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Depressive Symptom Severity Is Associated with Increased Cortical Thickness in Older Adults

Sarah M. Szymkowicz[1], **Molly E. McLaren**[1], **Joshua W. Kirton**[1], **Andrew O'Shea**[2,3], **Adam J. Woods**[2,3,4], **Todd M. Manini**[2], **Stephen D. Anton**[2], and **Vonetta M. Dotson**[1,4]

[1]Department of Clinical & Health Psychology, University of Florida

[2]Department of Aging & Geriatric Research, University of Florida

[3]Cognitive Aging and Memory Clinical Translational Research Program, University of Florida

[4]Department of Neuroscience, University of Florida

Abstract

Objective—Structural neuroimaging studies in older adults have consistently shown volume reductions in both major and subthreshold depression. Cortical thickness, another measure of brain structure, has not been well studied in this population. We examined cortical thickness in older adults across a range of depressive symptom (DS) severity.

Methods—Forty-three community-dwelling older adults (mean age = 68.80±7.00) underwent magnetic resonance imaging. Based on *a priori* hypotheses, we examined cortical thickness in regions of interest (ROIs) in the rostral anterior cingulate, orbitofrontal cortex, middle frontal gyrus and isthmus cingulate using multiple linear regressions with depression questionnaire scores as the independent variable and age, sex, and mean hemispheric thickness as covariates. We also performed an exploratory whole-brain vertex-wise analysis.

Results—After correction for multiple comparisons, we found an association between increased DSs and greater cortical thickness in the right isthmus cingulate [$F(1, 38) = 8.09$, FDR-corrected $p = .028$; $R^2 = 35.78$] in the ROI analysis and in the left precuneus (cluster size = 413, $p = 0.00002$) in the vertex-wise analysis.

Conclusions—Older adults with higher DSs also have greater cortical thickness in the isthmus cingulate and precuneus, areas import for emotion regulation and self-referential processing. Additional research is needed to elucidate the mechanisms and potential clinical significance underlying this relationship.

Keywords

brain volume; subclinical depression; aging; MRI

For correspondence contact: Vonetta M. Dotson, Ph.D., Department of Clinical & Health Psychology, University of Florida, P.O. Box 100165, Gainesville, FL 32610-0165. Phone: +1 (352) 273-6041. Fax: +1 (352) 273-6156. vonetta@phhp.ufl.edu.

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1. Introduction

Major depression is one of the most common psychiatric disorders in older adults (Seitz *et al.*, 2010; Byers *et al.*, 2010), with an estimated prevalence of 1–5% in individuals over age 65 years (Hasin *et al.*, 2005). Depression can be conceptualized on a continuum, ranging from no depressive symptoms (DSs) to severe depressive disorders (Judd and Akiskal, 2000; Rodriguez *et al.*, 2012). In older adults, subthreshold depression—symptoms of depression that do not fully meet the clinical criteria for major depression—has an estimated prevalence of 7–15% (Polyakova *et al.*, 2014; Laborde-Lahoz *et al.*, 2014) and is associated with adverse health outcomes (Chachamovich *et al.*, 2008; Cuijpers *et al.*, 2013), increased economic costs (Cuijpers *et al.*, 2007; Meeks *et al.*, 2011), and increased risk for major depression and other psychiatric disorders (Laborde-Lahoz *et al.*, 2014).

Major depression in older adults has consistently been associated with structural and functional alterations in frontal-subcortical circuitry (Ajilore *et al.*, 2014; Kumar *et al.*, 2014b; Sexton *et al.*, 2013; Sacher *et al.*, 2012). The neuroanatomical basis of subthreshold symptoms has received less attention. Research has consistently shown frontal volume reductions (Kumar *et al.*, 1998; Kumar *et al.*, 1997b; Dotson *et al.*, 2009b; Taki *et al.*, 2005) in older adults as a function of DS severity, even in the subthreshold range, while fewer studies show changes in other regions, such as the temporal lobes (Dotson *et al.*, 2009b).

The purpose of the current study was to determine whether or not DS severity is associated with cortical thickness in older adults. Cortical volume, the more common measure of brain structure in previous studies in this area, is a three-dimensional index of the brain's structural integrity that combines cortical surface area and cortical thickness, and thus does not allow a determination of the properties that are unique to each component. There is evidence that these measurements may be driven by different underlying mechanisms (Panizzon *et al.*, 2009; Winkler *et al.*, 2010). Specifically, cortical thickness is thought to be more closely related to features of the cortex such as the organization of cortical layers and the size, number, and density of cell bodies in the neurons, as well as synaptic connections (Du *et al.*, 2007; Kabani *et al.*, 2001). Thickness and surface area appear to be genetically independent and affected by distinct neurobiological factors, such as myelin growth, during development (Panizzon *et al.*, 2009; Rakic, 2009; White *et al.*, 2010). Consistent with this evidence are findings of either no correlation or a weak correlation between thickness and surface area (Hogstrom *et al.*, 2013; Winkler *et al.*, 2010). Consequently, understanding the relationship between DSs and cortical thickness may provide additional and more specific information about the neuroanatomical basis of DSs.

In terms of major depression, most studies find cortical thinning in prefrontal, temporal, and parietal regions (Tu *et al.*, 2012; van Eijndhoven *et al.*, 2013; Wagner *et al.*, 2012; Jarnum *et al.*, 2011; Truong *et al.*, 2013). However, some studies have reported increased cortical thickness in frontal regions, as well as the posterior cingulate, anterior insula, and temporal pole (Tu *et al.*, 2012; Qiu *et al.*, 2014; van Eijndhoven *et al.*, 2013). Less work has investigated cortical thickness in older adults with subthreshold depression, although a recent study (Kumar *et al.*, 2014a) indicated cortical thinning in the right isthmus cingulate. Based on this finding, our previous structural and functional studies of subthreshold

depression (Dotson *et al.*, 2009a; Dotson *et al.*, 2009b), and evidence of primarily prefrontal volume deficits related to subthreshold symptoms (Ma *et al.*, 2013; Dotson *et al.*, 2009b; Webb *et al.*, 2014; Kumar *et al.*, 1998; Kumar *et al.*, 1997a; Taki *et al.*, 2005), we were interested in elucidating the relationship between DSs and cortical thickness in regions of interest (ROIs) in the orbitofrontal cortex, middle frontal gyrus, rostral anterior cingulate and isthmus cingulate. We also performed an exploratory whole-brain vertex-wise analysis. Given the preponderance of evidence of volumetric decreases and cortical thinning in depression, we predicted that higher DSs would be associated with cortical thinning in these regions.

2. Methods

2.1. Participants

Forty-nine community-dwelling older adults (mean age = 68.80±7.00) were recruited. All were right-handed, native English speakers with normal or corrected-to-normal vision, an education of at least 9 years, and a score of greater than 30, the suggested cutoff for dementia, on the Telephone Interview for Cognitive Status (TICS; Brandt *et al.*, 1988). Initial exclusionary criteria included self-reported history of major medical or neurological illness, head trauma, learning disorders, current antiepileptic or antipsychotic use, language comprehension difficulties, and MRI contraindications. We did not exclude participants with major depression in order to increase the range of DS severity in the sample. Two participants met criteria for major depression per clinical interview. Both were taking antidepressant medication, as were five additional subjects who did not meet criteria for depression. Six subjects were excluded from the analyses due to either missing data, MRI evidence of past stroke, current substance abuse, or a learning disorder diagnosis. The local Institutional Review Board approved the study and all participants gave verbal and written informed consent. Demographic data for the final sample (n=43) are presented in Table 1.

2.2. Measures

Symptoms of depression were assessed using the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977), a 20-item self-report questionnaire measuring the frequency and severity of DSs experienced in the past week. The CES-D has been well validated for use in community-dwelling older adults (Beekman *et al.*, 1997; Haringsma *et al.*, 2004).

2.3. MRI Data Acquisition

Participants received an MRI scan in a second experimental session within one week of completing the CES-D. MRI data were collected on a Phillips (Amsterdam, Netherlands) 3-Tesla scanner at the University of Florida's McKnight Brain Institute using a Philips 8-channel radio-frequency coil. A high resolution, T_1-weighted turbo field echo anatomical scan was collected using the following parameters: TR = 8.1 ms, TE = 3.7 ms, 170 slices acquired in a sagittal orientation, flip angle = 8 degrees, 1 mm cubic resolution.

2.4. Cortical Thickness Measurement

Cortical reconstruction was conducted with the Freesurfer image analysis suite (version 5.3), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Processing included motion correction, removal of non-brain tissue (Segonne *et al.*, 2004), automated Talairach transformation, segmentation of the subcortical structures (Fischl *et al.*, 2004; Fischl *et al.*, 2002), intensity inhomogeneity correction (Sled *et al.*, 1998), tessellation of the gray/white matter boundary, topology correction (Fischl *et al.*, 2001; Segonne *et al.*, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid (CSF) borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale *et al.*, 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). This method uses both intensity and continuity information in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). Automated cortical thickness measures have been validated against histological analysis (Rosas *et al.*, 2002) and manual measurements (Kuperberg *et al.*, 2003; Salat *et al.*, 2004). Based on *a priori* hypotheses, cortical thickness was calculated in primary ROIs in the left and right rostral anterior cingulate, orbitofrontal cortex (calculated by summing the weighted means [regional thickness divided by regional volume] of the medial and lateral orbitofrontal cortex), middle frontal gyrus (calculated by summing the weighted means of the rostral and caudal middle frontal gyrus), and isthmus cingulate. Exploratory analyses used a whole-brain vertex-wise analysis. For each subject, a thickness measurement was mapped on each vertex of the cortical surface, allowing an examination of cortical thickness across the brain. Images were smoothed using a Gaussian kernel with a full-width-half-maximum of 10 mm.

2.5. Statistical Analysis

Primary analyses were conducted using separate mixed-effects regression analyses for each ROI, performed in SAS 9.4 (Cary, NC). CES-D scores were the independent variable and age, sex, and mean total thickness were covariates. All variables besides sex were continuous measures in the models. Antidepressant use was initially included as a covariate, but was removed since it was not significant in any of the models. Statistical significance was set at a false-discovery rate (FDR; Benjamini and Hochberg, 1995) corrected threshold of $\alpha \leq 0.05$. For the exploratory whole-brain analysis, general linear models were conducted in Freesurfer with CES-D scores predicting cortical thickness at each vertex. A Monte Carlo null-Z correction for multiple comparisons was implemented to account for type I error.

3. Results

3.1. ROI Analysis

Results of the primary analyses are summarized in Table 2 and Figure 1. Higher CES-D scores were significantly associated with increased thickness in the right isthmus cingulate [$F(1, 38) = 8.09$, $p = 0.007$] and the bilateral middle frontal gyrus [left $F(1, 38) = 6.30$, $p = 0.017$; right $F(1, 38) = 4.25$, $p = 0.046$]. Follow-up analyses segmenting the middle frontal gyrus found increased CES-D scores were significantly associated with increased thickness

in the rostral [left $F(1, 38) = 5.10$, $p = 0.030$; right $F(1, 38) = 3.79$, $p = 0.059$], but not caudal [left $F(1, 38) = 2.75$, $p = 0.106$; right $F(1, 38) = .87$, $p = 0.356$], portion of the middle frontal gyrus. The pattern of results was unchanged when the two participants with major depression were excluded and when a covariate for antidepressant use was included. Only the effect in the right isthmus cingulate remained after FDR correction [FDR corrected $p = .028$]. The effect in the left middle frontal gyrus was marginal [FDR corrected $p = .071$].

3.2 Whole-brain analysis

The uncorrected vertex-wise analysis revealed multiple regions of increased thickening as a function of higher depressive symptoms, including bilateral middle frontal and inferior frontal regions (Table 3 and Figure 2). Other areas of thickening included the left precuneus and posterior cingulate, and the right middle temporal and supramarginal gyri. Only the left precuneus survived correction for multiple comparisons.

4. Discussion

This study examined the relationship between DSs in older adults and cortical thickness using both an ROI approach centering on the cingulate and prefrontal regions, and a whole-brain analysis. We expected higher DSs to be associated with cortical thinning, but instead found significant positive relationships between DS severity and thickness in the isthmus cingulate and middle frontal gyrus in primary analysis of ROIs in cingulate and prefrontal regions. Follow-up analyses revealed an effect in the rostral, but not caudal, middle frontal gyrus. The rostral middle frontal gyrus and isthmus cingulate are portions of the dorsolateral prefrontal cortex and posterior cingulate, respectively. Both of these regions are involved in mood regulation (Beauregard *et al.*, 2001; Price and Drevets, 2010) and have consistently been implicated in neuroimaging and post-mortem studies of major and subthreshold depression (Chang *et al.*, 2011; Dotson *et al.*, 2009b; Kempton *et al.*, 2011; Liao *et al.*, 2012; Rajkowska *et al.*, 1999). Thus, our results are consistent with prevailing theories of the etiology of depression that focus on abnormalities in frontolimbic brain networks (e.g., Price and Drevets, 2010).

We also conducted an exploratory whole-brain analysis and found evidence of greater thickness in the left precuneus at higher DS severity. Though rarely the primary focus of neuroimaging studies of depression, this region has been implicated in multiple structural and functional studies of mood disorders (Greicius *et al.*, 2007; Kroes *et al.*, 2011; Li *et al.*, 2014; Freton *et al.*, 2014). Consistent with our findings, a recent study reported a positive relationship between scores on an anxiety/depression subscale and cortical thickness of the precuneus and posterior cingulate in young women with subthreshold depression (Ducharme *et al.*, 2014). Moreover, there is evidence that higher DS levels are associated with larger volumes and increased activity during an emotion recognition task in the precuneus (Scheuerecker *et al.*, 2010). The precuneus is a medial part of the parietal lobes and a core component of the default mode network. It is thought to be involved in integrating mental processing through its role in visual imagery, self-referential processing, and episodic memory (Cavanna and Trimble, 2006). In depression, the precuneus may underlie symptoms such as abnormal self-processing, over-general autobiographical memory, poor emotion regulation, and intrusive imagery involving past life stressors (Zhu *et al.*, 2012). Our results

suggest that abnormalities in the precuneus are also evident in subthreshold levels of depressive symptoms.

The present results add to a very limited literature examining cortical thickness in depression. Previous work has primarily focused on young to middle-aged samples and has yielded conflicting results. Some studies reported cortical thinning in various frontal regions, as well as the superior temporal cortex, posterior cingulate, and insula in depressed patients compared to controls (Jarnum *et al.*, 2011; Li *et al.*, 2014; Na *et al.*, 2014). In older adults, two recent investigations reported that late-onset depression is associated with thinning of frontal and temporal regions and the corpus callosum compared to early-onset depression or non-depressed controls (Ballmaier *et al.*, 2008; Lim *et al.*, 2012). Only one known study examined subthreshold depression; older adults with minor depression were found to have cortical thinning in the right isthmus cingulate compared to controls (Kumar *et al.*, 2014a). Of note, the right isthmus cingulate was the only region in our ROI analysis to remain significant after FDR correction, while the middle frontal gyrus became marginally significant. In contrast to thinning of the isthmus cingulate that was previously reported, we found increased thickness at higher DS levels. The duration and severity of symptoms in the two studies may explain the difference. The former study defined minor depression as having depressed mood or anhedonia plus one additional symptom for one month, and compared patients to controls. The present study used a continuous measure of scores on the CES-D, which assesses symptoms experienced in the previous week. Our results are in line with previous suggestions that cortical thickness changes differ in the early course of depressive disorders compared to later stages. For example, a recent study reported increased cortical thickness in the medial orbitofrontal, inferior frontal, rostral middle frontal, and supramarginal gyri in untreated patients with first episode mid-life depression (Qiu *et al.*, 2014), consistent with an earlier study reporting similar increases in frontal cortical thickness in treatment-naïve depression (van Eijndhoven *et al.*, 2013). At least three additional studies reported increased frontal thickness in major depression (Grieve *et al.*, 2013; Reynolds *et al.*, 2014; Tu *et al.*, 2012), and increased thickness of the precuneus and multiple frontal regions has been associated with anxious/depressed symptoms and familial risk for depression (Ducharme *et al.*, 2014; Peterson and Weissman, 2011).

Increased cortical thickness in first-episode treatment-naïve depressed patients led to the hypothesis that the early course of depression is associated with increased thickness, while more chronic symptoms may eventually lead to decreased thickness (Qiu *et al.*, 2014; van Eijndhoven *et al.*, 2013). Along those lines, some researchers argue that the early stage of depression is associated with a compensatory inflammatory response (Dowlati *et al.*, 2010) in which astrocytes, the primary constituents of cortical tissue volume, are activated by proinflammatory cytokines and lead to cellular hypertrophy, astrocyte proliferation, process extension and interdigitation. This process in turn could increase cortical thickness (Liberto *et al.*, 2004). Thus, increased cortical thickness may be observed in first episode depression or in the early stages of a depressive episode, while cortical thinning may result from neurotoxic effects due to prolonged physiological changes in chronic or recurrent depression (Sheline *et al.*, 2003). Potential roles of glutamate-related toxicity and glial pathology have also been identified as important contributors to cortical thickness changes in depression

(Rajkowska *et al.*, 1999; van Eijndhoven *et al.*, 2013). Moreover, it has been speculated that compensatory mechanisms in subthreshold depression may prevent the progression to a clinical mood disorder by mitigating negative emotional experiences associated with an overly active limbic system (Ducharme *et al.*, 2014).

More research is needed to elucidate the mechanisms underlying increased cortical thickness in depression, and to identify demographic and clinical variables, such as age and comorbid anxiety, that may moderate the relationship between depression and cortical thickness. Information about anxiety symptoms was not available for all participants in our sample; therefore, we were not able to examine the potential impact of anxiety on the present results. The cross-sectional nature of the study is also a limitation, as we are not able to determine causality in regards to the relationship between increased thickness and DSs.

5. Conclusion

Our findings add to a limited but growing literature on cortical thickness changes in depression and provide further evidence of brain alterations as a function of DSs in older adults. Longitudinal studies are needed to elucidate causal associations. Understanding the relationship between depression and cortical thickness may increase our understanding of the pathophysiology of depression and provide new targets for treatment.

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Key Points

- Examined the relationship between depressive symptom severity and cortical thickness in older adults.
- Increased depressive symptoms were associated with cortical thickening in the isthmus cingulate in ROI analysis and the precuneus in exploratory vertex-wise analysis.
- Results add to limited literature examining structural changes in subthreshold depression.

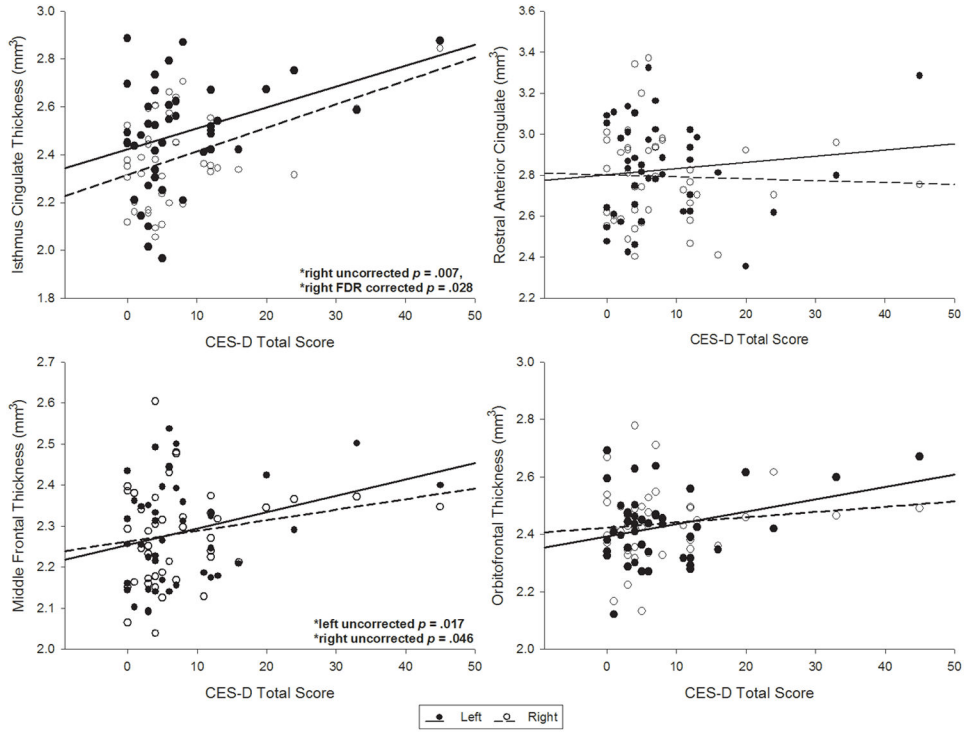

Figure 1.

Relationship between Center for Epidemiologic Studies Depression Scale (CES-D) scores and cortical thickness in the ROI analysis.

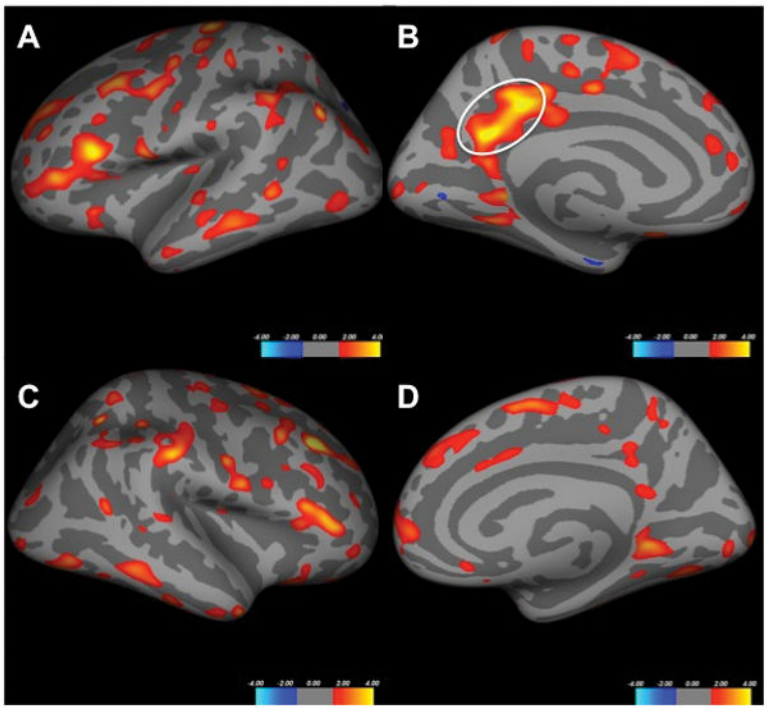

Figure 2.

Left lateral (A), left medial (B), right lateral (C), and right medial (D) views of uncorrected voxel-wise associations between cortical thickness and scores on the Center for Epidemiologic Studies Depression Scale (CES-D). Areas in the red to yellow range showed a positive relationship with CES-D scores, with a greater yellow hue representing greater statistical significance. The color scale is represented as log(p). The left precuneus, which survived Monte Carlo correction for multiple comparisons, is circled.

Table 1

Sample demographic characteristics

Demographic	Mean	SD
Age	68.8	7.00
Sex (% female)	69.76	------
Education (years)	15.07	2.53
CES-D	7.84	8.90

Note: CES-D = Center for Epidemiologic Studies Depression Scale.

Table 2

Regression results for the ROI analysis

	Age		Sex		Total Thickness		CES-D	
Region	**B**	**SE(df)**	**B**	**SE(df)**	**B**	**SE(df)**	**B**	**SE(df)**
Rostral Anterior Cingulate								
Left (R^2 = 26.05)	0.01	0.00(38)	0.01	0.07(38)	0.49**	0.16(38)	0.00	.00(38)
Right (R^2 = 47.05)	0.01	0.00(38)	−0.01	0.06(38)	0.71***	0.13(38)	−0.00	.00(38)
Isthmus of the Cingulate								
Left (R^2 = 37.18)	−0.00	0.00(38)	0.06	0.06(38)	0.45**	0.14(38)	0.01	0.00(38)
Right (R^2 = 35.78)	−0.00	0.00(38)	0.04	0.06(38)	0.31*	0.12(38)	0.01†**	0.00(38)
Orbitofrontal Cortex								
Left (R^2 = 28.10)	0.00	0.00(38)	−0.01	0.04(38)	0.25**	0.08(38)	0.00	0.00(38)
Right (R^2 = 47.01)	−0.00	0.00(38)	−0.04	0.03(38)	0.40***	0.07(38)	−0.00	0.00(38)
Middle Frontal Gyrus								
Left (R^2 = 61.34)	0.00*	0.00(38)	0.01	0.03(38)	0.39***	0.06(38)	0.00*	0.00(38)
Right (R^2 = 73.05)	0.01***	0.00(38)	0.03	0.02(38)	0.41***	0.05(38)	0.00*	0.00(38)

Note: CES-D = Center for Epidemiologic Studies Depression Scale, SE = standard error, df = degrees of freedom

† indicates significance after correction for multiple comparisons.

* indicates significance at $p < 0.05$,

** $p < .01$,

*** $p < .001$

Table 3

Brain regions showing a significant relationship between increased thickness and higher CES-D scores in the vertex-wise analysis.

Region	Side	Coordinate			Cluster Size (mm^2)	*p*
		x	*y*	*z*		
Precuneus*†	L	−8.4	−52.5	22.5	413.04	0.00002
Rostral Middle Frontal*	R	30.6	29.4	38.8	106.61	0.000005
Pars Opercularis*	L	−48.4	22.1	18.2	141.43	0.00007
Fusiform Gyrus	R	42.1	−33.9	−20.4	82.43	0.00008
Precentral Gyrus*	L	−18.1	−24.3	63.8	58.07	0.0002
	R	58.4	5.9	19.6	0.42	0.001
Superior Parietal	R	29.3	−55.4	42.9	10.95	0.0002
Inferior Parietal*	L	−39.7	−68.5	34.3	18.11	0.0003
Supramarginal Gyrus	R	59.9	−26.5	36.6	37.97	0.0003
Caudal Middle Frontal	L	−40.9	15.8	47.5	28.91	0.0005
Lingual Gyrus	R	21.7	−46.7	−4.5	16.48	0.0006
Pars Triangularis	L	−42.5	38.5	2.6	17.16	0.0007
	R	47.5	34.3	5.4	66.94	0.0004
	R	49.9	27.3	11.9	4.7	0.0009
Posterior Cingulate	L	−12.4	−30.7	38.2	0.37	0.001
Middle Temporal	R	47.3	7.5	−36.3	0.53	0.001

Note. Talairach coordinates reflect location of peak voxel within cluster. CES-D = Center for Epidemiologic Studies Depression Scale, L = left, R = right.

† indicates significance after correction for multiple comparisons.

* indicates significant at FDR < 0.10

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