

Brief Communication

Cortical thickness abnormalities associated with depressive symptoms in temporal lobe epilepsy

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ABSTRACT

Depression in patients with temporal lobe epilepsy (TLE) is highly prevalent and carries significant morbidity and mortality. Its neural basis is poorly understood. We used quantitative, surface-based MRI analysis to correlate brain morphometry with severity of depressive symptoms in 38 patients with TLE and 45 controls. Increasing severity of depressive symptoms was associated with orbitofrontal cortex (OFC) thinning in controls, but with OFC thickening in TLE patients. These results demonstrate distinct neuroanatomical substrates for depression with and without TLE, and suggest a unique role for OFC, a limbic region for emotional processing strongly interconnected with medial temporal structures, in TLE-related depressive symptoms.

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1. Introduction

Depression is a significant yet underappreciated problem affecting up to 55% of patients with treatment-resistant epilepsy [1]. Mood more powerfully predicts quality of life than seizure severity [2], and patients with epilepsy have a fivefold increased risk for suicide [3]. Although depressed mood may result partly from an expected psychological reaction to lifestyle limitations and stigma, there is evidence that depression in people with epilepsy differs phenomenologically and perhaps neurobiologically from depression in people without epilepsy.

Phenomenologically, depression in people with versus without epilepsy has been characterized by greater temporal variability in symptoms related to peri-ictal mood changes [1], prominent anhedonia [1], and decreased sadness [4]. These differences mean that depressive symptoms in epilepsy, although significant and requiring treatment, may not qualify for a diagnosis of major depression according to standard DSM-IV [5] criteria [6–8].

Neurobiologically, potential differences underlying depression in people with versus without epilepsy has not to our knowledge been investigated directly; the small number of prior studies examining the neuroanatomical correlates of depression in epilepsy has not included healthy controls. These studies have shown that in patients with temporal lobe epilepsy (TLE), the most common treatment-resistant adult epilepsy, major depression as well as subsyndromic depressive symptoms are associated with hippocampal atrophy [9,10] and relative amygdalar enlargement [11–13]. In patients with depression but without epilepsy, a similar neuroanatomic pattern of hippocampal atrophy and relative amygdalar enlargement has been demonstrated [14,15]. However, the majority of recent research attention has been focused on depression-related abnormalities in frontal regions involved in emotional regulation such as orbitofrontal cortex (OFC) [16,17], anterior cingulate cortex [18], and dorsolateral prefrontal cortex [19]. Because studies of epilepsy-related depression have focused primarily on the temporal lobe, it is not known whether these frontal or other extratemporal regions are also involved in epilepsy-related depression.

To address these issues, we used unbiased whole-cortex MRI morphometric assessment to identify brain regions associated with depressive symptoms in patients with TLE and control subjects without TLE. To assess depressive symptoms, we used the Beck

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Depression Inventory II [20]. The BDI-II is self-report inventory assessing symptoms of depression that has been validated for use in medically healthy people as well as patients with epilepsy [21].

2. Methods

2.1. Participants

Thirty-six patients (mean age = 37, 22 females) with mesial TLE were recruited from the Epilepsy Centers at New York University (NYU, $n = 16$) and the University of California, San Diego (UCSD, $n = 20$). On the basis of clinical information (MRI, video-EEG, and intracranial EEG when available) 22 patients were categorized as having left TLE, 12 as having right TLE, and 2 as having bilateral TLE.

Forty-five subjects (mean age = 40, 19 females) were recruited through online advertisement at both institutions (NYU, $n = 24$; UCSD, $n = 21$). Controls were medically healthy with no history of epilepsy. Their responses to a questionnaire indicated no prior psychiatric diagnosis or treatment.

Participants provided informed consent to participate in this study, which was approved by each center's institutional review board.

2.2. Assessment

The BDI-II [20] was administered as part of a neuropsychological assessment. The BDI-II is a 21-item self-report inventory used to assess affective, somatic, and cognitive symptoms of depression that has been validated for use in patients with epilepsy [21].

2.3. MRI acquisition

Imaging was performed at either the NYU Center for Brain Imaging on a 3-T Siemens Allegra scanner or at the UCSD Radiology Imaging Laboratory on a GE 1.5-T EXCITE scanner with an eight-channel phased-array head coil. Acquisition parameters were optimized for gray/white contrast. Acquisition included two T1-weighted images (NYU: TE = 3.25 ms, TR = 2530 ms, TI = 1.1 ms, flip angle = 7°, FOV = 256 mm, voxel size = $1 \times 1 \times 1.33$ mm; UCSD: TE = 3.8 ms, TR = 10.7 ms, TI = 1000 ms, flip angle = 8°, FOV = 240 mm, voxel size = $1.25 \times 1.25 \times 1.2$ mm) which were averaged to improve signal-to-noise.

2.4. MRI analysis

Cortical thickness was measured using FreeSurfer 5.0 (<http://surfer.nmr.mgh.harvard.edu>) which employs the following procedures, described in detail elsewhere [22]: white matter segmentation; tessellation of the gray/white boundary; inflation of the folded surface tessellation; correction of topological defects; measurement of the distance between each point on the white and pial surfaces; smoothing (15 mm FWHM); and averaging across participants using a spherical technique that matches homologous regions while minimizing distortions. For each hemisphere, a general linear model estimated the effects of BDI-II score on cortical thickness at each vertex along the cortical surface. Subject age and scanning site were included as covariates of no interest. The correlation between BDI-II score and cortical thickness was assessed within and between subject groups. Results were mapped onto the average brain and considered significant at $P < 0.05$ corrected for multiple comparisons using cluster-based thresholding [23].

3. Results

3.1. Assessment

Scores on the BDI-II ranged from 0 to 34 in controls and from 0 to 36 in patients with TLE, indicating a spectrum of depressive symptoms in both patients and controls. Patients with TLE were more depressed than controls (TLE mean = 11.7, control mean = 5.6, $t(65) = 3.1$, $P < 0.005$). There was no difference in severity of depression between patients with right and left seizure foci (right TLE mean = 9.8, left TLE mean = 10.4, $t(32) = 0.87$, $P > 0.5$).

3.2. MRI results

3.2.1. Within-group analysis

In controls, BDI-II scores correlated positively with cortical thickness in right dorsolateral prefrontal cortex and negatively with left lateral OFC and right precuneus, as shown in Fig. 1. In patients with TLE, BDI-II scores correlated positively with cortical thickness in left lateral OFC and right fusiform gyrus, and negatively with a small region of right superior parietal cortex.

3.2.2. Between-group analysis

In a direct comparison between patients and controls, the BDI-thickness correlation differed significantly only in bilateral lateral OFC, as shown in Fig. 2. The correlation was positive in patients with TLE and negative in controls.

4. Discussion

We show for the first time, to our knowledge, that the neuroanatomical correlates of depressive symptoms in patients with epilepsy differ from those in controls without epilepsy, and include opposite findings in OFC, a limbic component of prefrontal cortex involved in the subjective experience of emotional and social stimuli [24].

Within-group comparison showed that in controls, higher levels of self-reported depressive symptoms were associated with thinning of left lateral OFC. These results are consistent with prior studies demonstrating OFC abnormalities in major depression [16,17], and extend the association between OFC abnormality and depression to subjects with subclinical depressive symptoms (as no enrolled subjects had a current or past diagnosis of depression). In contrast, patients with TLE had *thickening* of left lateral OFC in association with greater self-reported depressive symptoms. See Appendix for discussion of brain regions other than OFC that showed significant BDI-thickness correlations in either patients with TLE or controls.

Between-group comparison confirmed that BDI-thickness correlations in left OFC differed significantly between patients with TLE and controls. In addition, this analysis revealed similar between-group differences in right OFC, suggesting bilateral OFC involvement in TLE-related depressive symptoms. However, conclusions about laterality effects are limited by the underrepresentation of patients with right TLE in our sample (12/35), precluding separate analyses of patients with right and those with left TLE [25].

Orbitofrontal cortex has bidirectional connections with sensory association cortices and temporal lobe regions [24]. In particular, lateral OFC has robust, direct connections with the amygdala [26], suggesting a mechanism by which mesial temporal epileptic activity could affect lateral OFC structure. In depressed patients with TLE, FDG PET studies revealed OFC hypometabolism [27,28]. Together with our demonstration of OFC thickening in association with depression, this suggests that the cellular components contributing to OFC thickening are unlikely to be normally functioning neurons or glia. Future studies, perhaps using MR spectroscopy, may better define the nature of this thickening.

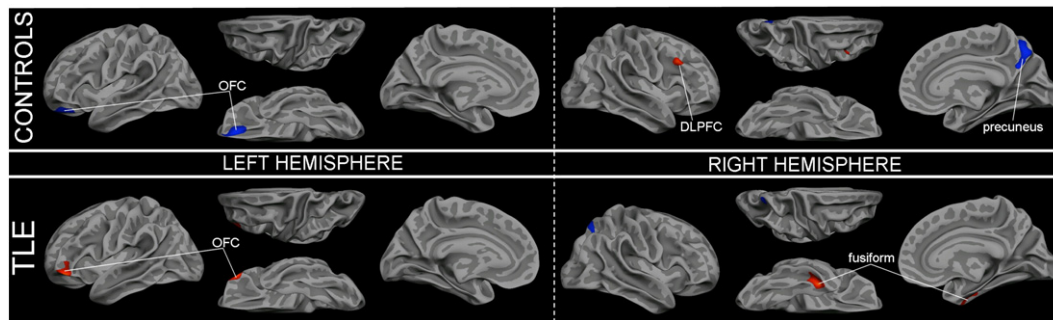


Fig. 1. Results of within-group analysis showing correlation between BDI-II score and cortical thickness in controls (top) and patients with TLE (bottom). Red indicates a positive correlation between BDI-II score and cortical thickness, and blue, a negative correlation. Note opposite findings in the two groups in left OFC. See Appendix for discussion of findings in other regions.

Although a potential limitation of this study is the use of two different MRI scanners, prior multisite studies of cortical thickness have shown negligible impact of initial scan acquisition [29]. In addition, we scanned roughly equal numbers of patients and controls on each scanner, and included site as a covariate in analyses, making it unlikely that findings relate to local hardware or other factors.

It is a limitation of this study that we did not perform structured diagnostic interviews to diagnose major depression. Our findings can be considered relevant to understanding the neural basis only of depressive symptoms, not major depression. However, it is important to note that DSM-IV [5] was not designed for the diagnosis of psychiatric disorders in neurological patients, and we believe use of a symptom measure such as the BDI-II is appropriate in patients with epilepsy who often do not meet DSM-IV criteria for major depression [1,6–8]. Use of the BDI-II, an instrument validated in people both with and without epilepsy [21], facilitates comparison between these two groups. Our use of a symptom measure rather than an all-or-none diagnosis is also in accord with the idea that depression may be best investigated using a dimensional rather than a categorical approach [30]. Still, it will be important for future studies to use a measure of symptom severity like the BDI-II

as well as a structured clinical interview to fully assess depression, and to include subjects both with and without a formal diagnosis of major depression and with and without epilepsy. It will also be important to investigate different components of depression (e.g., affective, somatic, and cognitive) to learn if they have specific neural correlates in subjects with and without epilepsy; although the BDI-II has been used for this purpose [31], it has not been independently validated [32].

Our findings support the idea that depression associated with temporal lobe epilepsy is not only phenomenologically distinct from depression unassociated with epilepsy, but is also neurobiologically distinct, thus highlighting the need for specifically designed diagnostic instruments [4] and perhaps, specific antidepressant treatments different from those used in patients without epilepsy.

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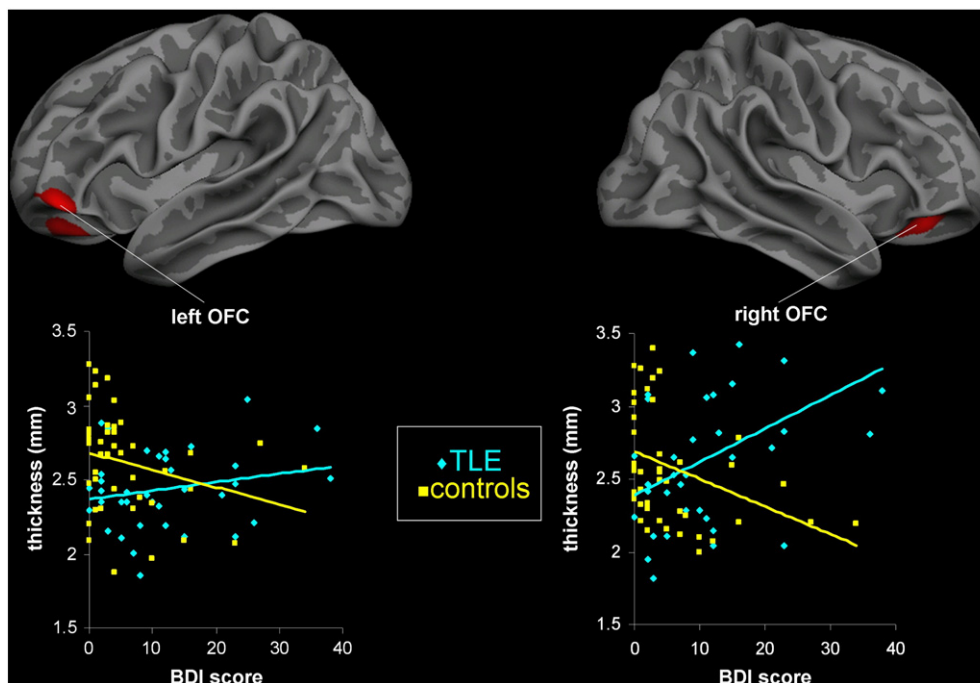


Fig. 2. Results of between-group analysis showing difference in the correlation between BDI-II and cortical thickness between patients with TLE and controls. The correlation differed only in bilateral OFC. Red indicates areas in which the thickness–depression correlation is significantly more positive (or less negative) in patients with TLE as compared with controls. As shown in scatterplots, increased thickness corresponded to increased depressive symptoms in patients with TLE and decreased depressive symptoms in controls.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.yebeh.2011.10.001.

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