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Frontolimbic Brain Networks Predict Depressive Symptoms in Temporal Lobe Epilepsy

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Abstract

Psychiatric co-morbidities in epilepsy are of great concern. The current study investigated the relative contribution of structural and functional connectivity (FC) between medial temporal (MT) and prefrontal regions in predicting levels of depressive symptoms in patients with temporal lobe epilepsy (TLE). Twenty-one patients with TLE [11 left TLE (LTLE); 10 right TLE (RTLE)] and 20 controls participated. Diffusion tensor imaging was performed to obtain fractional anisotropy (FA) of the uncinate fasciculus (UF), and mean diffusivity (MD) of the amygdala (AM) and hippocampus (HC). Functional MRI was performed to obtain FC strengths between the AM and HC and prefrontal regions of interest including anterior prefrontal (APF), orbitofrontal, and inferior frontal regions. Participants self-reported depression symptoms on the Beck Depression Inventory-II. Greater depressive symptoms were associated with stronger FC of ipsilateral HC-APF, lower FA of the bilateral UF, and higher MD of the ipsilateral HC in LTLE, and with lower FA of the contralateral UF in RTLE. Regression analyses indicated that FC of the ipsilateral HC-APF was the strongest contributor to depression in LTLE, explaining 68.7 % of the variance in depression scores. Both functional and microstructural measures of frontolimbic dysfunction were associated with depressive symptoms. These connectivity variables may be moderating which patients present with depression symptoms. In particular, FC MRI may provide a more sensitive measure of depression-related dysfunction, at least in patients with LTLE. Employing sensitive

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measures of frontolimbic network dysfunction in TLE may help provide new insight into mood disorders in epilepsy that could eventually guide treatment planning.

Keywords

Temporal Lobe Epilepsy; Depression; Comorbidity; DTI; Functional Connectivity; Uncinate Fasciculus

1. INTRODUCTION

Depression is a common co-morbidity in patients with temporal lobe epilepsy (TLE; Garcia, 2012). The past literature has suggested both psychosocial and neurobiological explanations (Kanner et al., 2012; Selassie et al., 2014) for this higher prevalence of depression in TLE than in the general population. It is well established that patients with epilepsy encounter social, cognitive, and psychological difficulties that can lead to poor quality of life and may contribute to a higher incidence of depression (Cramer et al., 2003; Lehrner et al., 1999). In particular, some studies suggest an association between cognitive deficits and depression indicating that some patients experience a “double burden” of cognitive and affective comorbidities (Helmstaedter et al., 2004; Tracy et al., 2007). Greater seizure frequency and duration are factors of clinical concern as they may lower the quality of life in patients with epilepsy. The past studies, however, have not shown a clear link between these variables and depression (Attarian et al., 2003). Therefore, although the confluence of these studies indicate that psychosocial and seizure-related variables may contribute to depressive symptomatology, the relationship between TLE and depression appears to be more complex, including a strong neurobiological component.

Among the leading neurobiological explanations, there is compelling evidence for the contribution of limbic structures, and in particular, the hippocampus. Although hippocampal atrophy has long been associated with depression in TLE (Valente and Busatto Filho, 2013), there are recent data to suggest that functional connectivity (FC) between medial temporal (MT) lobe structures and the prefrontal cortex (PFC) is a stronger predictor of depressive symptoms in patients with TLE (Kemmotsu et al., 2013). These data provide support for the notion that both TLE and depression are network disorders that may arise from disruption within multiple frontolimbic regions or to the white matter pathways connecting them. However, little is known about how functional and structural connectivity are related to each other or to levels of depressive symptoms in TLE.

In order to investigate MT-PFC functional and structural connectivity in TLE and their association with depression symptoms, we employed FC MRI in conjunction with diffusion tensor imaging (DTI). DTI provides an estimate of the microstructural integrity of white matter tracts in the brain by measuring the relative motility of water within a voxel and determining its directionality (Bick et al., 2012). In this study, we focus on the integrity of the uncinate fasciculus (UF)—a prominent white matter tract that connects the orbital, medial, and prefrontal cortices to MT regions (Schmahmann et al., 2007; Von Der Heide et al., 2013). The UF has been implicated in major depressive disorder, with greater white matter compromise associated with higher levels of depression (Dalby et al., 2010; Taylor et

al., 2007; Zhang et al., 2012). DTI can also probe the microstructure of deep gray matter structures, which may provide a more sensitive marker for damage to MT structures than volume loss. The present study examined the relationships among the microstructural integrity of the UF, hippocampus (HC), and amygdala (AM), with frontotemporal FC and depression symptomatology in order to better understand the frontolimbic circuitry underlying depressive symptoms in TLE. We also aimed to explore the relative contributions of DTI and FC measures in predicting levels of depressive symptoms in patients with TLE, as well as the potential contribution of seizure-related variables and cognitive deficits.

2. MATERIAL AND METHODS

2.1 Participant

Twenty-one patients with a diagnosis of medically refractory TLE and 20 healthy controls were prospectively enrolled in the study. All patients were under evaluation for surgical treatment at the UCSD Epilepsy Center. Patients were classified into left TLE (LTLE; $n = 11$) or right TLE (RTLE; $n = 10$) based on seizure onsets recorded by video-EEG. All patients underwent Phase II video-EEG monitoring using 5-contact foramen ovale electrodes. MRI findings suggested the presence of ipsilateral hippocampal sclerosis (HS) in 10 patients (6 LTLEs, 4 RTLEs). All patients were treated with antiepileptic medications (AEDs), and one patient was prescribed a selective serotonin reuptake inhibitor to treat mood problems at the time of the study (see supplemental table). No patients showed evidence of contralateral HS or extra-hippocampal pathology on clinical MRI. Control participants were right-handed English speakers who were recruited from the community via an IRB approved advertisement. Exclusion criteria for healthy controls included a history of self-reported neurological or psychiatric disorder, or past or current substance abuse.

2.2 Procedure

The study was approved by the institutional review board at University of California, San Diego. The procedures followed were in accordance with the Helsinki Declaration of 1975. Written informed consent was obtained from all participants. Participants were compensated for their time.

2.2.1 Assessment of Depression and Cognition—Participants completed the Beck Depression Inventory-II (BDI-II), a widely used 21-item multiple-choice measure that assesses affective, cognitive, and vegetative symptoms of depression (Beck et al., 1996). The total score (range 0 to 63) served as a dependent variable, with higher scores indicating greater levels of depressive symptoms. In addition, all participants were administered a battery of neuropsychological tests. For the purpose of the current investigation, we examined scores on language and memory measures to determine whether cognitive deficits contributed to depressive symptoms. These tests included the Boston Naming Test (BNT; Kaplan, 1983), Letter Fluency (LF) and Category Fluency (CF) subtests of the Delis-Kaplan Executive Function System (Delis et al., 2001), Logical Memory and Faces subtests of the Wechsler Memory Scale Third Edition (WMS-3; Wechsler, 1997), and California Verbal Learning Test Second Edition (CVLT-II; Delis, 2000).

2.2.2 Image Acquisition—All patients were seizure-free per self-report for a minimum of 24 hours prior to the MRI scan (Yogarajah and Duncan, 2008). All MRIs were performed on a General Electric Discovery MR750 3T scanner with an 8-channel phased-array head coil. Image acquisition included a conventional three-plane localizer, GE calibration scan, a T1-weighted 3D structural scan (TR = 8.08 msec, TE = 3.16 msec, TI = 600 msec, flip angle = 8°, FOV = 256 mm, matrix = 256 × 192, slice thickness = 1.2 mm), two functional T2*-sensitive echo planar imaging (EPI) scans (TR = 3000 msec, TE = 30 msec, flip angle = 90°, FOV = 220 mm, matrix = 64 × 64, slice thickness = 2.5 mm), and a diffusion sequence (single-shot EPI scan with matrix size = 96 × 96, FOV = 24 cm, 53 axial slices, slice thickness = 2.5 mm, partial k-space acquisition, TE = 77.5 msec, TR = 8000 msec). The two functional scans utilized two different phase encoding directions (forward and reverse) to adjust for signal loss due to geometric distortions in the EPI images (Holland et al., 2010). For DTI scans, one volume series was acquired with 30 diffusion gradient directions using a b-value of 1000 mm²/s with an additional b = 0 volume. For use in nonlinear B0 distortion correction, two additional b = 0 volumes were acquired with either forward or reverse phase-encode polarity. Image files in DICOM format were transferred to a Linux workstation for processing.

2.2.3 Image Processing and Analyses

2.2.3.1 Structural MRI: Individual T1-weighted images were used to construct models of each participant's cortical surfaces using FreeSurfer software 5.1.0 (<http://surfer.nmr.mgh.harvard.edu>). The structural MRI data were used to obtain volumes of the HC using automated atlas-based segmentation, (Fischl et al., 2002) to register the functional and DTI images, and to obtain ROI parcellations.

2.2.3.2 Functional Connectivity MRI: Functional imaging data were analyzed using the Analysis of Functional Neuroimages (AFNI), (Cox, 1996) Surface Mapping (SUMA) software (Saad and Reynolds, 2011) and MatLab (MathWorks, Natick, MA). Low-frequency BOLD fluctuations (0.008-0.08 Hz) were isolated from a task fMRI dataset as described previously (Kucukboyaci et al., 2013) and treated analogous to resting state data. This task-regressed method has been previously used and shown to approximate resting-state data (Arfanakis et al., 2000; Fair et al., 2007; Kucukboyaci et al., 2013). Corresponding motion files were also filtered using a bandpass filter of 0.008-0.08 Hz. Cerebral parcellations according to the Destrieux cortical atlas (Destrieux et al., 2010) and subcortical volume segmentation obtained from the T1 images were converted to volume data. Binary masks of the HC and AM were projected to the functional images in native space to extract the average time-series from each seed. Each of the averaged time-series was correlated with every voxel in the brain at the individual-subject level to obtain the intrinsic connectivity maps, in which motion parameters, global signal level, scanner drift, and white matter signal fluctuations were regressed out as nuisance variables. Voxel-wise correlation coefficients were then converted into Fisher's Z.

Multiple parcelled Destrieux regions were combined to create anterior prefrontal (APF), orbital frontal (OF), and inferior frontal (IF) regions of interest (ROIs), as shown in Figure 1. These ROIs were chosen due to the UF's connectivity and contributions of the PFC in

mood regulation (Price and Drevets, 2012). The means of Fisher's Z of these ROIs were obtained bilaterally for the connectivity between the bilateral HC and AM seeds.

2.2.3.3 DTI variables: Five pre-processing steps were performed 1.) Head motion between scans was removed by rigid body registration between the $b = 0$ images of each diffusion weighted scan. 2.) Within-scan motion was removed by calculating diffusion tensors, synthesizing of diffusion-weighted volumes from those tensors, and rigid body registering each data volume to its corresponding synthesized volume. 3.) Image distortion in the diffusion-weighted volumes caused by eddy currents was minimized by nonlinear optimization 4.) Image distortion caused by magnetic susceptibility artifacts was minimized with a nonlinear B0-unwarping method using paired images with opposite phase-encode polarities (Chang and Fitzpatrick, 1992; Morgan et al., 2004; Reinsberg et al., 2005). 5.) Images were resampled using cubic interpolation to 1.875 mm^3 isotropic voxels.

Fractional anisotropy (FA) values for the bilateral UF were derived using a probabilistic diffusion tensor atlas developed using in-house software written in Matlab and C++. A full description of the atlas and the steps used to create the atlas are described elsewhere (Hagler et al., 2009). Mean diffusivity (MD) values were obtained for the HC and AM based on co-registered diffusion and T1 images using FreeSurfer's automatic segmentation ROIs.

2.2.4 Statistical analysis—Correlation coefficients were calculated between BDI-II scores and FC strengths, FA of the UF, MD values of the HC and AM, and cognitive test scores. For these screening analyses, an alpha of .05 was used. Then, the relative contributions of DTI and FC measures were formally tested using stepwise multiple regression analysis and hierarchical regression analysis. Finally, correlation coefficients were calculated between FC strengths and MD and FA values of the UF to examine the relationship between structural and functional frontolimbic connectivity.

3. RESULTS

Table 1 presents demographic, clinical, and neuropsychological characteristics of patients and controls. There were no statistically significant differences in age or education among the controls, LTLE, or RTLE patients. The distribution of the two genders was comparable across groups, $\chi^2(2) = 1.52, p = .47$. Patients with LTLE and RTLE showed significantly smaller whole-brain adjusted volume of their ipsilateral HC relative to the other two groups, $F(2, 40) = 4.962, p = .012$, $F(2, 40) = 6.415, p = .004$, respectively. The mean BDI-II score was statistically different between the healthy controls and patients, $F(1, 41) = 8.353, p = .006$, with patients showing higher BDI scores. There was no difference in BDI scores between LTLE and RTLE groups. There was no difference between LTLE and RTLE in duration of seizure disorder. Patients' BDI-II scores were not correlated with disease duration or seizure frequency. Patients with LTLE were more impaired than patients with RTLE across most tests of language and memory. The LTLE group demonstrated significantly lower performance relative to controls on visual naming ($p < .001$), story recall ($p = .035$), learning ($p = .015$) and recall ($p = .046$) of faces, verbal list learning ($p = .007$) and short ($p = .009$) and long delay recall ($p = .034$), verbal phonemic fluency ($p = .005$), and verbal category fluency ($p < .001$), while RTLE group performed significantly lower

than controls on story learning ($p = .010$), verbal list learning ($p = .003$), and verbal category fluency ($p = .003$).

3.1 Group differences in the DTI and FC MRI measures

Table 2 presents the means and standard deviations of DTI variables. LTLE and RTLE patients showed significantly higher MD values of their ipsilateral HC relative to the other two groups, $F(2,40) = 19.426, p < .001$, $F(2,40) = 8.030, p = .001$, respectively. There were no group differences in the MD values of the AM or FA values of the UF.

Table 3 summarizes the means and standard deviations of frontolimbic FC strengths. Patients with LTLE showed lower FC between right AM- right IF, $F(2,40) = 5.19, p = .010$, and patients with RTLE showed lower FC between left AM – left IF $F(2,40) = 4.17, p = .023$.

3.2 Association with BDI-II score

3.2.1 FC measures—In patients with LTLE, a positive correlation was observed between BDI-II scores and the FC of the ipsilateral HC to the ipsilateral APF ($r = .829, p = .002$), indicating that *increased* FC of the HC seed was associated with higher depression scores (Figure 2). In patients with RTLE, no correlations reached the statistical significance between the MT seeds and the prefrontal ROIs. In healthy controls, higher BDI-II scores were associated with increased FC of the right AM to left IF ($r = .503, p = .024$) and OF ($r = .486, p = .030$) ROIs, and left AM to left IF ($r = .445, p = .049$) ROI.

3.2.2 DTI measures—In patients with LTLE, higher BDI-II scores were associated with lower FA values of the left and right UF, $r = -.690, p = .019$, $r = -.682, p = .021$, respectively. In RTLE, higher BDI-II scores were associated with lower FA values of the left UF ($r = -.697, p = .025$, Figure 2). Healthy controls did not show relationship between the UF and BDI-II.

With regard to MD measures, higher BDI-II scores were associated with higher MD of the left HC in LTLE, $r = .656, p = .028$. Patients with RTLE and healthy controls did not show relationships between BDI-II, and MD values of the HC and AM.

3.2.3 Cognitive scores—None of the memory and language test scores correlated with BDI-II scores in LTLE, RTLE, or in the control groups.

3.3 Relative contributions of imaging correlates to depressive symptoms

In patients with LTLE, the stepwise regression analysis indicated that FC of the ipsilateral HC-APF was the best predictor of BDI-II scores ($R^2 = .687, ! = .829, p = .002$). Having other predictors identified as significant correlates (i.e., bilateral UF FA values, left HC MD values) did not improve the model. Hierarchical regression analyses with FC of the left HC-APF at step 1 and FA of the left UF or right UF at step 2 revealed that UF FA values did not add significantly to the model.

3.4 Relationship between anisotropy of UF and frontolimbic FC strengths

In patients with LTLE, lower FA of the ipsilateral UF was associated with higher FC of ipsilateral HC-APF ($r = -.642, p = .033$), indicating disrupted white matter microstructure was associated with stronger frontolimbic functional connectivity (Figure 3).

4. DISCUSSION

There were four primary findings in the current study. First, microstructural compromise to the UF was associated with higher levels of self-reported depressive symptomatology in patients with LTLE and RTLE. Second, the levels of depressive symptomatology in LTLE were most associated with increased functional coupling between the ipsilateral HC and APF. Third, there was an inverse relationship between the functional and structural connectivity of the MT to prefrontal regions in LTLE. Fourth, levels of depression do not appear to be associated with poorer cognitive functioning and/or disease duration or seizure frequency.

Our results showed that the structural connectivity between MT and prefrontal regions is an important variable in explaining the levels of depression symptoms in patients with TLE. In particular, the left UF may be important (Taylor et al., 2007) as reduced FA on the left was related to higher depression scores in both LTLE and RTLE groups. Alternatively, it may be that the structural integrity of the contralateral UF is important in comorbid depression in TLE, as both LTLE and RTLE showed reduced FA of the contralateral UF to be related with higher BDI-II scores. The involvement of the UF in mood symptoms has been implicated in major depressive disorder, with most adult studies revealing greater levels of depression to be associated with reduced microstructural integrity of the UF (Dalby et al., 2010; Kwaastien et al., 2013; Taylor et al., 2007; Zhang et al., 2012). However, one recent study in treatment naïve adolescents showed the opposite pattern, with greater depression associated with increased FA (Aghajani et al., 2013). Regardless of the directionality of the relationship, our data extend these previous findings by showing that the UF may also be involved in mood regulation in patients with TLE. One possible explanation of this UF-depression relationship is that in response to the compromise to the ipsilateral hippocampus and limbic structures, structural reorganization took place in the contralateral hemisphere, which, when successful, contributed to improving the patient's affective functioning. Another way to explain this association is that pre-existing depression is interfering with structural reorganization and strengthening of the limbic-frontal network in the contralateral side, in which case, depression may be the cause of individual differences in FA values of the UF.

Despite the importance of the UF, our data indicated that FC between the ipsilateral HC and APF cortex is the strongest predictor of self-reported depression symptoms in LTLE. That is, frontolimbic FC is a stronger predictor than microstructural compromise to the UF or to other MT lobe structures. Our results support the advantage of investigating functional cooperation among brain regions rather than focusing on structural or microstructural damage to isolated brain regions. On the contrary to previous studies linking the AM to psychiatric symptoms in TLE (Doucet et al., 2013; Tebartz Van Elst et al., 2002; Tebartz van Elst et al., 2000), the AM networks were not associated with levels of depressive

symptoms in our patient groups, despite the observed reductions of FC strengths of the AM. It is also of note that HC-APF FC was not predictive of depressive symptoms in patients with RTLE. Although the reason for the lack of a relationship is unclear, inspection of Figure 2 suggests that the pattern in RTLE may be more complex. Specifically, patients with RTLE who self-reported mild to moderate symptoms of depression appear to demonstrate a trend towards greater HC-APF FC, whereas the patients with minimal depressive symptoms had a range of FC strengths. Thus, perhaps increased left frontolimbic FC coupled with other biological and/or psychosocial variables (ones that are not measured in our study) confers the greatest risk for depression in RTLE, and that our paper addresses only a small number of these variables.

Perhaps our most intriguing finding was an inverse relationship between our structural and FC measures, with greater compromise to the UF accompanied by increased frontolimbic FC. Available evidence in TLE is sparse, and most studies on functional and structural connectivity in clinical populations show a concurrent decrease in FC and white matter microstructure (Sui et al., 2013). However, our finding is in line with several recent studies from the depression literature (Kwaasteniet et al., 2013; Steffens et al., 2011; Wu et al., 2011). In particular, Kwaasteniet *et al.* demonstrated an aberrant increase in the frontolimbic FC (Kwaasteniet et al., 2013) accompanying reduced microstructural integrity of the UF in major depressive disorder. Two possible explanations raised by the authors are that microstructural compromise to the UF leads to a compensatory but aberrant increase in frontolimbic FC, or that increased FC itself leads to microstructural damage to the UF. The authors speculate that prolonged depression leads to increased FC of the limbic network, which then leads to microstructural damage. One interesting question with strong implications for treatment is whether these changes are reversible or permanent. Studies of depressive disorder indicate that white matter structure may recover in response to treatment (Lai et al., 2013). On the other hand, the extant epilepsy literature suggests that decreases in FA may be permanent and progressive (Yogarajah et al., 2010). Therefore, whether FA decreases are reversible may depend on a myriad of factors that would best be addressed with longitudinal data. Nevertheless, although cross-sectional data cannot speak to the temporal or causal nature of these structural-functional changes, it is of interest that our structure-function associations of depression in patients with TLE are commensurate with the three studies described above. Our results appear to suggest that aberrant function-structure relationships observed in depression are also observed in patients with TLE and comorbid depressive symptomatology. Whether this increase in functional connectivity in the face of compromised white matter tracts represents a compensatory mechanism in response to depression or epilepsy is unclear.

The confluence of our current data and previous studies on comorbid depression in TLE suggest that HC atrophy alone is a modest predictor of depressive symptoms in TLE, but that frontolimbic structural and functional networks seem to be modulating which patients present with depression symptoms. Why increased frontolimbic FC and reduced structural connectivity are associated with depressive symptoms in TLE or in major depression is unclear. However, recent evidence indicates that aberrant FC in depression is related to the serotonin transporter genotype, in that individuals who carry the short allele of the serotonin

transporter-linked polymorphic region show either increased or decreased functional coupling of the limbic and PFC regions (Hariri and Holmes, 2006). Given reported serotonin receptor abnormalities in TLE (Martinez et al., 2013), it is possible that serotonin-related genetic variations account for altered functional coupling in patients with TLE who have higher levels of self-reported depression symptoms. Exploring the mechanisms underlying the altered FC may be essential not only for understanding co-morbid depression but also for predicting post-surgical emotional functioning, since surgical resection alters frontolimbic FC and may further disrupt serotonergic transmission.

Despite the importance of neurobiological factors, there are possible alternative explanations and additional mediators for the observed relationships and changes. Neurobiological and psychosocial factors related to depression in TLE are not mutually exclusive. For example, seizure episodes themselves as well as structural and/or functional pathology due to epilepsy (e.g., unemployment, restrictions on daily activities, feelings of stigma, fear of seizures, memory and language difficulties) may impact psychosocial functioning, which in turn leads to greater depressive symptomatology. Given that factors such as duration of epilepsy and seizure frequency have been shown to contribute to psychiatric symptoms (Swinkels et al., 2006), one may hypothesize that better control of seizure may lead to less psychosocial difficulties thus less depression. There is also evidence that patients with epilepsy who have a pessimistic attributional style demonstrate more severe levels of depression (Hermann et al., 1996). However, we believe that these variables are at least partially unique in that no one set of variables seems to adequately predict depressive symptoms in TLE (Lin et al., 2012). Therefore, clinical care may benefit from future studies that evaluate how best to determine the cause(s) of depression for each patient, and to develop multifactorial models of depression in TLE that consider neurobiological, psychosocial, and cognitive factors.

Several limitations of our study should be noted. First, our FC MRI data were derived from task fMRI data, which may have produced results that are slightly different from data derived from resting state. Nevertheless, previous studies from our laboratory (Kucukboyaci et al., 2013) and others (Arfanakis et al., 2000; Fair et al., 2007) have shown that the findings were comparable with resting state studies and the concordance may speak to the robustness of the FC MRI techniques. Second, some patients were prescribed antidepressant and antiepileptic medications with known mood-stabilizing properties, and it is unclear what effect these medications had on the presentation of their depressive symptoms and/or our FC and DTI results. Third, although our preliminary analysis of the impact of HS indicated a lack of its effect on DTI and FC variables, it is possible that the presence of HS as verified with post-surgical histological studies provides more definitive answer. Fourth, only mild to moderate levels of depressive symptoms were reported in our patients with TLE, and whether our results would apply to a group of moderately to severely depressed patients with TLE is not clear. To date, microstructural compromise to the UF coupled with increased frontolimbic FC has been reported in patients with moderate to severe level of depression (Kwaastieniet et al., 2013). Therefore, our findings extend the literature by revealing this same relationship in patients with lower, perhaps subclinical, levels of depressive symptoms. Although many of these patients may not meet criteria for major depressive disorder, depressive symptoms in TLE are concerning and are known to reduce

quality of life (Jehi et al., 2011). Achieving a better understanding of comorbid depression and other mood disorders in TLE is critical to patient care and health outcomes.

5. CONCLUSIONS

In conclusion, our data suggest that frontolimbic structural and functional networks may modulate which patients with TLE present with depression symptoms. DTI and FC MRI appear to be promising techniques due to their sensitivity in explaining depression symptoms, relative to studying isolated single structures. Use of these measures may facilitate understanding of the current levels of depression in patients with TLE, and when combined with important psychosocial variables, may help to predict post-surgical psychiatric functioning of these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

APF	anterior prefrontal
FC	functional connectivity
UF	uncinate fasciculus
MT	medial temporal
PFC	prefrontal cortex
TR	repetition time
TE	echo time
FOV	field of view
SUMA	Surface Mapping
AFNI	Analysis of Functional Neuroimages

HIGHLIGHTS

- Frontolimbic functional connectivity strongly correlated with depressive symptoms
- Integrity of the uncinate fasciculus contributes to depressive symptoms in epilepsy
- Functional and structural frontolimbic connectivities were negatively correlated

Figure 1. Uncinate fasciculus (left panel) and regions of interest in the prefrontal cortices (middle and right panels). yellow = inferior frontal; cyan = orbitofrontal; red = anterior prefrontal

Figure 2.

Scatterplots showing the relationship between BDI-II scores and functional connectivity of the ipsilateral HC – APF (left) and BDI-II and fractional anisotropy values of the left uncinate fasciculus (right) in patients with left temporal lobe epilepsy (filled circles), right temporal lobe epilepsy (triangles), and healthy controls (gray diamonds). The dashed lines show a linear trend for left temporal lobe epilepsy group, while dot and dashed line indicates a linear trend for right temporal lobe epilepsy group.

Figure 3.

A scatterplot showing the relationship between the ipsilateral HC – APF and ipsilateral UF FA values in patients with left temporal lobe epilepsy (filled circles), right temporal lobe epilepsy (triangles), and healthy controls (gray diamonds). The dashed line shows a linear trend for left temporal lobe epilepsy group.

Table 1

Means and standard deviations (in parentheses) of demographic, clinical, and cognitive variables of patients and healthy controls

	Healthy Control (n = 20)	LTLE (n = 11)	RTLE (n = 10)
Age (years)	36.86 (14.53)	40.27 (11.47)	34.80 (14.57)
Years of Education Attained	15.7 (2.18)	14.8 (1.78)	14.30 (2.45)
BDI-II	5.70 (5.89) Range: 0 – 21	11.55 (7.15) Range: 1 - 22	11.10 (6.28) Range: 0 - 20
Age of Onset	-	16.23 (15.73)	20.00 (14.69)
Disease Duration (years)	-	24.23 (17.35)	14.60 (16.04)
Seizure Frequency (times per month)	-	9.45 (16.94)	7.63 (15.14)
Left Hippocampus Volume (mm ³)	3884.65 (358.87)	3108.73 (1009.42)*	4080.90 (409.93)
Right Hippocampus Volume (mm ³)	3936.95 (304.56)	4014.90 (325.62)	3601.30 (803.99)^
WMS-3 LM1 Scaled Score	12.95 (2.69)	9.40 (3.78)*	9.29 (2.75)^
WMS-3 LM2 Scaled Score	14.00 (3.76)	9.70 (3.13)*	10.71 (1.89)
CVLT-II TOTAL T-score	63.50 (7.49)	50.11 (11.58)*	51.00 (7.38)^
CVLT-II Short Delay Free Recall (Standard Score)	.82 (.69)	-.44 (1.29)*	-.25 (.52)
CVLT-II Long Delay Free Recall (Standard Score)	.79 (.61)	-.61 (1.54)*	0.00 (.32)
DKEFS Letter Fluency (Scaled Score)	13.80 (3.29)	9.55 (3.33)*	10.22 (4.24)
DKEFS Category Fluency (Scaled Score)	13.40 (3.27)	7.91 (2.51)*	8.56 (2.88)^
BNT T-score	46.29 (11.87)	31.10 (4.53)*	39.50 (10.41)

Note: LTLE = left sided temporal lobe epilepsy; RTLE = right sided temporal lobe epilepsy; BDI-II = Beck Depression Inventory Second Edition; WMS-3 = Wechsler Memory Scale Third Edition; CVLT-II = California Verbal Learning Test Second Edition; DKEFS = Delis Kaplan Executive Function Systems; BNT = Boston Naming Test.

Scaled scores have a mean of 10 and a standard deviation of 3. T-scores have a mean of 50 and a standard deviation of 10. Standard Scores have a mean of 0 and a standard deviation of 1.

* indicates the mean of the LTLE group significantly different from healthy controls.

^ indicates that the mean of the RTLE group significantly different from healthy controls.

Table 2

Means and standard deviations (in parentheses) of fractional anisotropy and mean diffusivity values

	Healthy Control (n = 20)	LTLE (n = 11)	RTLE (n = 10)
Left Uncinate FA	.404 (.02)	.390 (.03)	.408 (.02)
Right Uncinate FA	.393 (.02)	.393 (.03)	.386 (.03)
Left Hippocampus MD	.894 (.03)	1.05 (.13)	.896 (.04)
Right Hippocampus MD	.905 (.04)	.918 (.02)	.979 (.08)
Left Amygdala MD	.832 (.06)	.907 (.11)	.873 (.12)
Right Amygdala MD	.864 (.06)	.846 (.05)	.914 (.10)

Note: LTLE = left sided temporal lobe epilepsy; RTLE = right sided temporal lobe epilepsy; MD = mean diffusivity; FA = fractional anisotropy.

Table 3

Means and standard deviations (in parentheses) of functional connectivity strengths between left and right amygdalae and hippocampi and three prefrontal ROIs

Seed	Left Amygdala		Right Amygdala		Left Hippocampus		Right Hippocampus	
	Left	Right	Left	Right	Left	Right	Left	Right
HEALTHY CONTROLS								
Anterior Prefrontal	-.012 (.063)	-.035 (.062)	-.028 (.054)	-.022 (.051)	-.020 (.057)	-.040 (.054)	-.025 (.052)	-.037 (.054)
Inferior Frontal	.016 [^] (.037)	-.018 (.044)	-.022 (.041)	.001* (.038)	-.027 (.039)	-.059 (.077)	-.041 (.057)	-.060 (.068)
Orbitofrontal	.031 (.032)	.003 (.023)	.006 (.029)	.014 (.029)	.011 (.032)	-.015 (.034)	-.005 (.028)	-.014 (.023)
LTLE								
Anterior Prefrontal	.015 (.028)	.003 (.034)	-.125 (.033)	-.021 (.025)	-.025 (.034)	-.020 (.034)	-.025 (.041)	-.023 (.026)
Inferior Frontal	-.006 (.042)	-.021 (.032)	-.032 (.032)	-.035* (.021)	-.027 (.101)	-.040 (.033)	-.018 (.032)	-.032 (.032)
Orbitofrontal	.014 (.025)	.004 (.023)	.005 (.020)	.005 (.023)	-.005 (.030)	-.010 (.023)	-.010 (.026)	-.012 (.020)
RTLE								
Anterior Prefrontal	.015 (.047)	.004 (.047)	-.005 (.059)	-.012 (.057)	-.014 (.059)	.005 (.032)	.005 (.026)	-.004 (.026)
Inferior Frontal	-.027 [^] (.041)	-.023 (.035)	-.031 (.055)	-.028 (.029)	-.050 (.097)	-.020 (.035)	-.028 (.041)	-.034 (.234)
Orbitofrontal	.016 (.029)	.005 (.024)	.006 (.021)	.003 (.034)	.005 (.016)	-.005 (.029)	-.001 (.022)	-.009 (.027)

Note: LTLE = left sided temporal lobe epilepsy; RTLE = right sided temporal lobe epilepsy.

[^] indicates RTLE's mean significantly different from controls, and

* indicates means of LTLE significantly different from healthy controls.