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Alterations in functional connectivity between the hippocampus and prefrontal cortex as a correlate of depressive symptoms in temporal lobe epilepsy

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ABSTRACT

Depression is a common comorbidity in temporal lobe epilepsy (TLE) that is thought to have a neurobiological basis. This study investigated the functional connectivity (FC) of medial temporal networks in depression symptomatology of TLE and the relative contribution of structural versus FC measures. Volumetric MRI and functional connectivity MRI (fcMRI) were performed on nineteen patients with TLE and 20 controls. The hippocampi and amygdalae were selected as seeds, and five prefrontal and five cingulate regions of interest (ROIs) were selected as targets. Low-frequency blood-oxygen-level-dependent signals were isolated from fcMRI data, and ROIs with synchronous signal fluctuations with the seeds were identified. Depressive symptoms were measured by the Beck Depression Inventory—II. The patients with TLE showed greater ipsilateral hippocampal atrophy (HA) and reduced FC between the ipsilateral hippocampus and the ventral posterior cingulate cortex (vPCC). Neither HA nor hippocampal–vPCC FC asymmetry was a robust contributor to depressive symptoms. Rather, hippocampal–anterior prefrontal FC was a stronger contributor to depressive symptoms in left TLE (LTLE). Conversely, right amygdala FC was correlated with depressive symptoms in both patient groups, with a positive and negative correlation in LTLE and right TLE (RTLE), respectively. Frontolimbic network dysfunction is a strong contributor to levels of depressive symptoms in TLE and a better contributor than HA in LTLE. In addition, the right amygdala may play a role in depression symptomatology regardless of the side of the epileptogenic focus. These findings may inform the treatment of depressive symptoms in TLE and inspire future research to help guide surgical planning.

1. Introduction

One of the most common comorbidities suffered by patients with temporal lobe epilepsy (TLE) is depression, with the prevalence of depressive disorders estimated at up to 50% [1]. Although depression in TLE was traditionally thought to be secondary to psychosocial variables (e.g., lack of independence, stigma), there is strong evidence of a neurobiological component to depression in TLE that may involve similar mechanisms to those that generate seizures [1]. Obtaining a better understanding of the neurobiological underpinnings of depression in TLE is important because depressive symptoms have been linked to both poor quality of life [2,3] and poor surgical outcomes [4,5].

Previous structural neuroimaging studies in individuals with TLE traditionally focused on the contribution of single medial temporal structures, including the hippocampus and amygdala, to depressive symptoms [6]. These studies have shown altered morphometry in depressed patients with TLE relative to those without depression, including bilaterally reduced hippocampal volumes [7] and enlarged amygdala volumes [8,9]. However, other studies have yielded conflicting results [10–14].

Given the often contradictory findings related to individual structures, a broader network of brain structures may better explain depression in TLE. Recent data have revealed widespread brain structural alterations [15–18] in patients with TLE that extend well beyond the medial temporal lobe (MTL). Importantly, these widespread abnormalities are linked with cognitive and psychiatric symptom manifestations in TLE [19]. Therefore, it is likely that brain networks involved in temporal lobe seizures overlap with those that contribute to depression. In particular, frontolimbic and cingulate networks have been implicated both in TLE [20,21] and in depression [22,23].

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The current investigation utilized functional connectivity (FC) magnetic resonance imaging (fcMRI) to examine whether connectivity of MTL structures to prefrontal and cingulate cortices relates to self-reported depressive symptoms in patients with TLE. Functional connectivity MRI analyses probe regions of the brain whose low-frequency blood-oxygen-level-dependent (BOLD) signal fluctuations are synchronous, implying network connectivity among regions. We isolated low-frequency BOLD fluctuations from task performances (i.e., task-regressed fMRI) — a method successfully utilized in investigations of healthy controls and other clinical disorders to study cooperation among regions [24].

To date, altered FC of the hippocampus [25,26] and the amygdala [27,28] has been reported in studies of patients with TLE, but only one study has examined limbic network alterations in depression in TLE [29]. This study revealed regions of decreased and increased FC in depressed patients relative to non-depressed patients with TLE, including decreased FC between the limbic system and the prefrontal lobe and increased FC between the limbic system and the angular gyrus. The current study extends the existing literature by (1) investigating how structural volumes and FC of these limbic networks differentially contribute to depression in TLE and (2) exploring differences in these relationships between left TLE (LTLE) and right TLE (RTLE). We hypothesized that alterations in FC of MTL networks would be associated with depression symptomatology in patients with TLE. Specifically, we predicted that decreased frontolimbic functional cooperation would be associated with higher self-reported symptoms of depression. We also predicted that frontolimbic FC would be a stronger contributor to depressive symptoms than structural volumes of the hippocampus or the amygdala. Because of potential differences in disease mechanisms between LTLE and RTLE, as indicated by difference in neuroanatomical compromise [30,31] and studies suggesting greater depressive symptoms in LTLE compared to RTLE [20], we predicted that LTLE would show greater reductions of frontolimbic FC than RTLE.

2. Material and methods

2.1. Participants

Nineteen patients with a diagnosis of medically refractory TLE and 20 healthy control individuals participated. This study received prior approval from the institutional review board, and informed consent was obtained from each participant. All patients who met the inclusion criteria were consecutively recruited from the UCSD Epilepsy Center where they were under evaluation for surgical treatment. They were diagnosed by experienced epileptologists (E.S.T. and V.J.I.), according to the International League Against Epilepsy criteria [32]. The patients were classified into LTLE ($n = 11$) or RTLE ($n = 8$) based on seizure onsets recorded by video-EEG including electrographic ictal onset, seizure semiology, and neuroimaging results. Where clinically indicated, the patients underwent Phase II video-EEG monitoring using 5-contact foramen ovale electrodes to exclude bilateral independent seizure onsets. Clinical MRI scans were available on all patients and were visually inspected by a board-certified neuroradiologist for the detection of hippocampal sclerosis (HS) and the exclusion of contralateral temporal lobe structural abnormalities. In 12 patients (7 LTLE, 5 RTLE), MRI findings suggested the presence of ipsilateral HS. No patients showed evidence of contralateral HS or extrahippocampal pathology on clinical MRI. Five patients had a history of febrile seizures (3 LTLE, 2 RTLE). All patients were treated with antiepileptic drugs (AEDs) at the time of the study (see Supplemental Table). Control participants were recruited from the greater San Diego area via study flyers and word of mouth. They were screened for neurological or psychiatric conditions as per their self-report.

2.2. Procedure

2.2.1. Measurement of depression

All participants completed the Beck Depression Inventory—II (BDI-II), a widely used 21-item multiple-choice measure that assesses emotional, cognitive, and vegetative symptoms of depression [33]. A value of 0 to 3 is assigned to each item, with 3 being the most severe, yielding a possible total score ranging from 0 to 63. The total score served as a dependent variable in the current study. The BDI-II was part of a larger neuropsychological battery and usually was administered within one week, if not on the same day, of the MRI scans.

2.2.2. Image acquisition

2.2.2.1. Structural MRI. Magnetic resonance imaging was performed on a General Electric Discovery MR750 3T scanner with an 8-channel phased-array head coil. Image acquisitions included a conventional 3-plane localizer and a T1-weighted 3D structural sequence (TR = 8.08 ms, TE = 3.16 ms, TI = 600 ms, flip angle = 8°, FOV = 256 mm, matrix = 256 × 192, slice thickness = 1.2 mm). All patients were seizure-free for a minimum of 24 h prior to the MRI scan.

2.2.2.2. Functional data acquisition. Functional T2*-sensitive echo planar imaging (EPI) sequence (TR = 3000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 mm, 64 × 64, slice thickness = 2.5 mm) was performed. Forty-seven axial slices were obtained during each TR, covering the entire cortex. The first five volumes were discarded, and a total of 172 volumes were obtained for each run. A total of two runs were acquired per participant, with two different phase encoding directions (forward and reverse) to correct for geometric distortions in the EPI images [34]. The order of the phase encoding directions and combination of the phase encoding directions and word lists were counterbalanced across the participants to control for order effects.

2.2.3. Image processing

2.2.3.1. Surface reconstruction, segmentation, and parcellation. Individual T1-weighted images were used to construct models of each participant's cortical surfaces using FreeSurfer software 4.5.0 (http://surfer.nmr.mgh.harvard.edu). Volumes of the hippocampi and amygdalae were obtained using FreeSurfer's automated atlas-based segmentation [35]. All segmentations and cortical parcellations were visually inspected by a trained image analyst to ensure accuracy of the results.

2.2.3.2. Functional connectivity analysis. Functional imaging data were processed and analyzed using the Analysis of Functional Neuroimages (AFNI) [36], Surface Mapping (SUMA) software [37], and MatLab (MathWorks, Natick, MA). We isolated low-frequency BOLD fluctuations (0.008–0.08 Hz) from a task fMRI dataset and performed a seed-based approach for FC analysis [38]. We chose the hippocampus and the amygdala as the "seed" regions because of their prominent roles in TLE and mood [10,39] and the frontal and cingulate cortices as target regions of interest (ROIs) due to the past literature in depression indicating altered FC between the limbic system and these regions [23,40,41]. The task performed during the functional runs was an event-related, semantic judgment task where participants pressed a button with their left index finger whenever a low-frequency animal word, interspersed with other words and false font sequences, appeared on the screen. The block-design implementation of this task is detailed in McDonald et al. [42].

Digital Imaging and Communications in Medicine images from the two functional runs were reconstructed into two separate 3d + time files, with the first volume used for correction of geometric distortions, resulting in 171 volumes per run. Each functional volume was registered to the first volume of each run using a 3D coregistration algorithm (the program *3dvolreg* of AFNI), and slice time correction