and right superior temporal lobe. However, focus side did not influence the effect of comorbid MDD in TLE patients for most regions. The only significant group-by-focus interaction was higher [^{18}F]FCWAY V/f_I raphe values in non-depressed patients with right temporal foci. Similarly, a group-by-laterality-by-focus interaction showed higher values for left parietal cortex in non-depressed patients only with right temporal foci. After Bonferroni correction, all the above results including focus side as a factor remained significant except for those in raphe nucleus, parietal cortex, and superior temporal lobe.

There were no differences in gray matter volumes between the two patient groups. In anterior cingulate, medial and superior temporal lobes, and right parahippocampal gyrus, TLE patients without depression had higher values than those with depression only when comparing patients with MTS. Only the parahippocampal results remained significant after Bonferroni correction.

To evaluate the influence of comorbid anxiety disorders, a secondary analysis excluded patients with any anxiety disorder. Patients without depression had significantly higher values in anterior and posterior cingulate cortex, raphe nucleus, anterior insula, hippocampus, and amygdala. No regional difference remained significant after correction for multiple comparisons. Excluding patients with comorbid anxiety disorders did not change results substantially, although a larger sample size would be needed to evaluate the role of anxiety disorders more reliably.

A similar approach was taken to the issue of current depression. When only those without a current major depressive episode were examined, the hippocampus, amygdala, anterior insula, and inferior and superior temporal lobes were higher in the non-depression group. The hippocampus remained significant after Bonferroni correction.

Discussion

TLE patients with and without comorbid MDD did not differ regarding age, gender, prevalence of MTS and epileptic focus side. After Bonferroni-correction, TLE patients with comorbid MDD had lower [^{18}F]FCWAY V/f_I values in the anterior cingulate, right hippocampus, and

medial and superior temporal lobe. In addition, we found a group-by-laterality effect in the hippocampus: reduced values associated with comorbid MDD were mainly found on the right side. Gender, age, current major depressive episode and comorbid anxiety disorders were not significant effect modifiers.

In a study using [carbonyl- ^{11}C]WAY-100635 PET imaging in 12 unmedicated depressives with primary, recurrent, familial mood disorders and 8 healthy controls, Drevets et al. found a 42% mean 5-HT $_1\text{A}$ receptor BP reduction in midbrain raphe and reductions of 25% to 33% in mesiotemporal and neocortical areas in depressives relative to controls (11,12). Reduction in mesiotemporal cortex was in line with a study on postmortem tissue showing that 5-HT $_1\text{A}$ receptor mRNA was decreased 31% to 49% across hippocampal subfields in suicide victims with MDD (31). Consistently reduced 5-HT $_1\text{A}$ receptor BP of 50% in dorsal and median raphe nuclei was found postmortem in another study of depressed, nonalcoholic suicide victims (26). Decreased 5-HT $_1\text{A}$ receptor BP in raphe was also compatible with blunting of the hypothermic response to a 5-HT $_1\text{A}$ receptor agonist in depression (28). In MDD, 5-HT $_1\text{A}$ receptor BP was reduced in both unmedicated and medicated depressed patients (45) suggesting that serotonin reuptake inhibitors do not reduce 5-HT $_1\text{A}$ receptor BP. One study, however, reported a potentially genotype-related increase in 5-HT $_1\text{A}$ receptor BP in MDD, and a possible long-term effect of antidepressants on 5-HT $_1\text{A}$ receptor binding (43).

In 12 patients with TLE, an initial PET study found lower [^{18}F]FCWAY V ipsilateral than contralateral to the epileptic focus in inferior medial and lateral temporal regions of patients; [^{18}F]FCWAY V was 29% lower in raphe and 34% lower in ipsilateral thalamic regions in TLE patients relative to healthy controls (52). The [^{18}F]FCWAY V mean asymmetry index was significantly greater than mean cerebral blood flow and mean glucose metabolism asymmetry index suggesting relatively specific reduction in 5-HT $_1\text{A}$ receptor BP in temporal lobe epileptic focus. Because of brain atrophy in some patients of this initial study, the same group enlarged the study sample to a total of 22 patients with TLE and used MR-based PVC to elucidate the biological significance of their initial finding (19). This study showed that in TLE patients, reductions of 5-HT $_1\text{A}$ receptor binding in mesial temporal structures, mainly ipsilateral to the epileptic focus, in the insula, and in the raphe were still significant after PVC, and these changes were also found in TLE patients with normal MR images. Of importance for the current investigation, a significant negative correlation between the Beck Depression Inventory score and the ipsilateral hippocampal [^{18}F]FCWAY V/f_I , both before and after PVC, was found. PET studies using [carbonyl- ^{11}C]WAY-100635 and [^{18}F]MPPF consistently reported reduced 5-HT $_1\text{A}$ receptor binding in ipsilateral temporal lobe but also outside the epileptic focus in contralateral temporal lobe, insula, and anterior cingulate cortex (35,36,47). Merlet et al. compared [^{18}F]MPPF BP with data from intracranial recordings with stereo-epileptogenic areas and found a strong correlation between BP decrease and the degree of regional epileptic activity in non-lesional regions (35). While Merlet et al. did not find a correlation between depressive symptoms and [^{18}F]MPPF BP (35), Savic et al. found a negative correlation between [carbonyl- ^{11}C]WAY-100635 BP in the anterior cingulate cortex and depressive symptoms as measured with the Montgomery-Asberg Depression Rating Scale (47).

The strengths of the current study include the relative large sample size ($n=37$) with [^{18}F]FCWAY data in TLE patients, representing the largest published study to date on 5-HT $_1\text{A}$ receptor binding in TLE. PVC and the use of V/f_I values helped to confirm the biological specificity of the findings. Another major strength was the use of both clinical and structured psychiatric interviews to assess lifetime prevalence of psychiatric disorders. Previous studies used only self-report of current depressive symptom ratings, which may not be optimal because the lack of effect of selective serotonin reuptake inhibitor treatment and hydrocortisone challenge on 5-HT $_1\text{A}$ receptors in recovered patients with MDD suggests state-independence of reduced 5-HT $_1\text{A}$ receptor BP in depression (4,5). Moreover, increased prevalence of anxiety

disorders in epilepsy (24) and reduced 5-HT_{1A} receptor BP in panic disorder (39) appear to make an evaluation of the role of comorbid anxiety disorders, as included in the current study, necessary, although it has to be kept in mind that anxiety and depression may be alternative manifestations of the same underlying diathesis rather than independent disorders (34). Sample size and appropriate psychiatric assessment may have contributed to the relatively clear results and made a detailed evaluation of possible effect modifiers including laterality, focus side, MTS, gender, current major depressive episode and comorbid anxiety disorders possible. This is the first study to report that reduced hippocampal [¹⁸F]FCWAY V/f_1 associated with comorbid MDD were mainly found on the right side, while epileptic focus side did not affect the relationship between 5-HT_{1A} receptor binding and psychiatric comorbidity.

Several methodological limitations of this study also merit comment. The recruitment strategy was not community-based, and all the patients had intractable epilepsy, reducing the specificity and generalizability of the results. The sample size was limited, particularly in stratified analyses, reducing reliability of the findings. Almost all subjects were taking at least one highly protein-bound AED including carbamazepine, phenytoin, or valproic acid; there was higher [¹⁸F]FCWAY free fraction in patients than controls, possibly due to AED displacement of [¹⁸F]FCWAY from protein-binding sites (19). However, there no substantial AED effect on B_{max} , K_D or 5-HT concentrations was identified in a previous study (51). Therefore, we used free fraction corrected V as the main outcome measure of 5-HT_{1A} receptor binding to reduce sensitivity to the effects of AED. Data from raphe may be less accurate than for cortical regions because PVC could not be applied, and partial volume effects are increased in structures with small volume relative to PET spatial resolution (11). However, there is no evidence for raphe volume loss in TLE.

Compared with other available 5HT 1A receptor ligands, [¹⁸F]FCWAY offers advantages and disadvantages. The longer half-life allows longer imaging time and thus acquisition than for 11C-WAY, improving imaging statistics. It has higher specific activity than 18F-MPPF. In contrast, it is necessary to correct for the fluoride metabolite (7). Because of the insensitivity of [carbonyl-¹¹C]WAY-100635 and [¹⁸F]FCWAY to endogenous 5-HT concentrations (6, 42), reductions in [¹⁸F]FCWAY V/f_1 may reflect either down-regulation of 5-HT_{1A} receptor gene expression or a decrease in cellular processes expressing the 5-HT_{1A} receptor. Abnormal intrasynaptic 5-HT concentrations or the administration of antiepileptic medication, serotonin reuptake inhibitors, or monoamine oxidase inhibitors did not appear to down-regulate postsynaptic 5-HT_{1A} receptor density (11,51). The strong relationship found between non-lesional epileptic activity and 5-HT_{1A} receptor BP decrease (35) suggests excitotoxic events following epileptic seizures leading to down-regulated or structurally altered 5-HT_{1A} receptors. Alternatively, since 5-HT_{1A} receptors have inhibitory properties on glutamatergic neurons (40), low 5-HT_{1A} receptor density may lead to greater epileptiform activity. Both mechanisms would be compatible with the finding of the current study that 5-HT_{1A} receptor binding was decreased in TLE patients with and without MDD. In addition, hyperactivity of the HPA axis found in patients with MDD (21) and TLE (53) may lead to reduced postsynaptic 5-HT_{1A} receptor BP. Stimulation of mineralocorticoid receptors down-regulates hippocampal 5-HT_{1A} receptor gene expression (31,33). This mechanism would be consistent with the finding that comorbid depression was associated with an additional decrease in 5-HT_{1A} receptor binding. Conversely, one might also hypothesize genetic factors that lead to decreased [¹⁸F]FCWAY V/f_1 possibly representing a shared risk of both TLE and depression (21). Mice with mutation in the 5-HT_{1A} receptor gene have been consistently found to display increased stress-like behaviors (3). However, the use of a tissue-specific, conditional rescue strategy revealed that 5-HT_{1A} receptor expression in hippocampus and cortex (but not raphe nuclei) during the early postnatal period (but not in adults) is sufficient to rescue the normal behavioral phenotype of the knock-out mice (20). Stimulation of 5-HT_{1A} receptors during the postnatal period may have important long-term effects on neuronal plasticity (2).

In summary, using partial volume-corrected [^{18}F]FCWAY V/f_1 values to estimate 5-HT $_{1A}$ receptor binding, we showed that comorbid MDD was associated with a significantly greater decrease in 5-HT $_{1A}$ receptor binding in the anterior cingulate cortex, the right hippocampus and the medial and superior temporal lobe in TLE patients. Group differences were found in non-lesional limbic brain areas outside the epileptic focus. Focus side and the presence of MTS were not associated with the presence of comorbid depression. Further longitudinal and experimental research has the potential to identify mechanisms leading to reductions in 5-HT $_{1A}$ receptor binding in both TLE and depression, and to elucidate explanations of the TLE-MDD comorbidity.

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Table 1

Demographic and Clinical Characteristics of TLE Patients with and without Major Depressive Disorder (MDD)

Characteristic	TLE Patients with MDD (N = 16)	TLE Patients without MDD (N = 21)	Fisher's Exact p
	N (%)	N (%)	
Current Major Depressive Episode	5 (31)	NA	NA
Sex (Female)	9 (56)	6 (29)	.11
Anxiety Disorder (Any)	5 (31)	2 (10)	.20
Generalized Anxiety Disorder	2 (13)	1 (5)	.57
Panic Disorder	1 (6)	0 (0)	.43
Social Phobia	3 (19)	1 (5)	.30
Obsessive Compulsive Disorder	1 (6)	0 (0)	.43
Alcohol Abuse	2 (13)	1 (5)	.57
Cannabis Abuse	2 (13)	0 (0)	.18
Focus			.74
Right	6 (38)	10 (48)	
Left	8 (50)	10 (48)	
Bilateral	1 (6)	0 (0)	
Unknown	1 (6)	1 (5)	
Mesial Temporal Sclerosis	8 (50)	10 (48)	1.00
Other focal neuropathology	1 (6)	2 (10)	1.00
Family history (FH)			
FH epilepsy	5 (31)	6 (29)	1.00
FH major depressive disorder	4 (25)	4 (19)	.71
FH alcohol dependence	7 (44)	4 (19)	.15
	Mean (SD)	Mean (SD)	t, p
Age (Years)	38.5 (12.0) Range: 20-55	35.4 (11.8) Range: 18-55	0.78, .44
Age at onset of seizures (Years)	15.0 (11.1)	16.0 (10.0)	0.29, .78
Epilepsy Duration (Years)	23.5 (16.9)	19.4 (11.9)	0.86, .40
Age at onset of MDD (Years)	20.8 (8.4)	NA	NA
Major Depressive Episodes	2.4 (1.6)	NA	NA
Beck Depression Inventory	14.4 (13.0) ^a	5.3 (5.2) ^b	2.72, .01

^a 2 scores missing^b 3 scores missing

Table 2

[¹⁸F]FCWAY V/f₁ Values in Temporal Lobe Epilepsy (TLE) Patients with and without Major Depressive Disorder (MDD) and Healthy Controls.

Region	TLE with MDD		TLE w/o MDD		Group F, p	Laterality ^a F, p	G-L Interaction	
	Mean	SD	Mean	SD			F, p	F, p
Anterior Cingulate	46.29	10.18	56.83	12.65	6.86, .013	-	-	-
Posterior Cingulate	43.36	9.47	52.52	15.10	4.57, .040	-	-	-
Raphe Nucleus	21.83	5.45	27.65	7.45	7.13, .011	-	-	-
Anterior Insula					6.85, .013	1.05, .314	0.24, .626	
Left	46.97	7.46	54.82	13.05				
Right	46.87	11.09	56.70	12.68				
Hippocampus					14.00, .001	0.00, .984	6.44, .016	
Left	79.99	16.52	91.30	31.93				
Right	69.21	16.16	98.35	18.68				
Amygdala					3.16, .084	0.86, .361	5.00, .032	
Left	60.82	24.26	65.60	21.00				
Right	55.78	20.01	71.54	17.97				
Cerebellum					0.05, .852	0.19, .663	0.34, .561	
Left	23.42	20.37	18.83	7.95				
Right	22.13	17.89	18.19	8.60				
Frontal Lobe					2.35, .134	42.02, .000	0.08, .781	
Left	58.54	24.68	64.44	16.42				
Right	62.58	15.47	72.75	20.55	3.09, .088	0.44, .512	0.69, .413	
Fusiform Gyrus								
Left	83.57	20.02	93.78	37.66				
Right	82.81	19.95	100.78	25.68				
Occipital Lobe					2.85, .101	0.64, .802	0.02, .903	
Left	46.50	13.28	54.01	13.87				
Right	46.64	15.47	54.41	13.61				
Parietal Cortex					3.97, .054	1.65, .21	0.06, .81	
Left	53.72	14.54	66.20	20.14				
Right	55.66	17.10	68.16	19.75				
Parahippocampal Gyrus					3.98, .054	0.82, .371	4.31, .045	
Left	89.98	16.66	98.45	31.49				
Right	86.23	20.61	104.73	21.52				
Temporal Lobe: Inferior					3.25, .080	1.56, .220	2.42, .129	
Left	80.93	19.87	90.58	32.77				
Right	79.92	16.59	99.55	28.97				
Medial					4.16, .049	12.75, .001	0.65, .424	
Left	69.88	15.44	79.97	25.51				
Right	78.59	13.86	94.80	26.03				
Superior					6.63, .014	15.46, .000	3.70, .063	
Left	64.11	18.98	72.88	20.37				
Right	69.44	17.57	92.62	24.63				

^aLaterality refers to right versus left anatomical side and is not related to epileptic focus

Table 3

Effects on Group (with and without Major Depression), Laterality, and Focus Side on [¹⁸F]FCCWAY V/f₁ Values in Temporal Lobe Epilepsy (TLE) Patients^a

Region	Group	Laterality	Focus Side	GxL	GxF	LxF	GxLxF
Primary regions-of-interest							
Anterior Cingulate	0.010 ^b	-	0.814	-	0.548	-	-
Posterior Cingulate	0.078	-	0.465	-	0.501	-	-
Raphe Nucleus	0.016 ^b	-	0.139	-	0.037 ^c	-	-
Anterior Insula	0.016 ^b	0.104	0.759	0.611	0.737	0.261	0.340
Hippocampus	0.001 ^b	0.513	0.312	0.000 ^{de}	0.276	0.000 ^f	0.472
Secondary regions-of-interest	0.081	0.365	0.163	0.006 ^d	0.837	0.000 ^f	0.383
Amygdala							
Cerebellum	0.681	0.928	0.617	0.591	0.519	0.333	0.441
Frontal Lobe	0.151	0.000 ^g	0.973	0.235	0.562	0.112	0.034 ^h
Fusiform Gyrus	0.086	0.633	0.482	0.227	0.585	0.000 ^f	0.654
Occipital Lobe	0.164	0.667	0.495	0.866	0.818	0.331	0.833
Parietal Cortex	0.070	0.119	0.489	0.914	0.244	0.455	0.013 ^h
Parahippocampal Gyrus	0.120	0.446	0.847	0.002 ^d	0.375	0.000 ^f	0.090
Temporal Lobe: Inferior	0.041 ^b	0.236	0.955	0.068	0.521	0.000 ^f	0.613
Temporal Lobe: Medial	0.025 ^b	0.000 ^g	0.581	0.642	0.054	0.008 ^f	0.967
Temporal Lobe: Superior	0.004 ^b	0.000 ^g	0.163	0.101	0.102	0.039 ^f	0.156

^a Values in table represent p values derived from analyses of variance

^b Subjects without MDD > subjects with MDD

^c Subjects without MDD > subjects with MDD in subjects with right focus

^d Subjects without MDD > subjects with MDD on the right anatomical side

^e Right anatomical side > left anatomical side in subjects without MDD; left anatomical side > right anatomical side in subjects with MDD

^f Right anatomical side > left anatomical side in subjects with left focus; left anatomical side > right anatomical side in subjects with right focus

^g Right anatomical side > left anatomical side

^h Subjects without MDD > subjects with MDD on the left anatomical side in subjects with right focus.